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Original Article

Risk stratification of hepatocellular carcinoma incidence using a fibrosis-4-based prediction model in patients with chronic hepatitis C receiving antiviral therapy: a nationwide real-world Taiwanese cohort study

Hung-Wei Wang[1,2], Pei-Chein Tsai[3,4], Chi-Yi Chen[5], Kuo-Chih Tseng[6,7], Hsueh-Chou Lai[1,8], Hsing-Tao Kuo[9], Chao-Hung Hung[10], Shui-Yi Tung[10], Jing-Houng Wang[11], Jyh-Jou Chen[12], Pei-Lun Lee[12], Ron-Nan Chien[13], Chun-Yen Lin[13], Chi-Chieh Yang[14], Gin-Ho Lo[15], Chi-Ming Tai[15], Chih-Wen Lin[15], Jia-Horng Kao[16,17], Chun-Jen Liu[16,17], Chen-Hua Liu[16,17], Sheng-Lei Yan[18], Ming-Jong Bair[19,20], Wei-Wen Su[21], Cheng-Hsin Chu[22], Chih-Jen Chen[22], Ching-Chu Lo[23], Pin-Nan Cheng[24], Yen-Cheng Chiu[24], Chia-Chi Wang[25], Jin-Shiung Cheng[26], Wei-Lun Tsai[26], Han-Chieh Lin[27,28], Yi-Hsiang Huang[27,28], Jee-Fu Huang[3,4], Chia-Yen Dai[3,4], Wan-Long Chuang[3,4], Ming-Lung Yu[3,4,29*], Cheng-Yuan Peng[1,2*]

[1]Centre for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; [2]School of Medicine, China Medical University, Taichung, Taiwan; [3]Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [4]School of Medicine and Hepatitis Research Center, College of Medicine, Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan; [5]Department of Internal Medicine, Chiayi Christian Hospital, Chiayi, Taiwan; [6]Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan; [7]School of Medicine, Tzuchi University, Hualien, Taiwan; [8]School of Chinese Medicine, China Medical University, Taichung, Taiwan; [9]Division of Hepatogastroenterology, Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan; [10]Division of Hepatogastroenterology, Department of Internal Medicine, Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan; [11]Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [12]Division of Gastroenterology and Hepatology, Chi-Mei Medical Center, Liouying, Tainan, Taiwan; [13]Division of Hepatology, Department of Gastroenterology and Hepatology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [14]Division of Gastroenterology, Department of Internal Medicine, Show-Chwan Memorial Hospital, Changhua, Taiwan; [15]Division of Gastroenterology and Hepatology, Department of Medicine, E-Da Hospital, School of Medicine, I-Shou University, Kaohsiung, Taiwan; [16]Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan; [17]Division of Gastroenterology and Hepatology, The National Taiwan University Hospital, Taipei, Taiwan; [18]Division of Gastroenterology, Department of Internal Medicine, Chang Bing Show-Chwan Memorial Hospital, Changhua, Taiwan; [19]Division of Gastroenterology, Department of Internal Medicine, Taitung Mackay Memorial Hospital, Taitung, Taiwan; [20]Mackay Medical College, New Taipei, Taiwan; [21]Division of Gastroenterology, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan; [22]Division of Gastroenterology, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan; [23]Department of Internal Medicine, St. Martin De Porres Hospital - Daya, Chiayi, Taiwan; [24]Department of Internal Medicine, National Cheng Kung University Hospital, Medical College, National Cheng Kung University, Tainan, Taiwan; [25]Division of Gastroenterology, Department of Internal Medicine, Tzuchi Hospital, Taipei, Taiwan; [26]Division of Gastroenterology and Hepatology, Department of Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [27]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [28]Institute of Clinical Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [29]Institute of Biomedical Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan. [*]Equal contributors.

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Abstract: A total of 1,589 patients who had received interferon-based treatment were enrolled and analyzed for the risk of hepatocellular carcinoma (HCC) in a real-world nationwide Taiwanese chronic hepatitis C cohort (T-COACH). We aimed to stratify HCC risk by non-invasive fibrosis index-based risk model. Of 1589 patients, 1363 (85.8%)

patients achieved sustained virological response (SVR). Patients with SVR had 1, 3, 5 and 10-year cumulative HCC incidence rates of 0.55%, 1.87%, 3.48% and 8.35%, respectively. A Cox proportional hazards model revealed that non-SVR (adjusted hazard ratio [aHR]: 1.92, 95% confidence interval [CI]: 1.19-3.12, p = 0.008), diabetes mellitus (aHR: 2.11, 95% CI: 1.25-3.55, p = 0.005), and fibrosis (FIB)-4 at the end of follow-up (EOF; aHR: 5.60, 95% CI: 2.97-10.57, p < 0.0001) were independent predictors of HCC. Risk score models based on the three predictors were developed to predict HCC according to aHR. In model 1, the 10-year cumulative incidence rates of HCC were 43.35% in patients at high risk (score 9-10), 25.48% in those at intermediate risk (score 6-8), and 4.06% in those at low risk (score 3-5) of HCC. In model 2, the 10-year cumulative incidence rates of HCC were 39.64% in patients at high risk (at least two risk predictors), 19.12% in those at intermediate risk (with one risk predictor), and 2.52% in those at low risk (without any risk predictors) of HCC. The FIB-4-based prediction model at EOF could help stratify the risk of HCC in patients with chronic hepatitis C after antiviral treatment.

Keywords: Chronic hepatitis C, FIB-4, hepatocellular carcinoma, T-COACH

Introduction

Treatment with either interferon (IFN)-based regimen or direct-acting antivirals (DAAs) for hepatitis C virus (HCV) decreases the incidence of hepatocellular carcinoma (HCC) but does not eliminate the risk [1, 2]. The impact of a sustained virological response (SVR) to IFN-based or DAA-based therapy for HCV on HCC risk is similar [3-5]. The severity of liver fibrosis is strongly associated with the occurrence of HCC [6]. However, the gold standard for diagnosing the status of liver fibrosis is liver biopsy. This is an invasive and potentially risky procedure for patients with chronic liver disease, especially for those with hepatic decompensation [7]. At present, noninvasive liver fibrosis indices are widely used to evaluate liver fibrosis status and predict liver-associated complications, including HCC [8]. Noninvasive liver fibrosis indices, including the aspartate transaminase (AST)-to-platelet ratio index (APRI) [9], fibrosis-4 (FIB-4) [10], and modified FIB-4 (mFIB-4), exhibit acceptable-to-excellent predictive performance for advanced liver fibrosis, with the area under the receiver operating characteristic curve (AUROC) ranging from 0.77 to 0.82 in our previous study [11]. Moreover, FIB-4 and APRI values decline after antiviral therapy because of rapid improvements in hepatic necroinflammation [12, 13]. Therefore, the optimal time point for evaluating liver fibrosis to predict liver-associated outcomes in patients with chronic hepatitis C (CHC) receiving antiviral treatment requires clarification. Recently, simplified HCC risk score models for predicting the risk of HCC occurrence in patients with CHC have become popular due to its feasibility and readiness to use compared to elastography-based models [14]. One critical parameter of these risk models is noninvasive fibrosis index, such as FIB-4, which reflects the severity of liver fibrosis. However, it remains to be elucidated how FIB-4 at different time points, either at baseline or post-treatment, or its dynamic change throughout treatment performs in these risk models. In this study, we compared the performance of fibrosis indices to predict HCC at baseline and at the end of follow-up (EOF), 24 weeks after the completion of antiviral treatment. Furthermore, we developed FIB-4-based prediction models to stratify HCC risk in a real-world nationwide Taiwanese CHC cohort (T-COACH).

Material and methods

Subjects

T-COACH is a nationwide Taiwanese HCV registry from 23 hospitals with a total of 15,836 patients with CHC recruited from January 2003 to December 2015. The key inclusion criteria were as follows: age more than 20 years, CHC confirmed by hepatic pathology or anti-HCV seropositivity for more than six months, detectable HCV RNA, and having undergone IFN-based therapy for at least four weeks. IFN-based therapy was defined as interferon (IFN) or pegylated interferon (PEG-IFN) with and without ribavirin combination for HCV therapy. For patients who received 2 or more courses of IFN-based therapy and attained an SVR at the last course, they were assigned as SVR with the last course as the index course and the data of the last course being used for analysis. For patients who received 2 or more courses of IFN-based therapy and did not attain an SVR at the last course, they were assigned as non-SVR with the first course as the index course and the data of the first course being used for analysis. An SVR was defined as undetectable HCV RNA both at the end-of-treatment and at 24 weeks after the end-of-treatment (EOF).

Our study cohort excluded patients with concurrent hepatitis B virus infection, unavailable SVR, mortality during therapy, hepatic malignancies before antiviral therapy or within six months of the end of antiviral therapy, and incomplete laboratory data at baseline or EOF (Figure S1). Patient demographic characteristics, laboratory data at baseline, and EOF were collected; collected data included age, sex, cirrhosis status, diabetes mellitus (DM) diagnosis, total bilirubin, alanine aminotransferase (ALT), AST, albumin, international normalized ratio, platelet count (PLT), and alpha-fetoprotein. APRI, FIB-4, and mFIB-4 were calculated according to the following formula [9-11]:

$$\text{APRI} = \frac{\text{AST (/ULN)}}{\text{Platelet count } (10^9/\text{L})} \times 100$$

PS: The ULN for AST was 30 U/L.

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

$$\text{mFIB-4} = \frac{10 \times \text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \times \text{ALT (U/L)}}$$

This study was conducted in accordance with the 1975 Declaration of Helsinki and was approved by the Research Ethics Committee of China Medical University Hospital (CMUH104-REC1-070), Taichung, Taiwan, and each study site. Written informed consent were obtained from all patients prior to enrollment.

Definition of hepatocellular carcinoma

Patients with HCC were identified based on the International Classification of Diseases, Ninth Revision, Clinical Modification codes at admission or on more than three visits to the outpatient department, as identified through Taiwan's National Health Insurance Research Database (Figure S1).

Statistical analysis

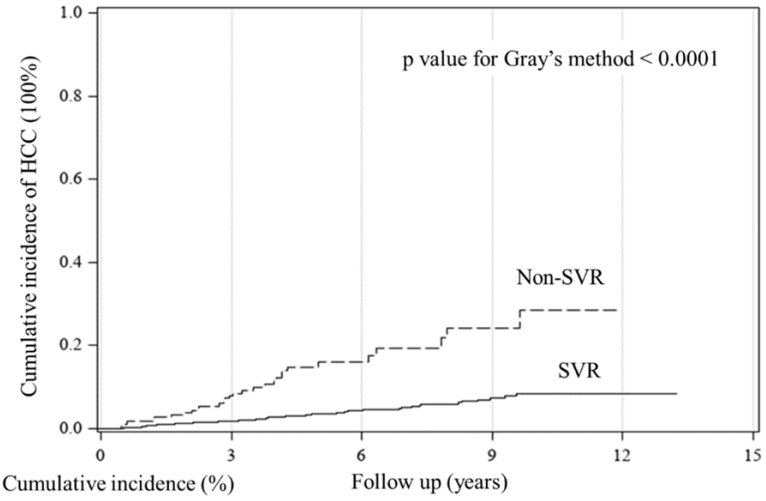
Continuous variables were expressed as the median ± interquartile range and analyzed using the Mann-Whitney U test. Categorical variables were analyzed using a chi-square test. The performance of different noninvasive fibrosis indices at baseline and EOF to predict HCC was compared using receiver operating characteristic (ROC) curves and the DeLong test. We considered death a competing event and modified the Kaplan-Meier method according to the Gray cumulative incidence method, comparing the incidence of new-onset HCC between patients with SVR and those without SVR. Subdistribution hazard models to estimate the HR and 95% CI were used to examine the independent factors associated with new-onset HCC. Risk models were established to evaluate HCC occurrence according to Cox regression analyses by using the aHR of predictors. Statistical analyses were performed using SAS Enterprise Guide software (version 9.4, SAS Institute, Cary, NC, USA). P values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

The present study cohort excluded patients with incomplete laboratory data at baseline or EOF from the original study cohort (Figure S1). For the 1,589 patients recruited, the median age was 53.5 ± 11.3 years, 50.7% (n = 806) were male, 14.6% (n = 197) had received a diagnosis of DM, the median follow-up period was 4.49 years (Q1-Q3: 2.63-7.15 years), and 1,363 (85.8%) patients achieved SVR. A total of 88 (5.5%) patients developed HCC during the 7,762 person-years of follow-up. Of the 12,256 patients in the original study cohort, the median age was 54.2 ± 11.3 years, 52.7% (n = 6457) were male, 17.7% (n = 1195) had received a diagnosis of DM, the median follow-up period was 4.17 years (Q1-Q3: 2.15-5.98 years), and 9,393 (76.6%) patients achieved SVR. The HCC incidence was 1.19% per person-year during the 52,220 person-years of follow-up (Table S1). Patients in the study cohort were younger on average (53.5 years vs. 54.2 years), had a lower proportion of liver cirrhosis and DM (12.1% vs. 17% and 14.6% vs. 17.7%, respectively), a higher SVR rate (85.8% vs. 76.6%), and higher levels of APRI, FIB-4, and mFIB-4, than those in the original study cohort (Table S1).

Patients with SVR had cumulative HCC incidence rates at 1, 3, 5, and 10 years of 0.55%, 1.87%, 3.48% and 8.35%, respectively (**Figure 1**). Significant differences between the non-SVR and SVR subgroups were revealed in terms of age, sex, liver cirrhosis, HCV genotype,



Cumulative incidence (%)

Years	1	3	5	8	10
SVR	0.55	1.87	3.48	5.92	8.35
Non-SVR	1.88	7.88	15.99	24.30	28.59

Figure 1. Effect of SVR on HCC occurrence when considering death as a competing risk. HCC, hepatocellular carcinoma; SVR, sustained virological response.

HCV viral load, baseline data including ALT, PLT, APRI, mFIB-4, and FIB-4, and EOF data including AST, ALT, PLT, APRI, mFIB-4, and FIB-4 (**Table 1**). Patients without SVR had higher levels of APRI, mFIB-4, and FIB-4, either at baseline or EOF, compared with those with SVR. In addition, patients without SVR had a higher annual incidence of HCC than those with SVR (3.14% vs. 0.76% per person-year).

Baseline and posttreatment factors associated with the occurrence of HCC

SVR, age, DM, cirrhosis, and FIB-4 at baseline and EOF were significant factors for HCC when analyzed using univariate Cox proportional hazards models after adjustment for competing mortality (**Table 2**). SVR (no vs. yes; aHR: 1.92, 95% confidence interval [CI]: 1.19-3.12), DM (yes vs. no; adjusted hazard ratio [aHR]: 2.11, 95% CI: 1.25-3.55), FIB-4 at EOF (≥ 2.87 vs. < 2.87; aHR: 5.60, 95% CI: 2.97-10.57) were independent factors for HCC in the analysis using a multivariate Cox regression model.

SVR effect on the cumulative incidence of HCC stratified by FIB-4 at EOF

FIB-4 at EOF was demonstrated as an independent factor for predicting HCC risk (**Table 2**). A Kaplan-Meier survival curve analysis showed that SVR stratified the risk of HCC in patients with FIB-4 at EOF ≥ 2.87 (p value for the Gray method = 0.0007; **Figure 2B**) but not in patients with FIB-4 at EOF < 2.87 (**Figure 2A**). The 3, 5, and 10-year cumulative incidences of HCC were 7.38%, 11.72%, and 25.61% and 15.09%, 30.01%, and 51.30%, respectively, in patients with FIB-4 at EOF ≥ 2.87 and SVR versus FIB-4 at EOF ≥ 2.87 and non-SVR (**Figure 2B**).

SVR effect on the cumulative incidence of HCC stratified by DM

DM was demonstrated as an independent factor predicting HCC risk (**Table 2**). A Kaplan-Meier survival curve analysis showed that SVR stratified the risk of HCC in patients with and without DM (p value for the Gray method < 0.031 and 0.0001; **Figure 3A**, **3B**). The 3, 5, and 10-year cumulative incidences of HCC were 2.74%, 9.76%, and 19.86% and 1.75%, 2.57%, and 6.76%, respectively, in SVR patients with and without DM (**Figure 3A**, **3B**).

Predictive performance of APRI, FIB-4, and mFIB-4 at baseline or EOF for HCC

For the prediction of HCC, the AUROCs for FIB-4 at baseline and EOF (AUROC = 0.832 and 0.829) were significantly or numerically higher than those for APRI (AUROC = 0.785 and 0.820) and mFIB-4 (AUROC = 0.801 and 0.775) at baseline and EOF (Table S2). Although FIB-4 at baseline and EOF exhibited a similar predictive performance for HCC (nonsignificant) with the ROC analysis (DeLong test, p = 0.813), FIB-4 at EOF (cutoff value: 2.87)-but not at baseline (cutoff value: 2.76)-was an independent predictor of HCC (**Table 2**) when analyzed using a multivariate Cox regression model.

Prediction models for HCC

We constructed FIB-4-based prediction models for HCC according to a Cox regression model (**Table 2**) and used aHR to determine the proportional effect and association of the three independent risk factors (SVR, DM, and FIB-4

Table 1. Patient demographics and characteristics

Variables	Total (n = 1589)	SVR (n = 1363)	Non-SVR (n = 226)	p Value
Baseline				
Age	53.5 ± 11.3	53.0 ± 11.3	56.9 ± 10.7	< 0.0001
< 50/50-60/≥ 60	539 (33.9)/540 (34.0)/510 (32.1)	485 (35.6)/464 (34.0)/414 (30.4)	54 (23.9)/76 (33.6)/96 (42.5)	0.0002
Sex, male/female	806 (50.7)/783 (49.3)	708 (51.9)/655 (48.1)	98 (43.4)/128 (56.6)	0.017
LC, no/yes	1,389 (87.9)/192 (12.1)	1,213 (89.4)/144 (10.6)	176 (78.6)/48 (21.4)	< 0.0001
DM, no/yes	1,149 (85.4)/197 (14.6)	990 (85.9)/162 (14.1)	159 (82.0)/35 (18.0)	0.147
HTN, no/yes	1,070 (79.5)/276 (20.5)	913 (79.3)/239 (20.8)	157 (80.9)/37 (19.1)	0.593
HLD, no/yes	1,252 (93.0)/94 (7.0)	1,068 (92.7)/84 (7.3)	184 (94.9)/10 (5.2)	0.280
BMI	25.1 ± 3.7	25.1 ± 3.7	25.5 ± 3.7	0.080
< 24/≥ 24	632 (39.8)/957 (60.2)	554 (40.7)/809 (59.4)	78 (34.5)/148 (65.5)	0.081
HCV genotype, 1/non-1	677 (42.6)/912 (57.4)	533 (39.1)/830 (60.9)	144 (63.7)/82 (36.3)	< 0.0001
HCV RNA (log_{10} IU/mL)	5.45 ± 0.98	5.38 ± 1.00	5.87 ± 0.70	< 0.0001
< 400/≥ 400 (10^3 IU/mL)	766 (48.6)/811 (51.4)	699 (51.6)/655 (48.4)	67 (30.0)/156 (70.0)	< 0.0001
Creatinine	0.95 ± 1.15	0.94 ± 1.10	1.00 ± 1.42	0.569
AST	92.4 ± 63.0	92.3 ± 63.8	93.1 ± 57.7	0.880
ALT	135.6 ± 111.6	139.0 ± 115.9	115.3 ± 78.1	0.0001
Platelet	172.4 ± 60.8	174.9 ± 59.9	157.6 ± 64.3	< 0.0001
APRI	1.63 ± 1.50	1.59 ± 1.46	1.90 ± 1.72	0.012
FIB-4	3.10 ± 2.64	2.95 ± 2.40	4.06 ± 3.63	< 0.0001
mFIB-4	2.92 ± 2.34	2.74 ± 2.10	3.99 ± 3.28	< 0.0001
EOF				
AST	32.0 ± 22.1	27.8 ± 14.7	57.4 ± 37.0	< 0.0001
ALT	30.6 ± 27.2	25.1 ± 16.4	63.9 ± 47.8	< 0.0001
Platelet	176.1 ± 62.2	180.3 ± 60.7	150.9 ± 65.5	< 0.0001
APRI	0.59 ± 0.72	0.47 ± 0.48	1.29 ± 1.29	< 0.0001
FIB-4	2.33 ± 2.10	2.09 ± 1.72	3.77 ± 3.30	< 0.0001
mFIB-4	4.44 ± 3.42	4.34 ± 3.29	5.05 ± 4.08	0.014
Person-years	7,762	6,807	955	
Follow-up duration (years), median (Q1-Q3)	4.49 (2.63-7.15)	4.57 (2.77-7.32)	3.82 (2.37-5.45)	0.0001
Annual HCC incidence, n (%, per person-year)	82 (1.06)	52 (0.76)	30 (3.14)	

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; EOF, end of follow-up; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLD, hyperlipidemia; HTN, hypertension; IU, international unit; LC, liver cirrhosis; mFIB-4, modified FIB-4; SVR, sustained virological response.

Table 2. Cox proportional hazards models for HCC risk after adjustment for competing mortality

Variables		HCC	Death Before HCC	Crude HR (95% CI)	Crude p	Adjusted Age, SVR, FIB4 (Stepwise)	
		Cumulative, n (%)	Cumulative, n (%)			Adjusted HR (95% CI)	Adjusted p
SVR	yes	52 (3.8)	21 (1.5)	1		1	
	no	30 (13.3)	9 (4.0)	4.11 (2.62-6.43)	< 0.0001	1.92 (1.19-3.12)	0.008
Age	< 50	5 (0.9)	6 (1.1)	1		1	
	50-60	33 (6.1)	7 (1.3)	2.57 (1.96-3.39)	< 0.0001	1.37 (0.98-1.92)	0.062
	≥ 60	44 (8.6)	17 (3.3)				
Sex	male	49 (6.1)	19 (2.4)	1			
	female	33 (4.2)	11 (1.4)	0.68 (0.44-1.06)	0.091		
BMI	< 24	26 (4.1)	13 (2.1)	1			
	≥ 24	56 (5.9)	17 (1.8)	1.48 (0.93-2.36)	0.097		
DM	no	54 (4.7)	23 (2.0)	1		1	
	yes	24 (12.2)	6 (3.1)	2.86 (1.78-4.61)	< 0.0001	2.11 (1.25-3.55)	0.005
HTN	no	60 (5.6)	23 (2.2)	1			
	yes	18 (6.5)	6 (2.2)	1.14 (0.68-1.92)	0.623		
LC	no	44 (3.2)	19 (1.4)	1		1	
	yes	38 (19.8)	10 (5.2)	5.1 (3.64-8.62)	< 0.0001	1.60 (0.94-2.73)	0.082
HCV RNA (10^3 IU/mL)	< 400	42 (5.5)	11 (1.4)	1			
	≥ 400	39 (4.8)	18 (2.2)	0.99 (0.64-1.53)	0.954		
Genotype	1	40 (5.9)	20 (3.0)	1			
	non-1	42 (4.7)	10 (1.1)	0.81 (0.53-1.23)	0.321		
BL-FIB-4	< 2.76	8 (0.9)	7 (0.8)	1			
	≥ 2.76	74 (11.3)	23 (3.5)	12.92 (6.23-26.82)	< 0.0001		
EOF-FIB-4	< 2.87	21 (1.7)	13 (1.1)	1		1	
	≥ 2.87	61 (17.1)	17 (4.8)	10.59 (6.46-17.37)	< 0.0001	5.60 (2.97-10.57)	< 0.0001

BMI, body mass index; BL, baseline; DM, diabetes mellitus; EOF, end of follow-up; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; HR, hazards ratio; HCV, hepatitis C virus; HTN, hypertension; LC, liver cirrhosis; SVR, sustained virological response.

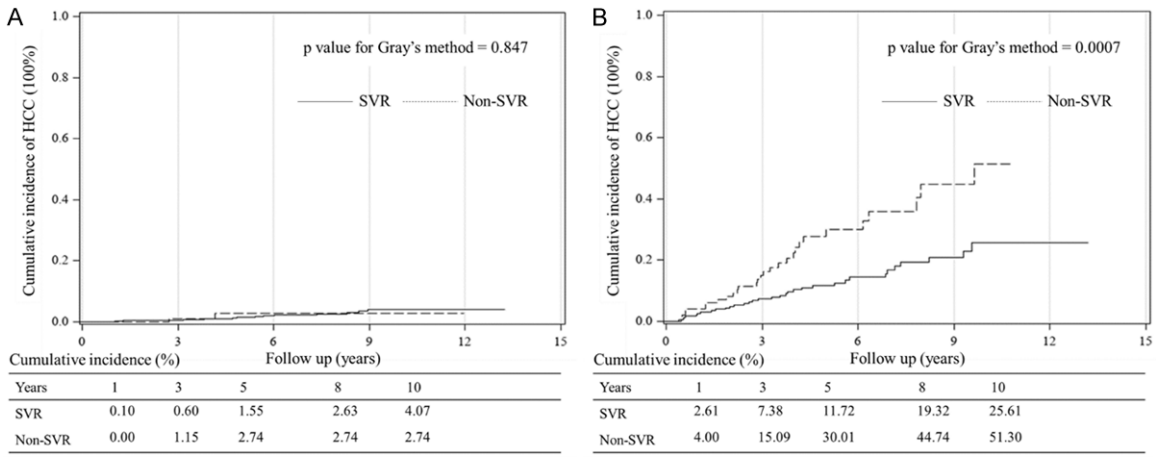
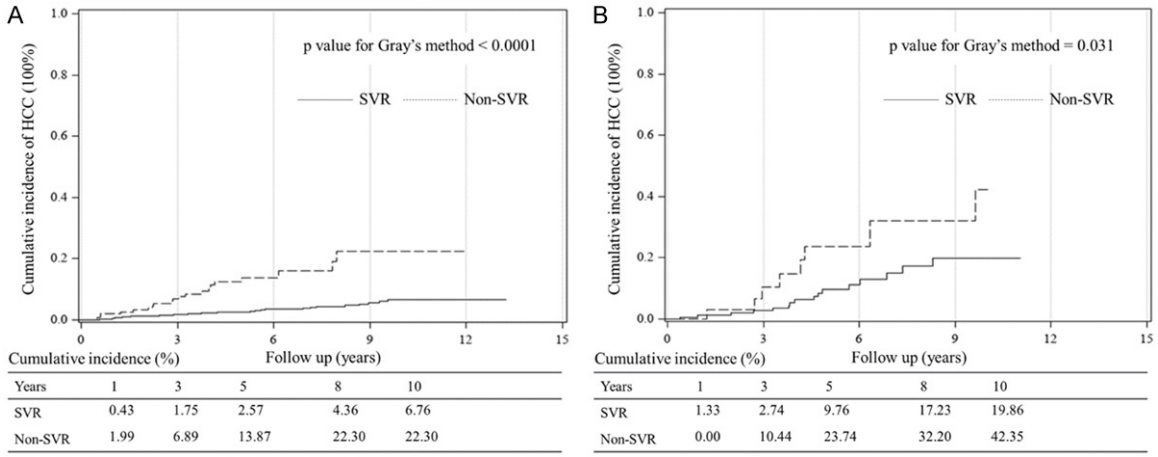


Figure 2. Effect of SVR on HCC occurrence stratified by EOF-FIB-4. A. EOF-FIB-4 < 2.87. B. EOF-FIB-4 ≥ 2.87. EOF, end of follow-up; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; SVR, sustained virological response.

at EOF), with a risk score sum ranging from 3 to 10 (model 1) or the number of risk predictors ranging from 0 to 3 (model 2; **Table 3**). In model 1, the 10-year cumulative incidence rates of HCC were 43.35% in patients at high risk (score 9-10), 25.48% in those at intermediate risk (score 6-8), and 4.06% in those at low risk (score 3-5; **Figure 4A**). In model 2, the 10-year cumulative incidence rates of HCC were 39.64% in patients at high risk (at least two risk predictors), 19.12% in those at intermediate risk (with one risk predictor), and 2.52% in those at low risk (without any risk predictors; **Figure 4B**).



Years	1	3	5	8	10
SVR	0.43	1.75	2.57	4.36	6.76
Non-SVR	1.99	6.89	13.87	22.30	22.30

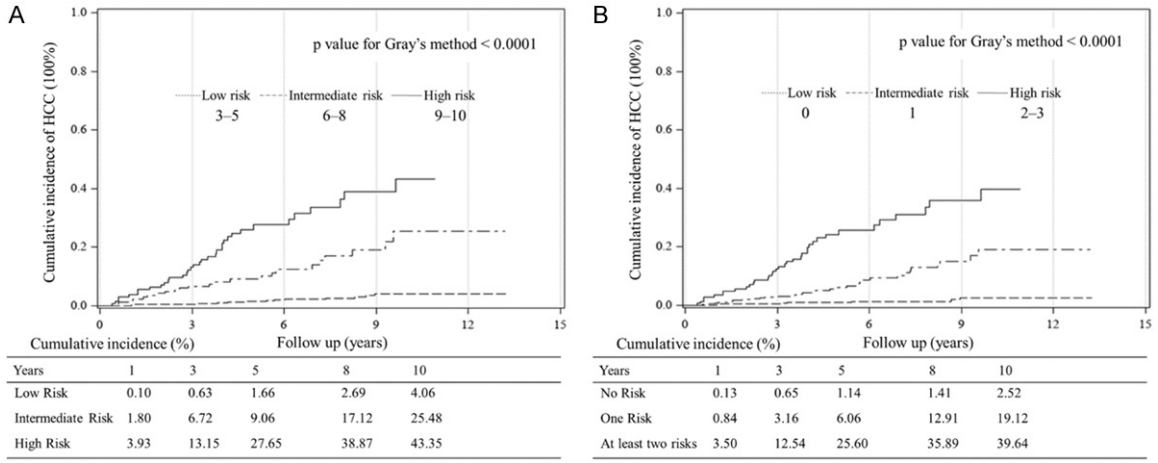
Years	1	3	5	8	10
SVR	1.33	2.74	9.76	17.23	19.86
Non-SVR	0.00	10.44	23.74	32.20	42.35

Figure 3. Effect of SVR on HCC occurrence stratified by DM. A. No DM. B. DM. DM, diabetes mellitus; HCC, hepatocellular carcinoma; SVR, sustained virological response.

Table 3. Risk score models to predict HCC according to HR

Variables		Adjusted HR	Risk Score	Model 1	Model 2
SVR	yes	1	1	Sum of risk score 3-10	Number of risk factors 0-3
	no	1.92	2		
DM	no	1	1		
	yes	2.11	2		
EOF-FIB-4	< 2.87	1	1		
	≥ 2.87	5.60	6		

DM, diabetes mellitus; EOF, end of follow-up; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; HR, hazards ratio; SVR, sustained virological response.



Years	1	3	5	8	10
Low Risk	0.10	0.63	1.66	2.69	4.06
Intermediate Risk	1.80	6.72	9.06	17.12	25.48
High Risk	3.93	13.15	27.65	38.87	43.35

Years	1	3	5	8	10
No Risk	0.13	0.65	1.14	1.41	2.52
One Risk	0.84	3.16	6.06	12.91	19.12
At least two risks	3.50	12.54	25.60	35.89	39.64

Figure 4. Predictive model for HCC incidence by using DM, EOF-FIB-4, and SVR. A. Model 1: by sum of risk score (3-10). B. Model 2: by number of risks (0-3). DM, diabetes mellitus; EOF, end of follow-up; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; SVR, sustained virological response.

Discussion

The T-COACH is a nationwide HCV registry accounting for almost a quarter of patients with CHC in Taiwan treated between January 2003 and December 2015. In this cohort, decreased risk of cancer occurrence, including HCC and non-HCC (gastric cancer and non-Hodgkin lymphoma), has been reported for patients who had achieved SVR [15]. Although the 10-year

cumulative incidence rates of liver-associated complications (including HCC) decrease to 21.4% in patients with cirrhosis who have attained SVR, compared with those without SVR (47%), the risk of HCC remains substantial [16]. Therefore, we investigated predictors to stratify HCC risk. In this study, DM, non-SVR, and FIB-4 at EOF were independently associated with HCC occurrence.

FIB-4 is a familiar noninvasive fibrosis index for patients with CHC [10]. ALT, AST, and platelet count are among the routine laboratory tests for CHC, and thus, FIB-4 can be readily calculated to facilitate the risk stratification of HCC for patients with chronic liver disease. The formula for FIB-4 was originally derived from patients co-infected with HCV and HIV with hepatic inflammation using the proportions of the corresponding regression coefficient of each independent factor to predict the fibrosis stage in a logistic regression model. However, studies have demonstrated that the FIB-4 value rapidly declines as a consequence of a decrease in transaminase levels and increase in platelet count after the commencement of DAA therapy in patients with CHC [12, 13, 17]. This finding suggests that FIB-4 values measured in the presence of hepatitis activity may overestimate the apparent severity of liver fibrosis, whereas FIB-4 values measured after the resolution of hepatic inflammation may more reliably reflect the severity of underling fibrosis. A study revealed that the predictive performance of FIB-4 for significant fibrosis (≥ F2) and advanced fibrosis (≥ F3) are similar in patients with persistent HCV infection and those with HCV eradication, but the optimal FIB-4 cutoff values for dichotomizing significant fibrosis (≥ F2) and advanced fibrosis (≥ F3) are higher in patients with persistent HCV infection than in those with eradicated HCV [18]. However, whether FIB-4 measurement in the presence or absence of hepatic inflammation correlates more strongly with the future risk of liver-related outcomes remains unclear. In this study, patients with SVR exhibited complete ALT and AST normalization, whereas patients with non-SVR exhibited a partial decrease in ALT and AST levels despite the failure to eradicate the virus. Median FIB-4 values declined from 2.95 and 4.06 at baseline to 2.09 and 3.77 at EOF in patients with SVR and non-SVR, respectively. The decline in FIB-4 values over a short period of time is consistent with previous observations of patients treated with DAA and highlights the influence of hepatic inflammation, although the possibility that part of the decline could be attributed to fibrosis regression cannot be completely excluded. We further investigated the predictive performance of FIB-4 at baseline versus at EOF for HCC development and identified the independent predictors of HCC occurrence. Although the AUROCs of FIB-4 at baseline and EOF for predicting HCC development were similar, the multivariate Cox regression model identified FIB-4 at EOF as an independent predictor, indicating that residual fibrosis status measured using FIB-4 at EOF was more relevant to HCC development than FIB-4 at baseline. Although we were not able to investigate the predictive performance of FIB-4 at time points between baseline and EOF, our results suggest that FIB-4 at EOF represents a feasible time point for conducting an assessment to predict HCC risk in patients with CHC completing antiviral treatment.

Many HCC risk models have been established for the treated CHC cohort, including simplified HCC score, elastography-based, multivariable regression, and deep learning HCC risk prediction models [14]. Simplified HCC score models contain readily available laboratory data and are easy to use. Of the prediction tools, elastography-based models require expensive measurement devices, multivariate regression models require a web-based calculator, and deep learning prediction models are still under development and require validation [14, 19, 20]. Several FIB-4-based HCC score models have been reported to stratify HCC risk (**Table 4**) [21-25]. FIB-4 at baseline was demonstrated to be an independent predictor of HCC risk in patients with CHC who attained SVR to IFN-based treatment [23]. Recent studies have further demonstrated that in addition to FIB-4 at baseline, FIB-4 at or after SVR could be used as a component variable of the predictive model for HCC risk [21-25]. The present study investigated the predictive role of FIB-4 at baseline versus at EOF for HCC risk by using a Cox regression model and verified FIB-4 at EOF as the more relevant covariate for establishing the risk model. Measurement of the FIB-4 index at SVR may represent a convenient point-of-care tool for predicting future HCC risk in patients with CHC completing antiviral therapy. Consistent with this finding, a recent study investigated the independent predictors of HCC occurrence in patients with advanced compensated CHC who had achieved SVR to DAA therapy, revealing that liver stiffness measured using FibroScan 1 year after completing DAA

Table 4. Summary of FIB-4-based risk models for HCC development in patients with treated CHC

Authors	Regimen	Patient numbers	Cirrhosis	Noninvasive Fibrosis Index	Component Variables	HCC Risk Stratification (Low HCC Risk Subgroup)
Tamaki et al. [21]	IFN-based	1,046	3.4%	FIB-4	Baseline FIB-4, delta FIB-4/y	FIB-4 ≤ 3.25 and a delta FIB-4/y < 0.3 7-y cumulative incidence: 4.8%
Chun et al. [22]	IFN-based	669	16.7%	FIB-4	Male, AFP at SVR, FIB-4 at SVR	HCV-SVR score: 0-2 2-y, 4-y, 6-y cumulative incidence: 0.01%, 0.01%, 0.01%
Ioannou et al. [23]	IFN-based DAA	19,102 29,033	11.8% 25.9%	FIB-4	Baseline FIB-4, post-SVR FIB-4	Cirrhosis: both baseline and post-SVR FIB-4 < 3.25 HCC risk: 1.02% per year
Toyoda et al. [24]	IFN-based	522	0%	FIB-4	Annually updated FIB-4	All post-SVR FIB-4 < 1.45 Cumulative incidence: 0%
Alonso Lopez et al. [25]	DAA	1,046	all advanced fibrosis	FIB-4	Baseline FIB-4, 1-y FIB-4, baseline albumin, 1-y GGT	FIB-4-based HCC risk score = 0 Cumulative incidence: 0.4%
T-COACH	IFN-based	1,589	12.1%	FIB-4	DM, non-SVR, FIB-4 at EOF	Model 1: risk score = 3; model 2: risk score = 0 10-y cumulative incidence: model 1: 4.1%, model 2: 2.5%

CHC, chronic hepatitis C; DAA, direct-acting antiviral agent; DM, diabetes mellitus; EOF, end of follow-up; FIB-4, fibrosis index based on four factors; GGT, γ-glutamyl transferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; SVR, sustained virological response; y, year.

therapy, rather than at baseline, was an independent predictor of HCC risk in a multivariate Cox regression model [26]. Furthermore, post-SVR FIB-4 has been utilized to identify a low-risk population of patients with an annual HCC risk close to 0% [22, 23]. According to our prediction models 1 and 2, both the annual HCC risks were less than 0.4% in the low-risk subgroup, which is close to the threshold of 0.2% per year for HCC surveillance recommended by the American Association for the Study of Liver Diseases (**Figure 4**). Identification of the intermediate-risk and high-risk subgroups may warrant a more intensive HCC surveillance program or chemoprevention trial of HCC in the future (**Figure 4**). Considering its ease of use, our prediction model may be implemented in future surveillance strategies for HCC in patients with CHC after antiviral treatment.

Our study has some clinical implications. First, this was a large multicenter cohort study investigating the predictive performance of post-treatment FIB-4 for HCC risk in patients with CHC. Thus, its findings may be applicable to the posttreatment follow-up of patients who have completed IFN-based therapy. Second, we explored the impact of hepatic inflammation on the predictive performance of FIB-4 in HCC risk in patients with CHC completing IFN-based therapy, demonstrating that FIB-4 at EOF is the preferred time point for predicting HCC risk compared with FIB-4 at baseline. Third, the proposed FIB-4-based risk model can be used routinely for predicting HCC risk given its non-invasive, simple, inexpensive, and reproducible features, obviating the need for liver biopsy in clinical practice, which has inherent risks. This study has several weaknesses. First, patients with incomplete FIB-4 data at baseline or EOF were excluded from the study cohort, which may have affected the HR estimation of the predictive factors (Figure S1). Second, an alternative method such as elastography was not performed to correlate the changes in FIB-4 values across the study timeline. However, this modality was unavailable to us during a large part of the study period. Third, we were unable to verify our finding through internal validation due to current unavailability of the dataset. An independent cohort for external validation is needed to verify the predictive performance of the FIB-4-based risk model. Finally, whether the present risk model can be used for the stratification of HCC risk in CHC patients receiving DAA treatment warrants further study given the growing number of patients undergoing DAA treatment.

In conclusion, our two FIB-4-based prediction models assessed at the time of SVR are simple and noninvasive and can effectively stratify HCC risk in patients with CHC who have completed IFN-based treatment. The stratification of HCC risk may help individualize HCC surveillance programs in the future.

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Disclosure of conflict of interest

Cheng-Yuan Peng has served as an advisory committee member for AbbVie, Bristol-Myers Squibb (BMS), Gilead, and Merck, Sharp, & Dohme. Ming-Lung Yu received research support from Abbott, BMS, Gilead, and Merck and served as a consultant for AbbVie, Abbott, Ascletis, BMS, Gilead, Merck, and Roche and as a speaker for AbbVie, Abbott, BMS, Gilead, Merck, and IPSEN. No other coauthors have conflicts of interest to declare.

Address correspondence to: Dr. Cheng-Yuan Peng, Centre for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 40447, Taiwan. Tel: +886-4-22052121 Ext. 2260; Fax: +886-4-22071-600; E-mail: cypeng@mail.cmuh.org.tw; Dr. Ming-Lung Yu, Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 80756, Taiwan; School of Medicine and Hepatitis Research Center, College of Medicine, Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan; National Pingtung University of Science and Technology, Pingtung, Taiwan. Tel: +886-7-3121101 Ext. 7475; Fax: +886-7-3123955; E-mail: fish6069@gmail.com

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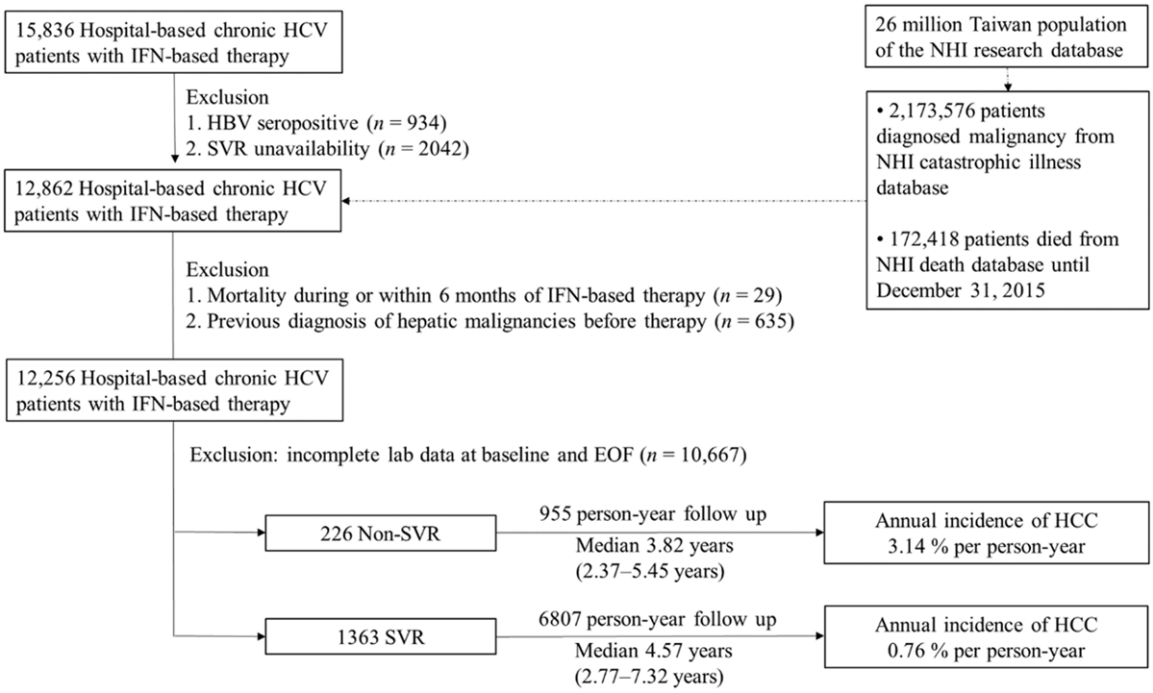

Figure S1. Flowchart of patients from the Taiwanese Chronic Hepatitis C Cohort (T-COACH) with links to the Taiwan National Health Insurance Research Database. HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon; NHI, National Health Insurance; SVR, sustained virological response.

Table S1. Baseline patient demographics and characteristics of the original study cohort and the present study cohort

Variables	Original study cohort n = 12,256	Present study cohort n = 1,589	p value
Age	54.2 ± 11.3	53.5 ± 11.3	0.020
< 50/50-60/≥ 60	4,039 (33.0)/4,039 (33.0)/4,178 (34.1)	539 (33.9)/540 (34.0)/510 (32.1)	0.287
Sex, male/female	6,457 (52.7)/5,799 (47.3)	806 (50.7)/783 (49.3)	0.141
LC, no/yes	8,475 (83.0)/1,734 (17.0)	1,389 (87.9)/192 (12.1)	< 0.001
DM, no/yes	5,503 (82.2)/1,195 (17.7)	1,149 (85.4)/197 (14.6)	0.005
HTN, no/yes	5,375 (80.2)/1,323 (19.8)	1,070 (79.5)/276 (20.5)	0.528
HLD, no/yes	6,075 (90.1)/623 (9.9)	1,252 (93.0)/94 (7.0)	0.006
BMI	25.0 ± 3.5	25.1 ± 3.7	0.308
< 24/≥ 24	4,204 (34.3)/8,052 (65.7)	632 (39.8)/957 (60.2)	< 0.001
HCV genotype, 1/non-1	5,765 (47.0)/6491 (53.0)	677 (42.6)/912 (57.4)	0.001
HCV RNA (log_{10} IU/mL)	5.69 ± 0.99	5.45 ± 0.98	1
< 400/≥ 400 (10^3 IU/mL)	4,156 (38.6)/6,599 (61.4)	766 (48.6)/811 (51.4)	< 0.001
SVR/Non-SVR	9,393 (76.6)/2,863 (23.4)	1,363 (85.8)/226 (14.2)	< 0.001
Creatinine	1.01 ± 1.02	0.95 ± 1.15	1
AST	90.8 ± 64.7	92.4 ± 63.0	0.342
ALT	137.9 ± 110.9	135.6 ± 111.6	0.439
Platelet	176.0 ± 53.9	172.4 ± 60.8	0.014
APRI	1.50 ± 1.48	1.63 ± 1.50	0.001
FIB-4	2.86 ± 2.46	3.10 ± 2.64	< 0.001
mFIB-4	2.74 ± 2.49	2.92 ± 2.34	0.006
Person-years	52,220	7,762	
Follow-up duration (years), median (Q1-Q3)	4.17 (2.15-5.98)	4.49 (2.63-7.15)	< 0.001
Annual HCC incidence, n (%, per person-year)	620 (1.19)	82 (1.06)	

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLD, hyperlipidemia; HTN, hypertension; IU, international unit; LC, liver cirrhosis; mFIB-4, modified FIB-4; SVR, sustained virological response.

Table S2. Comparisons of EOF and baseline APRI, FIB-4, and mFIB-4 for predicting HCC risk

AUC	Comparison p value	BL-FIB-4	EOF-FIB-4	EOF-APRI	BL-mFIB-4	BL-APRI	EOF-mFIB-4
0.832	BL-FIB-4		0.813	0.472	0.023	< 0.0001	0.002
0.829	EOF-FIB-4			0.394	0.02	0.051	< 0.0001
0.820	EOF-APRI				0.215	0.106	0.021
0.801	BL-mFIB-4					0.48	0.062
0.785	BL-APRI						0.698
0.775	EOF-mFIB-4						

APRI, aspartate aminotransferase to platelet ratio index; AUC, area under the curve; BL, baseline; EOF, end of follow-up; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; mFIB-4, modified FIB-4.