

Prediction Model for Risk of Hepatocellular Carcinoma After Hepatitis C Viral Eradication

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Purpose: The predictors of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC) and a sustained virologic response after direct-acting antiviral therapy are not well known.

Patients and Methods: Between September 2012 and March 2022, this retrospective study enrolled 4426 consecutive patients from 4 hospitals in Taiwan. The patients were divided into derivation (n = 3178) and validation (n = 1248) groups.

Results: In the derivation group, age, diabetes mellitus, platelet, albumin, and alpha-fetoprotein at 12 weeks after antiviral therapy were independent predictors of hepatocellular carcinoma. We incorporated these predictors into a novel risk prediction model called the AAAPD-C score (age, albumin, alpha-fetoprotein level, platelet count, and diabetes mellitus status), with total risk scores ranging from 0 to 12. The AAAPD-C score had an area under the receiver operating characteristic curve of 0.867 for the validation group at the end of follow-up. The risk score accurately classified patients in both groups into those with low, medium, and high risks. Patients without advanced liver fibrosis with medium-high AAAPD-C risk scores (4–12) had an annual incidence of HCC >4 per 1000 person-years.

Conclusion: The AAAPD-C score can predict the risk of HCC in patients with chronic hepatitis C and a sustained virologic response after direct-acting antiviral therapy. The tool is accurate and inexpensive, and clinicians can use it to identify patients with chronic hepatitis C at risk of HCC following viral eradication.

Plain Language Summary: AAAPD-C score (age, albumin, AFP level, platelet count, and DM status 12 weeks after antiviral therapy) can predict the risk of hepatocellular carcinoma in patients after hepatitis C viral eradication with direct-acting antivirals. It is an accurate, inexpensive, and convenient tool.

Keywords: AAAPD-C score, direct-acting antiviral agent, hepatitis C virus, hepatocellular carcinoma

Introduction

Chronic hepatitis C (CHC) is a significant liver disease because it can cause severe liver-related events, including esophageal or gastric varices, ascites, hepatic encephalopathy and hepatorenal syndrome, and even hepatocellular carcinoma (HCC). Direct-acting antivirals (DAAs) are highly efficacious and have an excellent safety profile for patients with CHC.^{1,2} However, patients can still develop HCC after achieving sustained virologic response (SVR) following DAA therapy. Therefore, identifying factors predictive of HCC in patients with SVR after DAA therapy is essential.

Liver stiffness measurement (LSM) using transient elastography (TE) or fibrosis-4 (FIB-4) along with albumin can identify patients at risk of HCC and is especially effective for patients with advanced chronic liver disease^{3,4} or advanced liver fibrosis.⁵ However, LSM using TE is not widely accessible. Liver-related parameters, including platelet count, albumin, alpha-fetoprotein (AFP), and FIB-4, exhibit dynamic changes following DAA therapy,⁶ and the predictive performance of these parameters at baseline and after DAA therapy may differ. A convenient and accurate predictive model using variables at an optimal time point is critical.

The recommendations on HCC surveillance following SVR are different among international societies.^{2,7–9} Liver fibrosis status is a major risk factor of HCC, and HCC surveillance in patients with higher fibrosis status is crucial.⁹ Nonetheless, some patients without advanced liver fibrosis may develop HCC following SVR in clinical practice. As a result, some guidelines also suggested HCC surveillance in patients without advanced liver fibrosis.^{7,8} Therefore, this retrospective multicentre study aimed to investigate the predictors of HCC. In addition, we proposed a risk prediction model for the risk of HCC in cured CHC patients with and without advanced liver fibrosis.

Materials and Methods

Patients

From September 2012 to March 2022, the study identified 6017 consecutive patients with CHC at China Medical University Hospital (CMUH, *n* = 1825), Chiayi Christian Hospital (CCH, *n* = 1777), Dalin Tzu Chi Hospital (DTCH, *n* = 1726), and St. Martin De Porres Hospital-Daya (StMH, *n* = 689). Patients were included in the study if they were aged ≥ 18 years; had CHC (presence of serum anti-hepatitis C virus [HCV] antibody for >6 months and detectable HCV RNA [detection limit = 15 IU/mL; COBAS Ampliprep/COBAS TaqMan HCV test, Roche Diagnostics, Branchburg, NJ, USA]); and had completed DAA therapy. Patients were excluded from the study if they had hepatitis B (defined as positive serum hepatitis B surface antigen) or human immunodeficiency virus, if they had not achieved SVR, if they had HCC at baseline or within 3 months after SVR, if they had decompensated liver disease (including ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome)^{10,11} at baseline, if they had end-stage renal disease, or if they were missing biochemistry data at 12 weeks after antiviral therapy (PW12). Some patients met more than one of the exclusion criteria. Finally, 4426 patients were eligible for inclusion, of which 3178 patients (from CCH, DTCH, and StMH) and 1248 patients (from CMUH) were assigned to derivation and validation groups, respectively, depending on which hospital they were treated ([Supplementary Figure 1](#)).

Demographic data and comorbidities were recorded at baseline. Complete blood count analyses, biochemical data, and virological features were collected at baseline and PW12.

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 (CMUH107-REC1-057). Each patient's identification number was encrypted for privacy; thus, the need for informed consent was waived and approved by the Research Ethics Committee.

Diagnosis and Laboratory Tests

Complete blood count analyses and blood biochemistry tests were performed in each hospital's central laboratory. HCV genotyping was performed using the Abbott RealTime HCV Genotype II assay (Abbott Molecular, Abbott Park, IL, USA). Liver cirrhosis (LC) was diagnosed using the results of unequivocal clinical, ultrasonographic, or pathological analysis. Abdominal ultrasonography and serum AFP measurement were conducted every 3 to 6 months for HCC surveillance.

Fibrosis-4 (FIB-4) was calculated using the following formula:¹²

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

Advanced liver fibrosis was defined as FIB-4 >3.25 at baseline.⁹

Diagnosis of HCC

HCC was diagnosed using histology or typical radiological presentations in at least 2 imaging modalities, including contrast-enhanced dynamic computed tomography, magnetic resonance imaging, and hepatic arterial angiography.¹³ Follow-up duration was calculated using the end-of-treatment (EOT) date. End of follow-up (EOF) was defined as any of the following: incident HCC, death, loss to follow-up, or till March 31, 2022.

Statistical Analyses

Continuous variables are presented as the median (interquartile range), and categorical variables are presented as a frequency (percentage). Between-group comparisons of continuous variables were performed using the Mann–Whitney *U*-test. Variables with $P < 0.20$ in univariate analysis were subjected to multivariable Cox regression analysis to determine their associations with HCC.¹⁴ Kaplan–Meier analysis with the Log rank test was used to compare HCC among patient subgroups. The Youden index was used to identify optimal AFP cut-off levels for predicting HCC.

An HCC risk prediction model was developed using a risk score.¹⁵ Briefly, the multivariable-adjusted coefficients and hazard ratios for HCC risk predictors were estimated using a Cox proportional hazards model. The coefficient for every 10-year increase in age for HCC prediction was used as the reference, and individual scores were computed by dividing the coefficient of each category by the reference and then rounded to the nearest multiple of 0.5. The predicted probabilities of HCC at 1-year, 2-year, 3-year, and EOF of the proposed scores at baseline and PW12 and the existing scores at PW12 were obtained in the univariate Cox proportional hazard models. The discriminative performance of the scores was assessed using the time-dependent area under the receiver operating characteristic curve (AUROC). For calibration, the patients were divided into five predicted risk groups (<0.3%, 0.30–0.59%, 0.60–0.89%, 0.90–2.39%, and $\geq 2.4\%$). The proposed score's predicted (using the Cox model) and observed probabilities (using the Kaplan–Meier estimator) were illustrated across the five predicted risk groups. We did not perform a statistical test of the calibration because of the study's large sample size.¹⁶ Model performance was quantified with metrics including Nagelkerke's R^2 and Brier score.¹⁷

All statistical analyses were performed using SPSS (version 25.0, IBM, New York, USA). A two-sided P value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

The median age was 62.0 (52.3–70.8) years, and 1987 patients (44.9%) were men. The demographic data are shown in [Table 1](#). The used regimens are listed in [Supplementary Table 1](#).

Compared with patients in the derivation group, those in the validation group were younger; had lower body mass index; had higher hemoglobin, albumin, AFP, and HCV RNA levels; had longer follow-up durations; were more likely to be male patients; and were less likely to have LC. The incidences of HCC were higher in the validation group than those in the derivation group ([Table 1](#)).

Predictors of HCC in Cured Hepatitis C Patients in the Derivation Group

Low platelet count ($< 100 \times 10^3/\mu\text{L}$) has been demonstrated to be a predictor of HCC in patients with CHC.¹⁸ We used the Youden index to identify the optimal cut-off value for AFP (> 4.6 ng/mL) at PW12 for predicting HCC. In a univariate Cox regression analysis, age, diabetes mellitus (DM), PW12 platelet count ($< 100 \times 10^3/\mu\text{L}$), ALT (> 40 U/L), albumin (< 3.5 g/dL), total bilirubin (> 1.3 mg/dL), and AFP (> 4.6 ng/mL) were the significantly associated factors in the derivation group. The multivariable Cox regression analysis identified age, DM, platelet count, albumin, and AFP as the independent predictors of HCC ([Table 2](#)). We then used variables at baseline to predict HCC, and the analysis revealed age, DM, baseline platelet count, and AFP as independent predictors of HCC ([Supplementary Table 2](#)).

Table 1 Patient Demographics and Baseline Characteristics

Variable	Total (n = 4426)	Derivation Group ^a (n = 3178)	Validation Group ^a (n = 1248)	P
Age (years)	62.0 (52.3–70.8)	64.4 (55.5–72.8)	55.0 (45.0–64.0)	< 0.001
Sex (male, %)	1987 (44.9)	1325 (41.7)	662 (53.0)	< 0.001
Body mass index (kg/m ²)	24.33 (21.94–27.01)	24.44 (22.04–27.11)	24.00 (21.78–26.73)	0.034
Follow-up (months)	27.53 (13.46–36.67)	26.60 (12.37–35.23)	32.23 (16.61–46.23)	< 0.001
Hemoglobin (g/dL)	13.7 (12.6–14.8)	13.5 (12.3–14.6)	14.2 (13.2–15.3)	< 0.001
Platelet count (× 10 ³ /μL)	184 (139–227)	185 (143–227)	181 (131–226)	0.019
AST (U/L)	40 (27–67)	38 (26–63)	43 (30–74)	< 0.001
ALT (U/L)	48 (30–87)	46 (28–83)	55 (33–98)	< 0.001
Total bilirubin (mg/dL)	0.7 (0.5–0.9)	0.6 (0.5–0.9)	0.8 (0.6–1.1)	< 0.001
Albumin (g/dL)	4.3 (4.0–4.5)	4.2 (4.0–4.4)	4.4 (4.1–4.6)	< 0.001
INR	1.02 (0.99–1.07)	1.03 (0.99–1.07)	1.02 (0.99–1.08)	0.200
AFP (ng/mL)	3.77 (2.35–6.80)	3.62 (2.22–6.60)	3.98 (2.73–7.79)	< 0.001
Creatinine (mg/dL)	0.80 (0.65–0.97)	0.80 (0.65–0.98)	0.81 (0.66–0.96)	0.558
Hypertension, n (%)	1222 (27.6)	890 (28.0)	332 (26.6)	0.348
Diabetes mellitus, n (%)	798 (18.0)	596 (18.8)	202 (16.2)	0.046
Liver cirrhosis, n (%)	890 (20.1)	692 (21.8)	198 (15.9)	< 0.001
HCV RNA (log ₁₀ IU/mL)	6.38 (5.68–6.80)	6.28 (5.56–6.68)	6.66 (5.97–7.12)	< 0.001
HCV genotype, n (%)				0.003
1	2441 (55.2)	1727 (54.3)	714 (57.3)	
2	1579 (35.7)	1284 (40.4)	295 (23.7)	
3	73 (1.6)	21 (0.7)	52 (4.2)	
6	263 (5.9)	87 (2.7)	176 (14.1)	
Mixed genotype ^b	43 (1.0)	34 (1.1)	9 (0.7)	
FIB-4	2.06 (1.28–3.41)	2.10 (1.36–3.38)	1.88 (1.08–3.53)	< 0.001
Incident HCC, n (%)	70 (1.6)	29 (0.9)	41 (3.3)	< 0.001

Notes: Data are presented as median (interquartile range). ^a The derivation group comprised patients from Chia-Yi Christian Hospital, Dalin Tzu Chi Hospital, and St. Martin De Porres Hospital; the validation group comprised patients from China Medical University Hospital. ^b 38, 1, 1, and 3 patients had genotypes 1+2, 1+6, 2+3, 2+6 infection, respectively. Genotype was unclassified in 27 patients.

Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio.

Table 2 Univariate and Multivariable Cox Regression Analyses of Factors at 3 Months After Therapy Associated with Hepatocellular Carcinoma

Variable	Univariate Analysis		Multivariable Analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age (years)	1.076 (1.038–1.115)	< 0.001	1.084 (1.042–1.128)	< 0.001
Sex: male vs female	0.799 (0.362–1.675)	0.522		
DM: yes vs no	2.869 (1.370–6.008)	0.005	2.863 (1.342–6.111)	0.007
Variables at 12 weeks after antiviral therapy				
PLT <100 vs ≥100 × 10 ³ /μL	7.608 (3.589–16.127)	< 0.001	2.951 (1.291–6.750)	0.010
ALT >40 vs ≤40 U/L	3.292 (1.406–7.708)	0.006	2.004 (0.817–4.916)	0.129
Albumin <3.5 vs ≥3.5 g/dL	7.788 (2.705–22.420)	< 0.001	3.180 (1.053–10.183)	0.045
Total bilirubin >1.3 vs ≤ 1.3 mg/dL	2.865 (0.997–8.234)	0.051	1.953 (0.618–6.169)	0.254
AFP >4.6 vs ≤4.6 ng/mL	7.706 (3.507–16.933)	< 0.001	5.493 (2.407–12.535)	< 0.001

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; DM, diabetes mellitus; PLT, platelet count.

Development of the HCC Risk Prediction Model

Of 3178 patients in the derivation group, 29 had incident HCC over a median follow-up duration of 26.60 (12.37–35.23) months. The annual incidence of incident HCC was 4.39 per 1000 person-years in the derivation group.

We constructed a baseline HCC risk prediction model that incorporated age, DM status, baseline platelet count, and AFP as well as a post-treatment HCC risk prediction model that incorporated age, DM status, platelet count, albumin, and AFP. To include an appropriate number of patients with HCC in each stratum, we introduced another cut-off level for AFP at 9 ng/mL (upper limit of normal) in addition to the optimal cut-off level (4.6 ng/mL). In total, 0.36% (9/2477), 1.44% (8/554), and 8.16% (12/147) of patients with post-treatment AFP levels of <4.60, 4.60–8.99, and ≥ 9.00 ng/mL, respectively, developed incident HCC ($P < 0.001$).

The risk scores were computed in the HCC risk prediction model by converting the regression coefficients of the independent predictors at baseline ([Supplementary Table 3](#)) and PW12 ([Table 3](#)). We examined the performance of the models at baseline and PW12. At the EOF, the time-dependent AUROCs of the predictive models at baseline and PW12 for HCC risk prediction were 0.830 and 0.877, respectively ($P = 0.150$; [Supplementary Figure 2a](#)). We also compared the AUROCs of the proposed models at baseline and PW12 for HCC risk prediction at 1, 2, and 3 years. The AUROCs of the HCC risk model at PW12 for predicting 1-, 2-, and 3-year risks of HCC were 0.889, 0.887, and 0.877, respectively. These values were higher than the proposed model at baseline ([Supplementary Figure 2b–d](#)).

We named the newly developed HCC risk prediction model the AAAPD-C score; this score is calculated based on the independent predictors of age, albumin, AFP level, platelet count, and DM status at PW12 in patients with hepatitis C viral eradication. The total risk score ranged from 0 to 12. In the calibration plot, patients were separated into 5 groups. There was a small discrepancy between the observed and predicted probabilities across the subgroups, except for patients with predicted HCC risk between 0.60 and 0.89% ([Supplementary Figure 3](#)).

Based on the tertile of the range of AAAPD-C score, patients in the derivation group were stratified into 3 risk subgroups: low (0–3.5, $n = 1616$), medium (4–7.5, $n = 1503$), and high (8–12, $n = 59$). The cumulative incidence of HCC

Table 3 Multivariable Cox Regression Analyses of Post-Treatment Factors Associated with Hepatocellular Carcinoma in the Derivation Group

Variable	Hazard Ratio (95% CI)	Parameter	P	Risk Score
Age (years)	2.120 (1.279–3.515)	0.751368	0.004	
<40				0
40–49				1
50–59				2
60–69				3
≥ 70				4
Albumin (g/dL) at PW12				
Albumin ≥ 3.5	Reference			0
Albumin <3.5	3.367 (1.083–10.470)	1.213914	0.036	1.5
AFP (ng/mL) at PW12				
<4.60	Reference			0
4.60–8.99	3.200 (1.213–8.441)	1.163148	0.019	1.5
≥ 9.00	14.895 (5.982–37.092)	2.701047	< 0.001	3.5
Diabetes mellitus				
No	Reference			0
Yes	2.936 (1.373–6.275)	1.215281	0.005	1.5
Platelet ($\times 10^3/\mu\text{L}$) at PW12				
≥ 100	Reference			0
<100	2.271 (1.075–4.795)	1.062095	0.012	1.5

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; PW12, 12 weeks after direct-acting antiviral therapy.

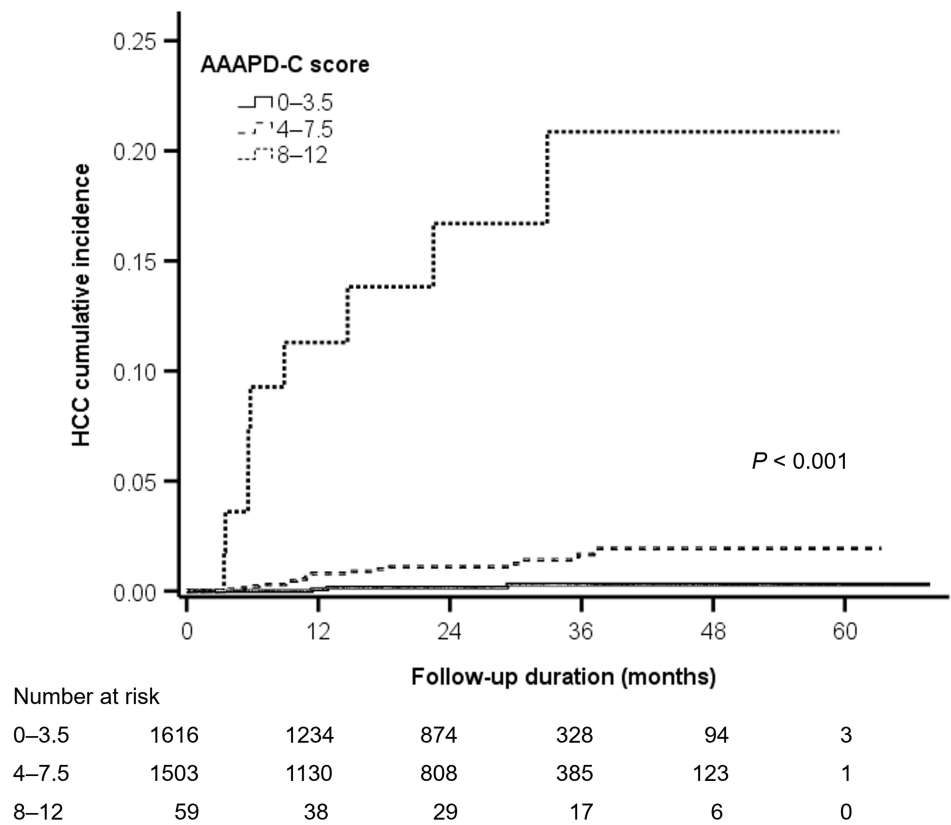


Figure 1 Cumulative incidence of HCC in patients with chronic hepatitis C who have achieved sustained virologic response after direct-acting antiviral therapy (Derivation group). **Abbreviation:** HCC, hepatocellular carcinoma.

in the 3 subgroups significantly differed (Figure 1). The annual incidence of incident HCC was 0.903 per 1000 person-years in the low-risk subgroup.

Validation of the AAAPD-C Model

Of 1248 patients in the validation group, 41 had incident HCC over a median follow-up duration of 32.23 (16.61–46.23) months. The annual incidence of incident HCC was 12.28 per 1000 person-years. The AUROC of the AAAPD-C score at EOF for HCC risk prediction in the validation group was 0.867 (0.823–0.911; Figure 2a). The AUROCs of the AAAPD-C score for predicting 1-, 2-, and 3-year risks of HCC were 0.868, 0.848, and 0.847 (Figure 2b–d), respectively. Again, we stratified patients into 3 risk subgroups: low (0–3.5, n = 860), medium (4–7.5, n = 362), and high (8–12, n = 26). The AAAPD-C model exhibited good discriminative capability in the validation group (Figure 3). The annual incidence of incident HCC was 2.25 per 1000 person-years in the low-risk subgroup.

Risk Stratification of HCC Through the AAAPD-C Score in Patients with and without Advanced Liver Fibrosis

Patients with FIB-4 >3.25 at baseline belonged to advanced liver fibrosis.⁹ Among all 4426 enrolled patients, the annual incidences of HCC were 1.44, 11.14, and 83.07 per 1000 person-years in the low, intermediate, and high-risk subgroups of the AAAPD-C score, respectively. The corresponding figures for patients with advanced liver fibrosis were 6.82, 16.23, and 91.31 per 1000 person-years, respectively (Table 4). Owing to limited patients belonging to the high-risk subgroup in patients without advanced liver fibrosis (n = 11), patients with intermediate- and high-risk subgroups were combined (mid-high risk: score 4–12), whose annual incidence of HCC was 6.22 per 1000 person-

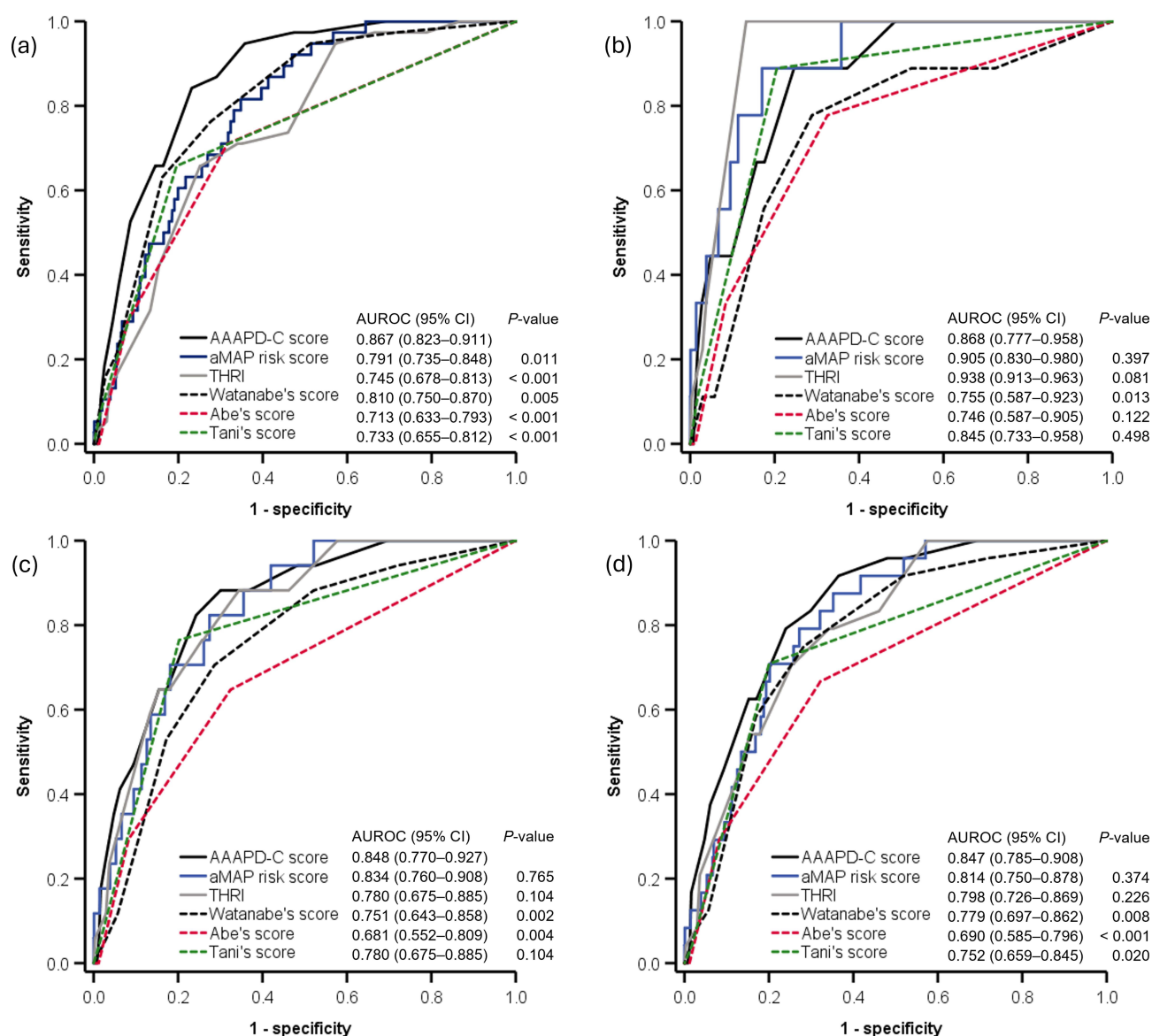


Figure 2 Time-dependent areas under receiver operating characteristic curves (AUROCs) for the predictive performance of different models for hepatocellular carcinoma in the validation group. (a) At the end of follow-up, (b) At year 1, (c) At year 2, (d) At year 3.

years (Table 4). The AAAPD-C model exhibited good discriminative capability in patients with and without advanced liver fibrosis for the risk of HCC in both the derivation (Figure 4a and b) and validation groups (Figure 4c and d).

Comparison of the AAAPD-C Score with Other HCC Risk Scores

Clinical HCC risk scores have been developed in patients with CHC with SVR to DAAs.^{19–21} The aMAP risk score²² and Toronto HCC risk index (THRI)²³ were developed for HCC risk prediction in patients with liver disease of various etiologies. We compared the predictive performance of the AAAPD-C score with other HCC risk scores in the validation group. The time points for measuring variables were not standardized,^{19–23} and we used the variables at PW12 to calculate the aMAP risk score, THRI, and scores in Abe's, Watanabe's, and Tani's scoring systems.

The AUROC of the AAAPD-C score at EOF (0.867) was significantly higher than that of the aMAP risk score, the THRI, and scores for Watanabe's, Abe's, and Tani's scoring systems (Figure 2a). We also compared the AUROCs of

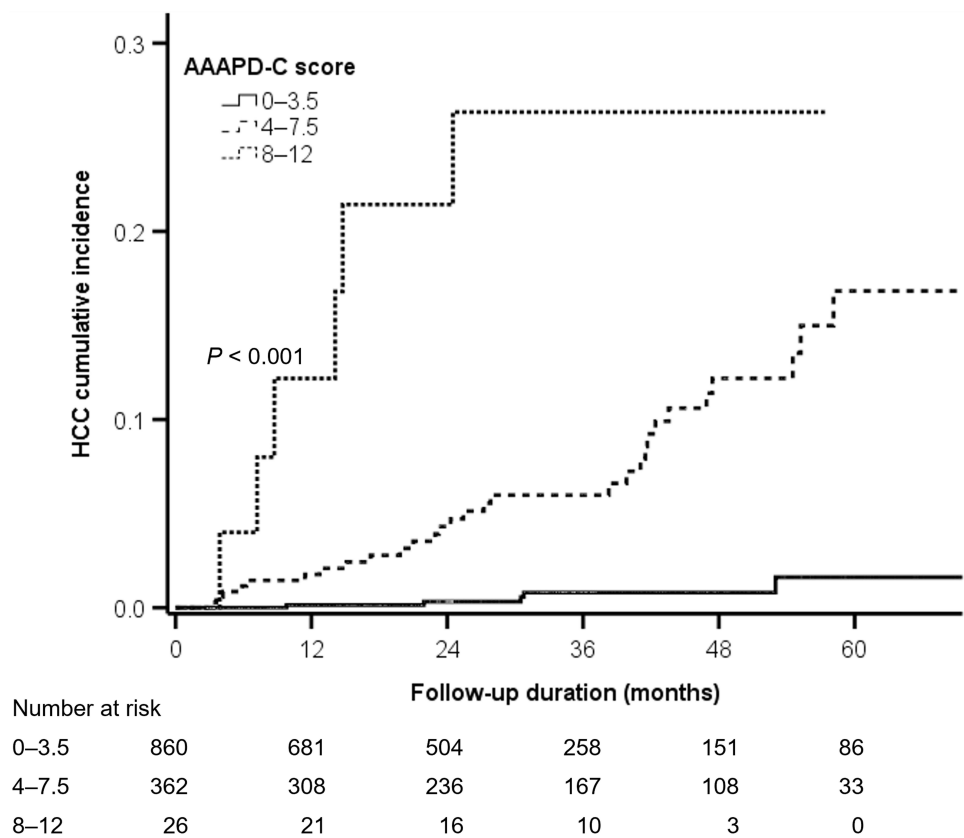


Figure 3 Cumulative incidence of HCC in patients with chronic hepatitis C who have achieved sustained virologic response after direct-acting antiviral therapy (Validation group). **Abbreviation:** HCC, hepatocellular carcinoma.

these models for HCC risk prediction at 1, 2, and 3 years. The values were higher than those of the aMAP risk score, the THRI, and scores for Watanabe’s, Abe’s, and Tani’s scoring systems for predicting 2- and 3-year HCC (Figure 2b–d). Among all evaluated models, the AAAPD-C score showed the most favorable overall performance, with the highest Nagelkerke’s R^2 (0.1227) and a low Brier score (0.0088, [Supplementary Table 4](#)), underscoring its potential applicability in clinical practice.

Table 4 Distribution and Incidence of Incident Hepatocellular Carcinoma in Patients of Different Risk Groups with and without Advanced Liver Fibrosis

Risk Groups ^a	Number (%) of Incident HCC	1-year Risk (%)	2-year Risk (%)	3-year Risk (%)	Annual Incidence (Per 1000 Person-Years)
Overall					
All risk scores (n = 4426)	70 (100)	0.69	1.23	1.89	7.04
Low risk (n = 2476)	8 (11.4)	0.09	0.21	0.52	1.44
Intermediate risk (n = 1865)	47 (67.1)	0.96	1.77	2.64	11.14
High risk (n = 85)	15 (21.4)	11.76	19.17	24.58	83.07
FIB-4 >3.25					
All risk scores (n = 1210)	54 (77.1)	1.73	3.12	5.08	17.75
Low risk (n = 284)	5 (7.1)	0	0.48	2.57	6.82
Intermediate risk (n = 852)	35 (50)	1.29	2.60	4.20	16.23
High risk (n = 74)	14 (20)	13.53	20.13	26.48	91.31

(Continued)

Table 4 (Continued).

Risk Groups ^a	Number (%) of Incident HCC	1-year Risk (%)	2-year Risk (%)	3-year Risk (%)	Annual Incidence (Per 1000 Person-Years)
FIB-4 ≤3.25					
All risk scores (n = 3216)	16 (22.9)	0.28	0.47	0.47	2.32
Low risk (n = 2192)	3 (4.3)	0.10	0.17	0.17	0.62
Mid-high risk (n = 1024)	13 (18.6)	0.67	1.14	1.14	6.22

Note: ^a low risk: AAAPD-C score 0–3.5; intermediate risk: AAAPD-C score 4–7.5; high risk: AAAPD-C score 8–12.

Abbreviation: Mid-high, intermediate and high (AAAPD-C score 4–12).

Discussion

We developed an HCC risk prediction model, namely the AAAPD-C score, to predict the risk of HCC in patients with CHC who have achieved SVR after DAA therapy. The components of the AAAPD-C score were the independent predictors of HCC and included age, DM status, platelet count (≥ 100 vs $<100 \times 10^3/\mu\text{L}$), albumin (≥ 3.5 vs <3.5 g/dL), and AFP (<4.60 , 4.60 – 8.99 , and ≥ 9.00 ng/mL) at PW12. The model exhibited good calibration and was externally validated with the CMUH cohort. The model stratified patients with hepatitis C viral eradication into 3 distinct HCC risk subgroups and exhibited a more nuanced stratification of HCC risk than did fibrosis status.

The annual incidence of HCC was 7.04 per 1000 person-years in the entire cohort (n = 4426). Therefore, regular HCC surveillance through abdominal ultrasound and AFP could be performed, even though these patients had viral eradication after DAA therapy.^{24–26} However, whether patients without advanced liver fibrosis should receive regular HCC surveillance after SVR is unclear.²⁴ A reliable HCC prediction model for risk stratification is desirable.

Several algorithms have been proposed to predict HCC risk in patients with CHC who have achieved SVR after DAA therapy. Pons et al showed that LSM through TE and albumin 1 year after antiviral therapy can identify patients with hepatitis C viral eradication at a higher or lower risk of HCC.³ Semmler et al demonstrated that age, follow-up LSM, albumin, AFP (without standardized time point), and alcohol consumption were predictors of HCC development.⁴ López et al revealed that baseline and dynamic changes in LSM or FIB-4 at 1 year after antiviral therapy and albumin at baseline can be used to stratify patients with SVR to DAA therapy into different HCC risk groups.⁵ Shiha et al proposed the General Evaluation Score, which incorporates age, gender, fibrosis stage, and baseline albumin and AFP, for HCC risk prediction in patients with advanced liver fibrosis (>10.2 kPa by TE) associated with HCV genotype 4 after HCV eradication.²⁷ Nonetheless, LSM using TE or acoustic radiation force impulse is not widely accessible.

Several nonelastography-based scoring systems for HCC prediction have also been proposed in patients with HCV eradication, including Watanabe's, Abe's, and Tani's scoring systems.^{19–21} Ioannou et al developed a web-based tool using data from the Veterans Affairs healthcare system in the United States. However, the exact formula of the tool is not available online.²⁸ Fan et al proposed the aMAP risk score. Their study enrolled patients with chronic liver disease of various etiologies, with 20.5% of the enrolled patients having HCV eradication by interferon-based therapy or DAAs.²² Sharma et al established the THRI to predict the risk of HCC in patients with LC of various etiologies.²³

Age is a well-known predictor of HCC.^{22,23,28} DM has consistently been associated with an increased risk of HCC in patients with chronic liver disease.²⁹ Low platelet count ($<100 \times 10^3/\mu\text{L}$) predicts HCC in patients with CHC before¹⁸ and after antiviral therapy.³⁰ Albumin at baseline or follow-up predicts HCC in patients with hepatitis C viral eradication with advanced liver fibrosis^{5,27} or advanced chronic liver disease,³ respectively. AFP after treatment has been demonstrated to be a predictor of HCC development.^{4,20,21} By enrolling a respectable number of patients with or without advanced chronic liver disease with CHC and SVR after DAA therapy, we demonstrated that each of these 5 parameters was an independent predictor of HCC. Each parameter exhibited differential predictive weight in the proposed AAAPD-C risk model. By combining the 5 parameters, we were able to generate a granular risk score with good performance. Age and platelet count are components of FIB-4, and we did not incorporate FIB-4 into our model.

The AAAPD-C score had higher AUROC values than the baseline HCC risk prediction model and other extant non-elastography-based HCC prediction models at 1 year, 2 years, 3 years, and EOF. The AAAPD-C model is an accurate,

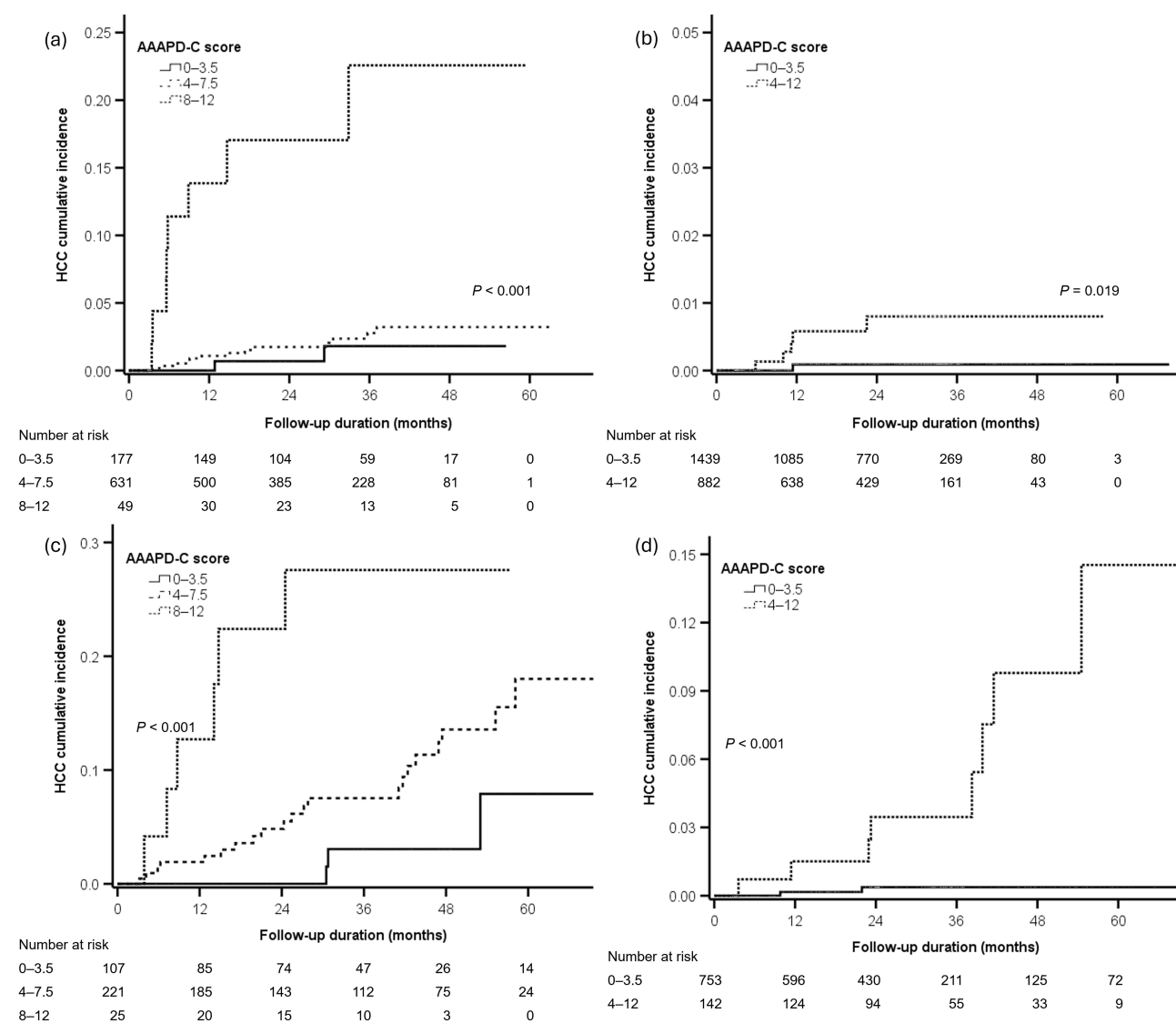


Figure 4 Cumulative incidence of HCC in patients with chronic hepatitis C who have achieved sustained virologic response after direct-acting antiviral therapy. (a) Derivation group with advanced liver fibrosis, (b) Derivation group without advanced liver fibrosis, (c) Validation group with advanced liver fibrosis, (d) Validation group without advanced liver fibrosis.

Abbreviation: HCC, hepatocellular carcinoma.

inexpensive, and convenient model based on variables collected at PW12 for risk prediction of HCC. Clinical guidelines recommend HCC surveillance for cirrhotic patients with an incidence of HCC ≥ 1.0 – 1.5% per year.^{13,31} However, the thresholds were established from the studies evaluating the cost-effectiveness in patients with active viral infection.³² Parikh et al demonstrated that HCC surveillance is cost-effective if the HCC incidence is $>0.4\%$ per year with a surveillance adherence $>19.5\%$,²⁴ and Chhatwal et al showed a higher threshold of HCC incidence (>7 per 1000 person-years) to be cost-effective.²⁶ Liver fibrosis is a major contributor to HCC.^{24–26} In this study, although patients without advanced liver fibrosis had a low incidence of HCC (2.32 per 1000 person-years), they represented 22.9% ($n = 16$) of incident HCC in the entire cohort ($n = 70$, Table 4). Although universal HCC surveillance in patients without advanced liver fibrosis is not cost-effective, identifying a subgroup of patients for surveillance using the risk model to increase the diagnosis rate of incident HCC may be feasible.

This study has several strengths. First, we enrolled a large number of patients to establish a readily available non-elastography-based HCC prediction model specific for patients with CHC with SVR to DAA therapy, and we internally and externally validated the model. Second, we identified a subgroup of patients without advanced liver fibrosis with mid-high

AAAPD-C risk scores who had a relatively high annual incidence of HCC (6.22 per 1000 person-years). Third, the patients in the low-risk group had a low annual incidence of incident HCC (1.44 per 1000 person-years in the entire cohort). This value is below the updated threshold (>4 per 1000 person-years) for a cost-effective HCC screening among patients with CHC with SVR to DAA therapy.²⁴ Thus, 55.9% (2476/4426) of the present cohort may be waived from HCC surveillance. Fourth, among extant non-elastography-based HCC risk models, the AAAPD-C model exhibited the highest AUROC values at 2 years, 3 years, and EOF. Further validation and implementation in independent cohorts is warranted.

This study also has several limitations. First, this is a retrospective study. Second, the follow-up duration was short (27.53 [13.46–36.67] months). The lower annual incidence of incident HCC in the derivation group compared with that in the validation group may have resulted from a shorter follow-up period. Third, we could not compare our model with gamma-glutamyltransferase (GGT)-containing nomograms for predicting HCC occurrence because our dataset lacked comprehensive GGT data.^{5,18} Fourth, most patients in this study had HCV genotype 1 and 2 infections (4020/4426, 90.8%). Further studies that involve patients with HCV infections of genotypes other than 1 and 2 and that have extended follow-up durations are warranted.

Conclusion

We proposed the AAAPD-C score to predict the risks of HCC in patients with CHC who have achieved DAA therapy-induced SVR. The model stratified cured patients into 3 risk groups. Patients without advanced liver fibrosis with mid-high AAAPD-C risk scores had an annual incidence of HCC >4 per 1000 person-years. The AAAPD-C score is an accurate, inexpensive, and convenient tool clinicians can use to identify patients with CHC at risk of HCC following viral eradication.

Abbreviations

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AUROC, area under the receiver operating characteristic curve; CCH, Chiayi Christian Hospital; CHC, chronic hepatitis C; CMUH, China Medical University Hospital; DAA, direct-acting antiviral; DM, diabetes mellitus; DTCH, Dalin Tzu Chi Hospital; EOF, end of follow-up; FIB-4, fibrosis-4; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis; LSM, liver stiffness measurement; PW12, 12 weeks after antiviral therapy; StMH, St. Martin De Porres Hospital-Daya; SVR, sustained virologic response; TE, transient elastography; THRI, Toronto HCC risk index.

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Author Contributions

Study concept and design: Wei-Fan Hsu and Cheng-Yuan Peng. All authors made a significant contribution to the work reported, whether that is in the execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

C. Y. P. has served as an advisory committee member for AbbVie, Bristol-Myers Squibb, Gilead, Merck Sharp & Dohme, and Roche. The other authors have no conflicts of interest to declare.

References

1. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol.* **2018**;69:461–511. doi:10.1016/j.jhep.2018.03.026
2. Bhattacharya D, Aronsohn A, Price J, et al. Hepatitis C guidance 2023 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis.* **2023**. doi:10.1093/cid/ciad319

3. Pons M, Rodriguez-Tajes S, Esteban JI, et al. Non-invasive prediction of liver-related events in patients with HCV-associated compensated advanced chronic liver disease after oral antivirals. *J Hepatol.* **2020**;72:472–480. doi:10.1016/j.jhep.2019.10.005
4. Semmler G, Meyer EL, Kozbial K, et al. HCC risk stratification after cure of hepatitis C in patients with compensated advanced chronic liver disease. *J Hepatol.* **2022**;76:812–821. doi:10.1016/j.jhep.2021.11.025
5. Alonso Lopez S, Manzano ML, Gea F, et al. A model based on noninvasive markers predicts very low hepatocellular carcinoma risk after viral response in hepatitis C virus-advanced fibrosis. *Hepatology.* **2020**;72:1924–1934. doi:10.1002/hep.31588
6. Hsu WF, Lai HC, Su WP, et al. Rapid decline of noninvasive fibrosis index values in patients with hepatitis C receiving treatment with direct-acting antiviral agents. *BMC Gastroenterol.* **2019**;19:63. doi:10.1186/s12876-019-0973-5
7. Kanda T, Lau GKK, Wei L, et al. APASL HCV guidelines of virus-eradicated patients by DAA on how to monitor HCC occurrence and HBV reactivation. *Hepatol Int.* **2019**;13:649–661. doi:10.1007/s12072-019-09988-7
8. Yu ML, Chen PJ, Dai CY, et al. 2020 Taiwan consensus statement on the management of hepatitis C: part (I) general population. *J Formos Med Assoc.* **2020**;119:1019–1040. doi:10.1016/j.jfma.2020.04.003
9. Reiberger T, Lens S, Cabibbo G, et al. EASL position paper on clinical follow-up after HCV cure. *J Hepatol.* **2024**;81:326–344. doi:10.1016/j.jhep.2024.04.007
10. Di Marco V, Calvaruso V, Ferraro D, et al. Effects of eradicating hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. *Gastroenterology.* **2016**;151:130–139e132. doi:10.1053/j.gastro.2016.03.036
11. Hsu CS, Kao JH. Management of hepatitis C patients with decompensated liver disease. *Expert Rev Gastroenterol Hepatol.* **2016**;10:679–688. doi:10.1586/17474124.2016.1143775
12. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* **2006**;43:1317–1325. doi:10.1002/hep.21178
13. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* **2018**;69:182–236. doi:10.1016/j.jhep.2018.03.019
14. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol.* **1993**;138:923–936. doi:10.1093/oxfordjournals.aje.a116813
15. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: the Framingham Study risk score functions. *Stat Med.* **2004**;23:1631–1660. doi:10.1002/sim.1742
16. Chen JJ, Lee TH, Kuo G, et al. Acute kidney disease after acute decompensated heart failure. *Kidney Int Rep.* **2022**;7:526–536. doi:10.1016/j.ekir.2021.12.033
17. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology.* **2010**;21:128–138. doi:10.1097/EDE.0b013e3181c30fb2
18. Ganne-Carrie N, Layese R, Bourcier V, et al. Nomogram for individualized prediction of hepatocellular carcinoma occurrence in hepatitis C virus cirrhosis (ANRS CO12 CirVir). *Hepatology.* **2016**;64:1136–1147. doi:10.1002/hep.28702
19. Abe K, Wakabayashi H, Nakayama H, et al. Factors associated with hepatocellular carcinoma occurrence after HCV eradication in patients without cirrhosis or with compensated cirrhosis. *PLoS One.* **2020**;15:e0243473.
20. Tani J, Morishita A, Sakamoto T, et al. Simple scoring system for prediction of hepatocellular carcinoma occurrence after hepatitis C virus eradication by direct-acting antiviral treatment: all Kagawa Liver Disease Group Study. *Oncol Lett.* **2020**;19:2205–2212. doi:10.3892/ol.2020.11341
21. Watanabe T, Tokumoto Y, Joko K, et al. Simple new clinical score to predict hepatocellular carcinoma after sustained viral response with direct-acting antivirals. *Sci Rep.* **2023**;13:8992. doi:10.1038/s41598-023-36052-0
22. Fan R, Papatheodoridis G, Sun J, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. *J Hepatol.* **2020**;73:1368–1378. doi:10.1016/j.jhep.2020.07.025
23. Sharma SA, Kowgier M, Hansen BE, et al. Toronto HCC risk index: a validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. *J Hepatol.* **2018**;68:92–99. doi:10.1016/j.jhep.2017.07.033
24. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-effectiveness of hepatocellular carcinoma surveillance: an assessment of benefits and harm. *Am J Gastroenterol.* **2020**;115:1642–1649. doi:10.14309/ajg.0000000000000715
25. Lockart I, Yeo MGH, Hajarizadeh B, Dore GJ, Danta M. HCC incidence after hepatitis C cure among patients with advanced fibrosis or cirrhosis: a meta-analysis. *Hepatology.* **2022**;76:139–154. doi:10.1002/hep.32341
26. Chhatwal J, Hajjar A, Mueller PP, et al. Hepatocellular carcinoma incidence threshold for surveillance in virologically cured hepatitis C individuals. *Clin Gastroenterol Hepatol.* **2024**;22:91–101.e6. doi:10.1016/j.cgh.2023.05.024
27. Shiha 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**;40:2828–2833. doi:10.1111/liv.14666
28. 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**;69:1088–1098. doi:10.1016/j.jhep.2018.07.024
29. Shin HS, Jun BG, Yi SW. Impact of diabetes, obesity, and dyslipidemia on the risk of hepatocellular carcinoma in patients with chronic liver diseases. *Clin Mol Hepatol.* **2022**;28:773–789. doi:10.3350/cmh.2021.0383
30. Kilany S, Ata L, Gomaa A, et al. Decreased incidence of hepatocellular carcinoma after directly acting antiviral therapy in patients with hepatitis C-related advanced fibrosis and cirrhosis. *J Hepatocell Carcinoma.* **2021**;8:925–935. doi:10.2147/JHC.S295330
31. Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology.* **2023**;78:1922–1965. doi:10.1097/HEP.0000000000000466
32. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol.* **2008**;6:1418–1424. doi:10.1016/j.cgh.2008.08.005

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