CLINICAL—LIVER

Accuracy of Risk Scores for Patients With Chronic Hepatitis B Receiving Entecavir Treatment

GRACE LAI–HUNG WONG,[1,2] HENRY LIK–YUEN CHAN,[1,2] HOI–YUN CHAN,[1,2] PETE CHI–HANG TSE,[1,2] YEE–KIT TSE,[1] CHRISTY WING–HIN MAK,[2] STANLEY KING–YEUNG LEE,[2] ZOE MAN–YI IP,[2] ANDREW TING–HO LAM,[2] HENRY WING–HANG IU,[2] JOYCE MAY–SUM LEUNG,[2] and VINCENT WAI–SUN WONG[1,2]

[1]*Institute of Digestive Disease and* [2]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China*

BACKGROUND & AIMS: Little is known about the validity of hepatocellular carcinoma (HCC) risk scores derived from treatment-naïve patients with chronic hepatitis B for patients treated with entecavir. **METHODS:** We performed a retrospective-prospective cohort study of 1531 patients with chronic hepatitis B (age, 51 ± 12 years; 1099 male; 332 with clinical cirrhosis) who were treated with entecavir 0.5 mg daily for at least 12 months at Prince of Wales Hospital in Hong Kong from December 2005 to August 2012. The patients were assessed once every 3 to 6 months for symptoms, drug history, and adherence; blood samples were collected for biochemical analyses. We validated 3 HCC risk scores (CU-HCC, GAG-HCC, and REACH-B scores) based on data collected when patients began treatment with entecavir and 2 years later. **RESULTS:** After 42 ± 13 months of follow-up, 47 patients (2.9%) developed HCC. The 5-year cumulative incidence of HCC was 4.3% (95% confidence interval [CI], 3.6%–5.0%). Older age, presence of cirrhosis, and virologic remission after 24 months or more of therapy were independently associated with HCC in the entire cohort; advanced age and hypoalbuminemia were associated with HCC in patients without cirrhosis. The area under the receiver operating characteristic curves (AUCs) for baseline CU-HCC, GAG-HCC, and REACH-B scores for HCC were 0.80 (95% CI, 0.75–0.86), 0.76 (95% CI, 0.70–0.82), and 0.71 (95% CI, 0.62–0.81), respectively; the time-dependent AUCs 1 to 4 years after patients started treatment were comparable to those at baseline. The cutoff value of the baseline CU-HCC score identified patients who would develop HCC with 93.6% sensitivity and 47.8% specificity, the baseline GAG-HCC score with 55.3% sensitivity and 78.9% specificity, and the baseline REACH-B score with 95.2% sensitivity and 16.5% specificity. Compared with patients with CU-HCC scores <5 at baseline, those with CU-HCC scores that either decreased from ≥5 to <5 or remained ≥5 had a higher risk of HCC (5-year cumulative incidences, 0% vs 3.9% and 7.3%; $P = .002$ and $P < .001$, respectively). **CONCLUSIONS: The CU-HCC, GAG-HCC, and REACH-B HCC risk scores accurately predict which patients with chronic hepatitis B treated with entecavir will develop HCC.**

Keywords: Cirrhosis; Entecavir; Hepatocellular Carcinoma; Risk Scores.

Chronic hepatitis B (CHB) is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) in Asia.[1] Older age, cirrhosis, and a high level of hepatitis B virus (HBV) DNA are the most important predictors of HCC in patients with CHB.[2,3] Based on these parameters, a number of prediction scores have been developed and validated in the community and clinic settings.[4–7] In general, these scores have high negative predictive value in identifying patients at low risk for developing HCC. Application of these scores in the clinic can assist prognostication and decisions on HCC surveillance.

In the past 2 decades, the development of antiviral therapy has further modified the natural history of CHB. Antiviral therapy is effective in suppressing HBV DNA and reducing the risk of HCC.[8] New antiviral drugs such as entecavir have potent antiviral activity and low risk of drug resistance[9,10] and are currently recommended by international guidelines as first-line antiviral agents.[11–13] Entecavir is also effective in preventing disease progression and liver decompensation.[14,15] The beneficial effect of entecavir is closely linked to virologic response. Cirrhotic patients who achieve complete virologic response (undetectable HBV DNA) to entecavir have a lower risk of HCC and hepatic complications than those with detectable HBV DNA.[16] After curative treatment of HBV-related HCC, patients with undetectable HBV DNA after 24 weeks of entecavir therapy also have better survival.[17]

The potential benefit of entecavir leads to the question concerning the validity of the HCC risk scores, because all of them were derived from and validated in cohorts of treatment-naïve patients with CHB.[4–7] Obviously, antivi-

Abbreviations used in this paper: AUC, area under the receiver operating characteristic curve; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; ROC, receiver operating characteristic.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.02.002

ral therapy would significantly decrease serum HBV DNA levels and at the same time may alter other laboratory parameters by improving the necroinflammation (ie, lowering the alanine aminotransferase [ALT] level) and hepatic function (ie, increasing the albumin level and lowering the total bilirubin level). In the era of antiviral therapy, it is important to know if these HCC risk scores remain accurate and applicable in patients with CHB receiving antiviral treatment. In addition, all previous studies only calculated risk scores based on baseline parameters. The clinical significance of changes in scores during longitudinal follow-up has not been evaluated.

In this large-scale, real-life cohort study, we aimed to determine the factors associated with HCC in entecavir-treated patients with CHB. We also assessed the accuracy and applicability of HCC risk scores at baseline and during treatment with entecavir.

Patients and Methods

Study Population

This was a retrospective-prospective cohort study. We included consecutive patients with CHB who were treated with entecavir 0.5 mg daily for at least 12 months in the hepatitis clinics at Prince of Wales Hospital from December 2005 to August 2012. The purpose of this inclusion criterion was to avoid including patients with preexisting or undiagnosed HCC at the start of treatment with entecavir. Patients who were treated with entecavir before October 2009 were retrospectively identified from the HBV DNA record and recruited into the prospective follow-up study. All patients newly started on entecavir after October 2009 were also recruited into the longitudinal study in a prospective manner. All patients had positive hepatitis B surface antigen (HBsAg) for at least 6 months and a life expectancy of >1 year at recruitment. Patients with other chronic liver diseases, preexisting HCC or HCC diagnosed within the first year of treatment with entecavir, or Child class C cirrhosis, autoimmune hepatitis, coinfection with hepatitis C virus, or another serious concurrent illness (eg, alcoholism, uncontrolled diabetes, or cancer) were excluded. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All patients provided informed written consent.

Clinical and Laboratory Evaluation

At baseline (ie, when treatment with entecavir was started), patients underwent an evaluation that included a full medical history, physical examination, trans-abdominal ultrasonography, and measurement of complete blood cell count, prothrombin time and international normalized ratio, liver and renal biochemistries, HBsAg, hepatitis B e antigen (HBeAg) and antibody to HBeAg, and HBV DNA. HBV DNA was measured by TaqMan (Roche Diagnostics, Basel, Switzerland) real-time polymerase chain reaction assay validated against the EUROHEP standard with a linear range of detection from 20 to 2×10^8 IU/mL.[18] HBsAg was quantified by Architect HBsAg QT (Abbott Diagnostics, Lake Forest, IL), with 1:500 autodilution according to the manufacturer's instruction. The sensitivity of the Architect assay was 175 to 124,950 IU/mL. Those assays less than 175 IU/mL were repeated by undiluted detection (sensitivity from 0.05 to 250 IU/mL).[19]

The patients were followed up once every 3 to 6 months. During each visit, patients' symptoms and drug history and adherence were recorded. Liver biochemistry and α-fetoprotein level were checked at every visit. HBV DNA level was checked every 6 months, and HBsAg, HBeAg, and antibody to HBeAg levels were checked at least yearly. Maintained virologic response was defined as undetectable serum HBV DNA until the last visit.[9] Duration of virologic remission referred to the time in which serum HBV DNA remained undetectable, including the remission period during prior treatment. Ultrasonography of the abdomen was performed every 1 to 2 years for surveillance of HCC or more frequently if the α-fetoprotein level increased to >20 μg/L. Cirrhosis was defined as a shrunken small liver with a nodular surface noted on imaging of the liver and clinical features of portal hypertension (eg, ascites, splenomegaly, and varices).[4]

HCC Risk Scores

Three HCC risk scores—CU-HCC score,[4] GAG-HCC score,[7] and REACH-B score[6] (Supplementary Table 1)—were estimated at the time patients began treatment with entecavir and 2 years later. The CU-HCC score is composed of 5 parameters: age, albumin level, bilirubin level, HBV DNA level, and cirrhosis; it ranges from 0 to 44.5.[4] The GAG-HCC score comprises sex, age, HBV DNA level, and cirrhosis; it ranges widely to >100 because age (in years) is one of the components of the formula.[7] The REACH-B score consists of 5 parameters: sex, age, ALT level, HBeAg status, and HBV DNA level; it ranges from 0 to 17 and is primarily designed for patients without cirrhosis.[6]

The baseline risk scores were estimated based on the clinical and laboratory parameters at the time patients began treatment with entecavir, and the 2-year risk scores were estimated based on those parameters 2 years after starting treatment with entecavir. Based on the original studies of treatment-naïve patients, cutoff values of 5 (CU-HCC), 101 (GAG-HCC), and 8 (REACH-B) were recommended to predict the 3-year and 5-year risks of HCC.[4,6,7]

Primary Outcome

The primary outcomes of this study were the 3-year and 5-year incidence rates of HCC. The diagnosis of HCC was established based on histopathologic confirmation, detection of a positive lesion with at least 2 imaging techniques (trans-abdominal ultrasonography, triphasic computed tomography, magnetic resonance imaging, or hepatic angiography), or detection with one imaging technique coupled with an α-fetoprotein concentration >400 ng/mL.[20]

Statistical Analyses

Statistical analysis was performed using SPSS version 20.0 (SPSS Inc, Chicago, IL) and SAS version 9.3 (SAS Institute, Cary, NC). Continuous variables are expressed as mean ± standard deviation or median (range) as appropriate. Qualitative and quantitative differences between subgroups were analyzed using χ^2 test or Fisher exact test for categorical parameters and Student t test or Mann–Whitney test for continuous parameters as appropriate. Univariate and multivariable analysis by time-dependent Cox proportional hazards regression model was performed to identify factors associated with HCC, allowing for certain covariates to have different values at different times while not being systematically related to time (see Supplementary Materials). Time-dependent variables include serum albumin, total bilirubin, and ALT levels and HBeAg. Effect sizes are

Table 1. Clinical Characteristics of the Patients

	Entire cohort											
	All patients				All patients			Noncirrhotic patients			Cirrhotic patients		
	All	Cirrhosis	No cirrhosis	*P*	HCC	No HCC	*P*	HCC	No HCC	*P*	HCC	No HCC	*P*
No. of patients	1531	332	1199		47	1484		21	1178		26	306	
Duration of follow-up (*mo*)	42 ± 13	40 ± 14	43 ± 13	.10	43 ± 13	42 ± 13	.10	43 ± 12	43 ± 13	.99	44 ± 14	40 ± 14	.94
Male sex	1099 (72)	236 (71)	863 (72)	.94	36 (77)	1063 (72)	.46	16 (76)	847 (72)	.66	20 (77)	216 (71)	.65
Age (*y*)	51 ± 12	56 ± 11	50 ± 12	<.001	59 ± 8	51 ± 12	<.001	59 ± 7	49 ± 12	<.001	59 ± 9	56 ± 11	.02
≥50	899 (59)	253 (76)	646 (54)		43 (92)	856 (58)		16 (76)	630 (53)		24 (92)	229 (74)	
Platelet count ($\times 10^9$/*L*)	171 ± 61	99 ± 49	185 ± 53	<.001	123 ± 42	173 ± 61	<.001	149 ± 33	186 ± 53	.002	101 ± 37	99 ± 50	.08
Prothrombin time (*s*)	12 ± 8	14 ± 8	12 ± 8	<.001	13 ± 2	12 ± 8	.79	12 ± 2	12 ± 9	.87	14 ± 2	14 ± 8	.22
Albumin (*g/L*)	44 ± 13	38 ± 6	46 ± 13	<.001	36 ± 7	45 ± 13	<.001	37 ± 6	46 ± 13	<.001	35 ± 7	39 ± 6	.004
Total bilirubin (*μmol/L*)	23 ± 13	24 ± 31	23 ± 66	<.001	24 ± 18	23 ± 62	.95	18 ± 17	23 ± 66	.76	29 ± 18	23 ± 31	<.001
ALT (*IU/L*)	147 ± 316	105 ± 179	156 ± 339	.97	90 ± 126	149 ± 320	.29	100 ± 165	157 ± 341	.47	81 ± 80	108 ± 186	.21
Upper limit of normal or greater	606 (40)	129 (39)	477 (40)		24 (51)	582 (39)		13 (62)	464 (39)		11 (42)	118 (39)	
α-Fetoprotein (*μg/L*)	6 ± 19	19 ± 27	12 ± 13	<.001	16 ± 23	12 ± 38	.83	20 ± 30	11 ± 9	.92	14 ± 15	19 ± 28	.96
HBeAg				<.001			.02			.86			.41
Positive	453 (30)	68 (21)	358 (32)		12 (26)	441 (30)		6 (29)	352 (30)		6 (23)	62 (20)	
Negative	1076 (70)	263 (79)	813 (68)		34 (72)	1042 (70)		15 (71)	798 (68)		19 (73)	244 (80)	
Equivocal	2 (0.2)	1 (0.3)	1 (0.1)		1 (2)	1 (0.1)		0 (0)	1 (0.1)		1 (4)	0 (0)	
HBV DNA (log_{10} *IU/mL*)	5.0 ± 2.2	4.9 ± 1.9	5.0 ± 2.2	.22	5.1 ± 1.8	4.9 ± 2.2	.70	5.1 ± 1.9	5.0 ± 2.2	.87	5.1 ± 1.8	4.9 ± 1.9	.83
≥2000 IU/mL	1185 (77)	257 (77)	928 (77)		40 (85)	1145 (77)		18 (86)	910 (77)		22 (86)	235 (77)	
HBsAg (log_{10} *IU/mL*)	3.0 ± 0.9	2.9 ± 0.8	3.0 ± 0.9	<.001	2.9 ± 0.8	3.0 ± 0.9	.22	3.0 ± 0.7	3.0 ± 0.9	.76	2.7 ± 0.8	2.9 ± 0.8	.003
≥1000 IU/mL	934 (61)	168 (51)	766 (64)		21 (45)	913 (62)		13 (62)	753 (64)		8 (31)	160 (52)	
Previous antiviral therapy	471 (31)	85 (26)	386 (32)	.003	8 (17)	463 (31)	.03	3 (14)	383 (33)	.08	5 (19)	80 (26)	.64
(Peg)Interferon	30 (2)	2 (0.6)	28 (2)		0 (0)	30 (2)		0 (0)	26 (2)		0 (0)	2 (1)	
Nucleos(t)ide analogues	441 (29)	83 (25)	358 (30)		8 (17)	433 (29)		3 (14)	355 (30)		5 (19)	78 (25)	
Maintained virologic response	1174 (77)	250 (75)	924 (77)	.46	30 (64)	1144 (77)	.03	15 (71)	909 (77)	.60	15 (58)	235 (77)	.05
Duration of virologic remission (*mo*)	34 ± 17	32 ± 19	35 ± 16	.10	31 ± 18	35 ± 17	.009	35 ± 17	35 ± 16	.76	24 ± 17	34 ± 20	<.001

NOTE. Data are presented as mean ± standard deviation or number (percentage) unless otherwise noted.

expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The Kaplan–Meier method was used to estimate the cumulative incidence of HCC, and differences between factors were evaluated by the log-rank test.

To assess the prognostic value of the 3 HCC risk scores, we used the time-dependent receiver operating characteristic (ROC) curve estimation from censored survival data with the nearest-neighbor estimation method.[21] The area under the receiver operating characteristic curve (AUC) was used to express prognostic accuracy. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of the risk scores to predict HCC were estimated and reported. The CU-HCC and GAG-HCC scores were tested in the entire population, whereas the REACH-B score was tested in a subgroup of noncirrhotic patients based on their original population of derivation. Sensitivity analysis was performed by repeating all the analyses in the subset of patients who were treatment naïve before the use of entecavir to avoid the confounding effect of prior antiviral therapy. All statistical tests were 2 sided. Statistical significance was taken as $P < .05$.

Results

Patient Characteristics

During the study period, 1598 patients with CHB were treated with entecavir for at least 12 months in the hepatitis clinics at Prince of Wales Hospital in Hong Kong. After excluding 36 patients who had evidence of preexisting HCC at baseline or within the first year of treatment with entecavir, 9 patients with Child's C cirrhosis, 2 patients with coinfection with hepatitis C, and 20 patients with unavailable results for baseline serum HBV DNA level, the final analysis included 1531 entecavir-treated patients who were followed up for 42 ± 13 months. The demographic, virologic, and clinical characteristics of the patients are summarized in Table 1. The mean age was 51 ± 12 years, and the patients were predominantly male (1099 [72%]). A total of 332 patients (22%) had cirrhosis. Patients with cirrhosis were older (56 ± 11 vs 50 ± 12 years; $P < .001$) and more likely to be HBeAg negative (79% vs 68%; $P < .001$) when compared with those without cirrhosis (Table 1).

Cumulative Incidence of HCC

At a mean follow-up of 42 months, 47 patients (2.9%) developed HCC. The cumulative incidence rates of HCC at 3 and 5 years were 2.9% (95% CI, 2.4%–3.4%) and 4.3% (95% CI, 3.6%–5.0%), respectively, in the entire cohort. In the subgroup of patients with cirrhosis, the cumulative incidence rates of HCC at 3 and 5 years were 7.6% (95% CI, 5.9%–9.3%) and 12.9% (95% CI, 10.0%–15.8%), respectively. In the subgroup of patients without cirrhosis, the cumulative incidence rates of HCC at 3 and 5 years were 1.8% (95% CI, 1.4%–2.2%) and 2.1% (95% CI, 1.6%–2.6%), respectively.

Factors Associated With HCC in All Patients

Patients who developed HCC were older (59 ± 8 vs 51 ± 12 years; $P < .001$) and had a lower platelet count (123 ± 42 vs 173 ± 61 × 10^9/L; $P < .001$) and serum albumin level (36 ± 7 vs 45 ± 13 g/L; $P < .001$) than those without HCC. Those who developed HCC were also

Table 1. Continued

Treatment naïve before entecavir												
All treatment-naïve patients				All treatment-naïve patients			Noncirrhotic patients			Cirrhotic patients		
All	Cirrhosis	No cirrhosis	*P*	HCC	No HCC	*P*	HCC	No HCC	*P*	HCC	No HCC	*P*
1060	247	813		39	1021		18	795		21	226	
41 ± 13	38 ± 14	42 ± 13	.02	38 ± 13	41 ± 13	.16	37 ± 14	42 ± 13	.13	37 ± 13	39 ± 14	.74
745 (70)	170 (69)	575 (71)	.54	30 (77)	715 (70)	.48	14 (78)	561 (71)	.61	16 (76)	154 (68)	.62
52 ± 11	57 ± 10	51 ± 11	<.001	59 ± 8	52 ± 11	<.001	60 ± 6	51 ± 11	<.001	58 ± 9	57 ± 11	.32
674 (64)	197 (80)	477 (59)		36 (92)	638 (63)		17 (94)	460 (58)		19 (91)	178 (79)	
170 ± 62	125 ± 69	184 ± 52	<.001	129 ± 46	172 ± 62	<.001	149 ± 33	184 ± 52	.002	111 ± 48	126 ± 71	.28
12 ± 6	13 ± 8	12 ± 6	<.001	13 ± 2	12 ± 6	.49	12 ± 1	12 ± 6	.87	13 ± 2	13 ± 8	.92
41 ± 6	37 ± 5	42 ± 6	<.001	35 ± 7	41 ± 6	<.001	36 ± 6	42 ± 6	<.001	34 ± 7	38 ± 5	.007
22 ± 42	22 ± 30	22 ± 46	.91	24 ± 18	22 ± 42	.85	20 ± 18	22 ± 45	.76	27 ± 18	21 ± 32	<.001
151 ± 329	93 ± 129	168 ± 367	.009	91 ± 132	153 ± 334	.22	97 ± 174	170 ± 370	.47	86 ± 85	94 ± 133	.23
447 (42)	104 (42)	343 (42)		21 (54)	426 (42)		10 (56)	333 (42)		11 (52)	93 (41)	
13 ± 38	9 ± 40	12 ± 39	<.001	18 ± 25	13 ± 38	.53	22 ± 32	12 ± 40	.32	14 ± 14	14 ± 41	.97
			.02			.59			.30			.42
294 (28)	54 (22)	240 (30)		9 (23)	285 (28)		3 (17)	237 (30)		6 (29)	48 (21)	
766 (72)	193 (78)	573 (70)		30 (77)	736 (72)		15 (83)	558 (70)		15 (71)	178 (79)	
5.7 ± 1.5	5.5 ± 1.4	5.7 ± 1.5	.17	5.6 ± 1.1	5.7 ± 1.5	.70	5.5 ± 1.2	5.0 ± 2.2	.87	5.7 ± 1.1	5.4 ± 1.4	.33
956 (90)	215 (87)	741 (91)		37 (5)	919 (90)		17 (94)	724 (91)		20 (95)	195 (86)	
3.0 ± 0.9	2.9 ± 0.8	3.0 ± 0.9	.002	2.9 ± 0.8	3.0 ± 0.9	.22	3.0 ± 0.7	3.0 ± 0.9	.76	2.7 ± 0.9	2.9 ± 0.8	.03
550 (52)	131 (53)	419 (52)		20 (51)	530 (52)		12 (67)	407 (51)		8 (38)	123 (54)	
829 (78)	192 (78)	637 (78)	.96	27 (69)	802 (79)	.17	13 (72)	624 (79)	.56	14 (67)	178 (79)	.27
29 ± 11	28 ± 13	29 ± 11	.12	19 ± 14	29 ± 11	<.001	20 ± 15	29 ± 11	.003	19 ± 15	29 ± 11	<.001

less likely to be previously exposed to antiviral therapy (17% vs 31%; $P = .03$) and achieve maintained virologic response (64% vs 77%; $P = .03$) with a shorter duration of virologic remission (31 ± 18 vs 35 ± 17 months; $P = .009$) (Table 1).

Table 2 shows the analysis by time-dependent Cox proportional hazards model concerning factors associated with HCC. On univariate and multivariable analyses, albumin level <35 g/L, presence of cirrhosis, and duration of virologic remission ≥24 months were associated with subsequent development of HCC in the entire cohort. The adjusted HRs were 13.9 (95% CI, 4.1–43.3; $P < .001$) for albumin level <35 g/L, 3.2 (95% CI, 1.5–6.4; $P = .002$) for cirrhosis, and 0.3 (95% CI, 0.1–0.6; $P = .007$) for duration of virologic remission ≥24 months. These 3 factors remained the independent risk factors in the subset of previously treatment-naïve patients.

Factors Associated With the Development of HCC in Noncirrhotic Patients

In the noncirrhotic subgroup, patients who developed HCC were again older (59 ± 7 vs 49 ± 12 years; $P < .001$) and had a lower platelet count (149 ± 33 vs 186 ± 53 × 10^9/L; $P = .002$) and serum albumin level (37 ± 6 vs 46 ± 13 g/L; $P < .001$) when compared with those who did not develop HCC (Table 1). On univariate analysis, albumin level <35 g/L and duration of virologic remission ≥24 months were associated with subsequent development of HCC in patients without cirrhosis. Only hypoalbuminemia remained independently associated with development of HCC on multivariable analysis (adjusted HR, 17.5; 95% CI, 2.0–63.4; $P = .004$) (Table 2). The findings were comparable in the subset of previously treatment-naïve patients.

Factors Associated With the Development of HCC in Cirrhotic Patients

In the cirrhotic subgroup, patients who developed HCC were again older (59 ± 9 vs 56 ± 11 years; $P = .02$) and had a lower serum albumin level (35 ± 7 vs 39 ± 6 g/L; $P = .004$), higher serum total bilirubin level (29 ± 18 vs 23 ± 31 μmol/L; $P < .001$), and shorter duration of virologic remission (24 ± 17 vs 34 ± 20 months; $P < .001$) when compared with those who did not develop HCC (Table 1). On univariate analysis, albumin level <35 g/L, total bilirubin level ≥18 μmol/L, and duration of virologic remission ≥12 months were associated with subsequent development of HCC in patients with cirrhosis (refer to the univariate Cox results in Table 2). Hypoalbuminemia (adjusted HR, 7.1; 95% CI, 1.8–28.7; $P = .02$) and duration of virologic remission ≥24 months (adjusted HR, 0.3; 95% CI, 0.08–0.5; $P = .003$) remained independently associated with development of HCC on multivariable analysis (Table 2). The findings were similar in the subset of previously treatment-naïve patients.

Performance of HCC Risk Scores at Baseline

Table 3 shows the risk scores and the associated 3-year and 5-year risks of developing HCC. The risk of HCC increased dramatically with CU-HCC score and

Table 2. Univariate and Multivariable Analysis of Factors Associated With Hepatic Events and HCC by Time-Dependent Cox Proportional Hazards Regression Model

	Entire cohort (N = 1531)						Treatment naïve before entecavir (n = 1060)					
	Univariate analysis			Multivariable analysis			Univariate analysis			Multivariable analysis		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
All patients												
Male sex	1.4	0.7–2.5	.46				1.3	0.6–2.2	.63			
Age ≥50 y	47.6	0.4–5602	.11				35.1	0.3–534	.37			
Albumin <35 g/L	23.5	7.6–72.5	<.001	13.9	4.1–43.3	<.001	26.1	8.9–82.3	<.001	15.3	5.9–46.2	<.001
Total bilirubin ≥18 μmol/L	4.1	0.8–21.0	.10				3.3	0.7–13.2	.19			
ALT upper limit of normal or greater	0.05	0–5×10^{13}	.86				0.1	0–3.3×10^{9}	.83			
Positive HBeAg	0.03	0–146.0	.41				0.08	0–93.2	.37			
Pretreatment HBV DNA ≥2000 IU/mL	1.7	0.7–4.0	.24				2.6	0.9–7.3	.09			
Pretreatment HBsAg ≥1000 IU/mL	0.6	0.3–1.2	.14				0.6	0.3–1.3	.16			
Cirrhosis	4.9	2.7–8.7	<.001	3.2	1.5–6.4	.002	5.3	2.9–9.1	<.001	3.4	1.6–6.9	.001
Duration of virologic remission ≥24 mo	0.4	0.2–0.7	.01	0.3	0.1–0.6	.007	0.5	0.3–0.8	.02	0.4	0.2–0.7	.009
Noncirrhotic patients												
Male sex	1.3	0.5–3.4	.67				1.2	0.4–2.9	.73			
Age ≥50 y	48.7	0–7.5×10^{4}	.30				39.4	0–1.1×10^{4}	.27			
Albumin <35 g/L	34.7	2.7–210	<.001	17.5	2.0–63.4	.004	31.3	3.3–236	<.001	16.7	1.8–54.2	.002
Total bilirubin ≥18 μmol/L	2.3	0.2–22.2	.46				1.7	0.1–17.6	.75			
ALT upper limit of normal or greater	0.05	0–1.6×10^{13}	.86				0.1	0–7.3×10^{9}	.82			
Positive HBeAg	0.03	0–136.0	.42				0.08	0–86.7	.47			
Pretreatment HBV DNA ≥2000 IU/mL	2.4	0.5–10.3	.25				2.9	0.7–12.4	.13			
Pretreatment HBsAg ≥1000 IU/mL	1.1	0.4–2.6	.92				1.0	0.5–2.9	.97			
Duration of virologic remission ≥24 mo	0.5	0.3–0.8	.02	0.6	0.4–1.1	.08	0.6	0.4–0.8	.02	0.5	0.3–1.1	.09
Cirrhotic patients												
Male sex	1.5	0.7–2.9	.55				1.4	0.6–2.6	.59			
Age ≥50 y	45.8	0–5.9×10^{5}	.43				33.5	0–4.4×10^{4}	.37			
Albumin <35 g/L	9.8	2.3–42.0	.002	7.1	1.8–28.7	.02	12.6	3.3–47.3	.001	8.3	2.0–31.5	.007
Total bilirubin ≥18 μmol/L	12.5	1.1–141.0	.04	5.9	0.5–59.5	.48	12.1	1.1–99.7	.04	3.8	0.4–22.6	.62
ALT upper limit of normal or greater	0.1	0–2.2×10^{8}	.77				0.2	0–4.7×10^{6}	.67			
Positive HBeAg	1.2	0.1–10.2	.85				1.3	0.1–11.2	.88			
Pretreatment HBV DNA ≥2000 IU/mL	1.2	0.3–3.6	.36				1.5	0.5–4.3	.17			
Pretreatment HBsAg ≥1000 IU/mL	0.5	0.2–1.9	.87				0.6	0.3–2.0	.74			
Duration of virologic remission ≥24 mo	0.4	0.2–0.6	.006	0.3	0.08–0.5	.003	0.4	0.2–0.7	.009	0.4	0.1–0.8	.01

NOTE. Albumin, total bilirubin, and ALT levels and hepatitis B e antigen were regarded as the time-dependent variables in the model.

Table 3. Risk Score and Associated 3-Year and 5-Year Cumulative Risks of HCC

Entire cohort (N = 1531)								Treatment naïve before entecavir (n = 1060)							
	Cumulative risk (%)			Cumulative risk (%)			Cumulative risk (%)		Cumulative risk (%)			Cumulative risk			Cumulative risk	
CU-HCC score	3 y	5 y	GAG-HCC score	3 y	5 y	REACH-B score	3 y	5 y	CU-HCC score	3 y	5 y	GAG-HCC score	3 y	5 y	REACH-B score	3 y	5 y
Risk score at baseline																	
0–4.5	0.4	0.4	0–40	0	0	0–4	0	0	0–4.5	0.5	0.5	0–40	0	0	0–4	0	0
5–10	3.4	3.4	41–60	0	0	5–7	0.4	0.4	5–10	3.7	3.7	41–60	0	0	5–7	0.4	0.4
10.5–20	3.6	8.2	61–80	0.8	0.8	8–10	0.7	0.7	10.5–20	4.0	8.5	61–80	0.8	0.8	8–10	0.9	0.9
20.5–30	6.8	13.2	81–100	3.9	3.9	11–13	2.6	2.6	20.5–30	7.4	13.9	81–100	4.2	4.2	11–13	3.1	3.1
30.5–40	16.7	16.7	101–120	6.2	13.1	14–15	2.9	4.4	30.5–40	17.3	17.3	101–120	6.6	13.8	14–15	3.3	5.0
>40	19.6	29.5	>120	7.6	12.3	16–17	6.6	6.6	>40	20.5	22.1	>120	8.4	13.1	16–17	7.9	7.9
Risk score at year 1																	
0–4.5	1.3	1.3	0–40	0	0	0–4	0	0	0–4.5	1.3	1.3	0–40	0	0	0–4	0	0
5–10	2.2	2.2	41–60	0.4	0.4	5–7	0.6	0.6	5–10	2.5	2.5	41–60	0.4	0.4	5–7	0.6	0.6
10.5–20	5.2	8.5	61–80	2.5	2.5	8–10	2.4	2.4	10.5–20	5.7	8.9	61–80	2.5	2.5	8–10	2.7	2.7
20.5–30	11.9	18.2	81–100	3.2	5.9	11–13	4.8	9.1	20.5–30	12.7	19.0	81–100	3.5	6.4	11–13	5.3	9.7
30.5–40	22.0	22.0	101–120	12.7	15.6	14–15	7.7	NA	30.5–40	22.8	22.8	101–120	13.2	16.3	14–15	8.2	NA
>40	46.4	NA	>120	32.6	NA	16–17	NA	NA	>40	47.5	NA	>120	33.5	NA	16–17	NA	NA
Risk score at year 2																	
0–4.5	1.3	NA	0–40	0	NA	0–4	0	NA	0–4.5	1.3	NA	0–40	0	NA	0–4	0	NA
5–10	2.1	NA	41–60	0.3	NA	5–7	0.6	NA	5–10	2.7	NA	41–60	0.3	NA	5–7	0.6	NA
10.5–20	8.2	NA	61–80	2.1	NA	8–10	2.5	NA	10.5–20	8.9	NA	61–80	2.1	NA	8–10	2.8	NA
20.5–30	13.9	NA	81–100	4.6	NA	11–13	7.7	NA	20.5–30	14.8	NA	81–100	4.9	NA	11–13	8.5	NA
30.5–40	33.5	NA	101–120	17.3	NA	14–15	8.8	NA	30.5–40	34.6	NA	101–120	17.9	NA	14–15	9.7	NA
>40	48.9	NA	>120	24.1	NA	16–17	NA	NA	>40	49.8	NA	>120	25.6	NA	16–17	NA	NA
Risk score at year 3																	
0–4.5	1.2	NA	0–40	0	NA	0–4	0	NA	0–4.5	1.2	NA	0–40	0	NA	0–4	0	NA
5–10	3.0	NA	41–60	0	NA	5–7	0.6	NA	5–10	3.8	NA	41–60	0	NA	5–7	0.8	NA
10.5–20	8.3	NA	61–80	2.3	NA	8–10	2.7	NA	10.5–20	9.0	NA	61–80	2.3	NA	8–10	3.2	NA
20.5–30	16.7	NA	81–100	4.7	NA	11–13	8.1	NA	20.5–30	17.8	NA	81–100	5.1	NA	11–13	9.0	NA
30.5–40	36.8	NA	101–120	15.7	NA	14–15	NA	NA	30.5–40	37.9	NA	101–120	16.3	NA	14–15	NA	NA
>40	67.9	NA	>120	23.0	NA	16–17	NA	NA	>40	69.4	NA	>120	25.5	NA	16–17	NA	NA

NA, not available.

Table 4. AUCs and Diagnostic Performance of Baseline Risk Scores for HCC Up to 5 Years of Follow-up

	Entire cohort (N = 1531)									
	Baseline		1 y		2 y		3 y		4 y	
	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
CU-HCC score										
Cutoff value	5		5		5		5		5	
TD-AUC	0.80	0.75–0.86	0.77	0.69–0.84	0.85	0.76–0.94	0.95	0.91–0.99	0.87	0.76–0.98
Sensitivity (%)	93.6	82.8–97.8	78.7	65.1–88.0	86.4	66.7–95.3	100	64.6–100	100	34.2–100
Specificity (%)	47.8	45.3–50.4	54.53	52.0–57.1	56.2	53.6–58.8	72.1	69.3–74.8	73.4	69.3–77.1
PPV (%)	5.4	2.3–9.7	5.2	1.1–16.3	3.0	0–9.4	2.4	0–21.3	1.5	0–9.3
NPV (%)	99.6	91.2–100	98.8	85.3–100	99.6	83.7–100	100	71.7–100	100	51.7–100
LR+	1.8	1.6–2.0	1.7	1.5–2.0	2.0	1.7–2.4	3.6	3.3–4.0	3.8	3.2–4.4
LR−	0.13	0.05–0.40	0.39	0.22–0.68	0.24	0.09–0.40	0	0–∞	0	0–∞
No. in high risk	818		710		627		291		132	
No. in low risk	713		819		783		735		359	
Correct prediction	44/47		37/47		19/22		7/7		2/2	
Correct exclusion	710/1484		809/1482		780/1388		735/1019		359/489	
GAG-HCC score										
Cutoff value	101		101		101		101		101	
TD-AUC	0.76	0.70–0.82	0.77	0.71–0.83	0.86	0.79–0.94	0.95	0.93–0.98	0.93	0.87–0.99
Sensitivity (%)	55.3	41.3–68.6	46.8	33.3–60.8	68.2	47.3–83.6	100	64.6–100	100	34.2–100
Specificity (%)	78.9	76.8–80.9	87.1	85.3–88.7	87.6	85.8–89.2	88.1	86.0–90.0	85.9	82.5–88.7
PPV (%)	7.7	3.1–15.2	10.3	3.6–17.8	8.0	4.2–12.8	5.5	1.2–12.8	2.8	0–16.8
NPV (%)	98.2	87.3–100	98.1	92.2–100	99.4	83.2–100	100	72.2–100	100	62.2–100
LR+	2.6	2.0–3.5	3.6	2.6–5.1	5.5	4.0–7.6	8.4	7.1–10.0	7.1	5.7–8.8
LR−	0.57	0.41–0.78	0.61	0.70–0.80	0.36	0.20–0.67	0	0–∞	0	0–∞
No. in high risk	339		213		187		128		71	
No. in low risk	1192		1316		1223		898		420	
Correct prediction	26/47		22/47		15/22		7/7		2/2	
Correct exclusion	1171/1484		1291/1482		1216/1388		898/1019		420/489	
REACH-B score[a]										
Cutoff value	8		8		8		8		8	
TD-AUC	0.71	0.62–0.81	0.74	0.65–0.82	0.79	0.66–0.92	0.97	0.95–0.99	0.74	0.44–1.00
Sensitivity (%)	95.2	77.3–99.2	85.7	65.4–95.2	100	56.6–100	100	20.7–100	100	20.7–100
Specificity (%)	16.5	14.5–18.7	50.0	47.1–52.8	52.8	49.9–55.7	50.7	47.3–54.1	47.2	42.4–52.1
PPV (%)	2.0	0.1–10.2	3.0	0–17.2	0.9	0–23.3	0.2	0–15.3	0.5	0–11.3
NPV (%)	99.5	82.3–100	99.5	94.2–100	100	68.2–100	100	48.2–100	100	48.2–100
LR+	1.1	1.0–1.3	1.7	1.4–2.1	2.1	2.0–2.3	2.0	1.9–2.2	1.9	1.7–2.1
LR−	0.29	0.04–2.0	0.29	0.10–0.82	0	0–∞	0	0–∞	0	0–∞
No. in high risk	1004		606		529		413		210	
No. in low risk	195		590		586		424		187	
Correct prediction	20/21		18/21		5/5		1/1		1/1	
Correct exclusion	194/1178		587/1175		586/1110		424/836		187/396	

TD, time-dependent; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio.
[a]Only patients with no cirrhosis were analyzed for the REACH-B score.

modestly with GAG-HCC and REACH-B scores. The AUCs for prediction of development of HCC are shown in Table 4. The AUC was 0.80 (95% CI, 0.75–0.86) for CU-HCC score, 0.76 (95% CI, 0.70–0.82) for GAG-HCC score, and 0.71 (95% CI, 0.62–0.81) for REACH-B score at baseline (Figure 1*A*). At a cutoff value of 5, the CU-HCC score had 93.6% sensitivity (44 of 47 HCCs identified) and 47.8% specificity (710 of 1484 patients without HCC classified in the low-risk group) to predict HCC during the follow-up period. At a cutoff value of 101, the GAG-HCC score had 55.3% sensitivity (26 of 47 HCCs identified) and 78.9% specificity (1171 of 1484 patients without HCC classified in the low-risk group) to predict HCC. When applied to noncirrhotic patients, the REACH-B score at a cutoff value of 8 had 95.2% sensitivity (20 of 21 HCCs identified) and 16.5% specificity (194 of 1178 patients without HCC classified in the low-risk group) to predict HCC (Table 4). The performance of the models was slightly inferior in the subset of previously treatment-naïve patients (Table 4).

On-Treatment Performance of HCC Risk Scores

Because of the short duration of follow-up, only the 3-year risk of developing HCC was available for the on-treatment risk scores at year 2 onward. Similar to the scores at baseline, the risk of HCC increased dramatically with the on-treatment CU-HCC score and modestly with the REACH-B score. The performance of the on-treatment GAG-HCC score was more satisfactory than its baseline counterpart, because the risk of HCC increased dramatically with the score.

The AUCs varied and tended to increase with time (Table 4). For the CU-HCC score, the time-dependent AUCs were 0.77 at 1 year, 0.85 at 2 years, 0.95 at 3 years, and 0.87 at 4 years of entecavir therapy. For the GAG-HCC score, the time-dependent AUCs were 0.77 at 1 year, 0.86 at 2 years, 0.95 at 3 years, and 0.93 at 4 years of entecavir therapy. For the REACH-B score, the time-dependent AUCs were 0.74 at 1 year, 0.79 at 2 years, 0.97 at 3 years, and 0.74 at 4 years of entecavir therapy. Figure 1*B* represents the ROC curves of risk scores at 2

Table 4. Continued

Treatment naïve before entecavir (n = 1060)									
Baseline		1 y		2 y		3 y		4 y	
Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI	Value	95% CI
5		5		5		5		5	
0.77	0.71–0.84	0.75	0.67–0.84	0.76	0.68–0.84	0.81	0.73–0.90	0.82	0.69–0.96
94.9	83.1–98.6	79.5	64.5–89.2	87.5	64.0–96.5	100	61.0–100	100	34.2–100
40.3	37.3–43.3	52.13	49.0–55.2	46.0	42.6–49.3	70.9	67.4–74.1	69.7	64.4–74.2
5.7	2.4–10.6	6.0	1.7–15.3	2.9	0–9.8	2.9	0–23.2	2.0	0–9.9
99.5	91.0–100	98.5	87.3–100	99.5	83.3–100	100	73.5–100	100	56.7–100
1.6	1.5–1.7	1.7	1.4–2.0	1.6	1.3–2.0	3.4	3.1–3.9	3.3	2.8–3.9
0.13	0.03–0.49	0.39	0.21–0.73	0.27	0.07–1.0	0	0–∞	0	0–∞
647		519		475		208		100	
413		539		394		491		225	
37/39		31/39		14/16		6/6		2/2	
411/1021		531/1019		392/853		491/693		225/323	
101		101		101		101		101	
0.73	0.66–0.80	0.75	0.69–0.81	0.76	0.69–0.83	0.82	0.75–0.89	0.83	0.71–0.95
53.8	38.6–68.4	43.6	29.3–59.2	56.3	33.2–76.9	50.0	18.8–81.2	50.0	9.5–90.6
75.8	73.1–78.3	86.0	83.7–88.0	84.8	82.2–87.0	86.9	84.2–89.2	80.2	75.5–84.2
7.8	3.0–15.4	10.6	3.9–18.1	6.5	3.2–10.4	3.2	0.2–17.6	0.4	0–15.8
97.7	84.2–100	97.6	93.0–100	99.0	82.6–100	99.5	78.2–100	99.6	69.2–100
2.2	1.6–3.0	3.1	2.1–4.6	3.7	2.3–5.8	3.8	1.7–8.7	2.5	0.6–10.3
0.61	0.43–0.86	0.66	0.50–0.87	0.52	0.30–0.90	0.58	0.26–1.28	0.62	0.16–65.6
268		213		139		94		65	
792		1316		730		605		260	
21/39		17/39		9/16		3/6		1/2	
774/1021		876/1019		723/853		602/693		259/323	
8		8		8		8		8	
0.67	0.59–0.74	0.71	0.61–0.82	0.72	0.66–0.95	0.67	0.56–0.78	0.67	0.47–0.86
100	82.4–100	89.9	67.2–96.9	100	51.0–100	100	20.7–100	100	20.7–100
16.0	13.6–18.7	39.3	36.0–42.8	41.3	37.7–45.0	43.8	39.5–48.1	52.6	46.4–58.6
2.6	0.3–12.3	3.2	0–17.8	1.0	0–23.7	0.3	0–15.7	0.8	0–13.3
100	82.3–100	99.4	93.8–100	100	75.3–100	100	48.4–100	100	47.2–100
1.2	1.2–1.2	1.5	1.2–1.7	1.7	1.6–1.8	1.8	1.6–1.9	2.1	1.9–2.4
0	0–∞	0.28	0.08–1.05	0	0–∞	0	0–∞	0	0–∞
686		496		411		289		121	
127		313		286		224		133	
18/18		16/18		4/4		1/1		1/1	
127/795		311/791		286/693		224/512		133/253	

years to predict HCC. The performance of the cutoff values to define low-risk and high-risk groups was comparable at different time points (Table 4).

Change in HCC Risk Scores From Baseline to 2 Years After Treatment With Entecavir

Among the 1410 patients who were treated with entecavir for at least 2 years and remained HCC-free, 586 patients had CU-HCC scores <5 at baseline and 2 years after treatment with entecavir, 87 patients had increased scores from <5 at baseline to ≥5 at 2 years, 197 patients had decreased scores ≥5 at baseline to <5 at 2 years, and 540 patients had scores that remained ≥5 at baseline and 2 years. No patient developed HCC if the baseline CU-HCC score was <5, regardless of the score at 2 years. Three of 197 patients who had decreased scores from ≥5 at baseline to <5 at 2 years developed HCC, while 19 of 540 patients who had scores that remained ≥5 at baseline and 2 years developed HCC. By Kaplan–Meier analysis, compared with patients with CU-HCC scores <5 at baseline, those with CU-HCC scores that decreased from ≥5 to <5 or remained ≥5 had a higher risk of developing HCC ($P = .002$ and $P < .001$, respectively) (Figure 2*A*).

Similarly, 1108 of 1410 patients had GAG-HCC scores <101 at baseline and 2 years after starting treatment with entecavir, no patient had an increase in scores <101 at baseline to ≥101 at 2 years, 115 patients had a decrease in scores from ≥101 at baseline to <101 at 2 years, and 187 patients had scores that remained ≥101 at baseline and 2 years. Five patients developed HCC if their GAG-HCC score was <101 at baseline and 2 years. Two of 115 patients who had decreased scores from ≥101 at baseline to <101 at 2 years developed HCC, while 15 of 187 patients whose scores remained ≥101 at baseline and 2 years developed HCC. By Kaplan–Meier analysis, compared with patients with GAG-HCC scores <101 at baseline, those with scores that decreased from ≥101 to <101 had a similar risk of HCC ($P = .07$), whereas those with scores that remained ≥101 had a higher risk of developing HCC ($P < .001$) (Figure 2*B*).

Only 158 of 1115 patients had REACH-B scores <8 at baseline and 2 years after starting treatment with entecavir, 31 patients had an increase in scores from <8 at baseline to ≥8 at 2 years, 427 patients had a decrease in scores from ≥8 at baseline to <8 at 2 years, and 499

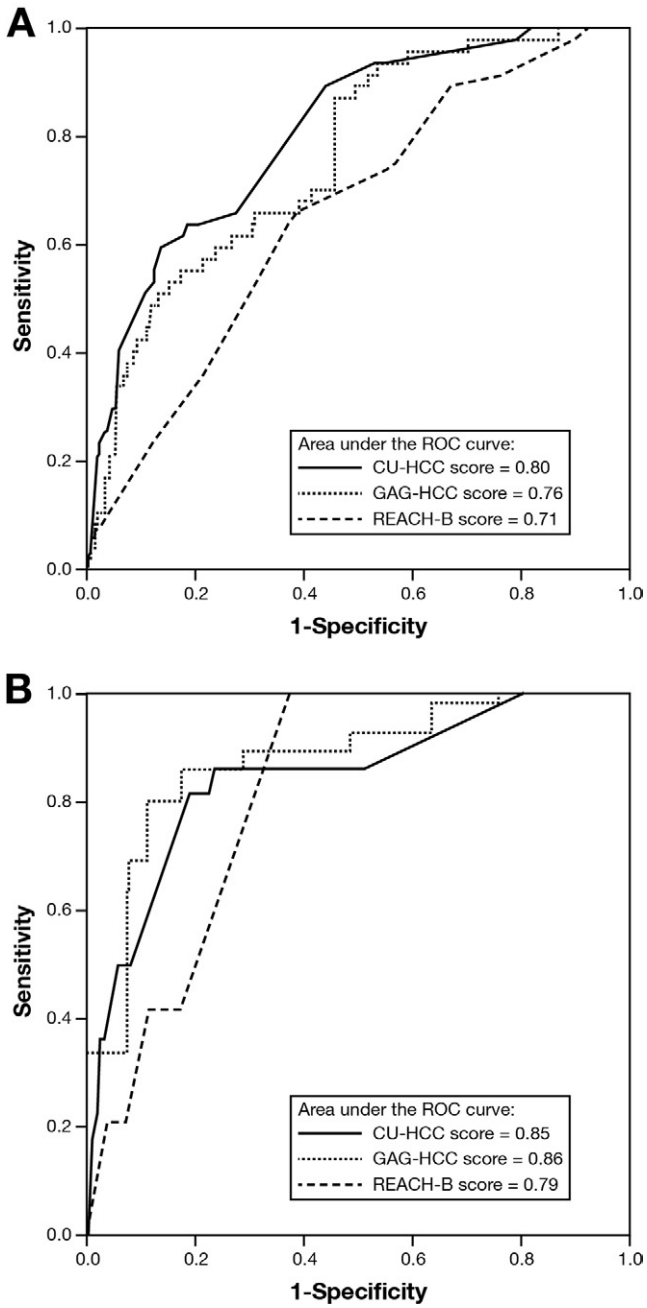

Figure 1. The AUCs of CU-HCC, GAG-HCC, and REACH-B scores at (*A*) baseline and (*B*) 2 years to predict HCC.

patients had scores that remained ≥8 at baseline and 2 years. No patient developed HCC if the REACH-B score was <8 at baseline and/or 2 years. Five of 499 patients with scores that remained ≥8 at baseline and 2 years developed HCC. By Kaplan–Meier analysis, compared with patients with REACH-B scores <8 at baseline and/or 2 years, those with scores that remained ≥8 had a significantly higher risk of developing HCC ($P = .056$) (Figure 2*C*).

Discussion

To our knowledge, this is the first study to assess the accuracy and applicability of different HCC risk scores

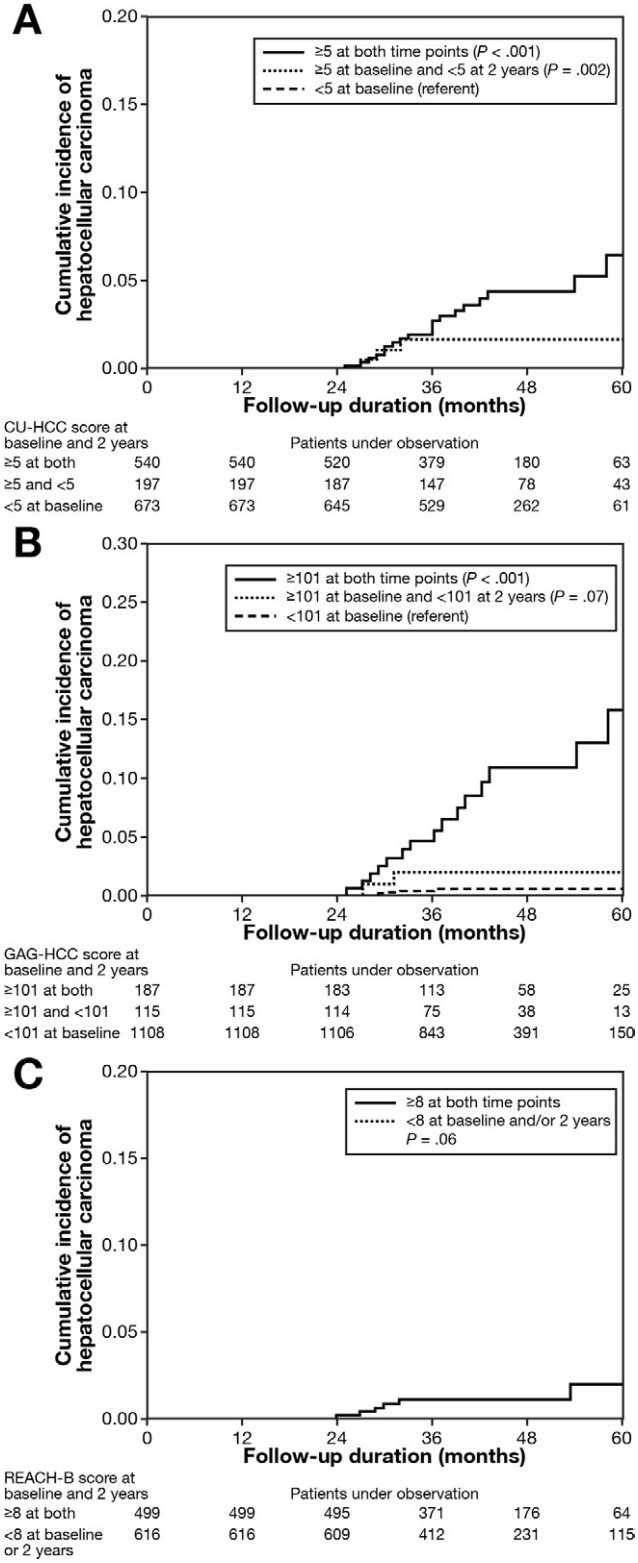

Figure 2. Kaplan–Meier analysis of the cumulative incidence of HCC in patients according to (*A*) CU-HCC scores at baseline and 2 years: <5 at baseline, ≥5 at baseline and <5 at 2-year score, and ≥5 at both time points (overall comparison, $P = .006$); (*B*) GAG-HCC scores at baseline and 2 years: <101 at baseline, ≥101 at baseline and <101 at 2-year score, and ≥101 at both time points (overall comparison, $P < .001$); and (*C*) REACH-B scores at baseline and 2 years: <8 at baseline and/or 2 years (referent) and ≥8 at both time points ($P = .056$).

to predict development of HCC in patients receiving antiviral treatment. First, we identified that the well-known risk factors of HCC in treatment-naïve patients, namely hypoalbuminemia and cirrhosis, also play important roles in entecavir-treated patients. Furthermore, maintained virologic response was an independent factor reducing the risk of HCC in entecavir-treated patients. With the large sample size and long-term follow-up, we showed that the performance of HCC risk scores remains satisfactory in patients receiving antiviral treatment. Another novel finding was the implication of changes in risk score on entecavir therapy; a decrease in risk scores lowers but does not eliminate the risk of subsequent development of HCC.

Despite the strong association between serum HBV DNA level and the risk of HCC, it remains uncertain whether HBV DNA level is a useful predictor of HCC in treated patients. Approximately three-fourths of patients treated with entecavir can achieve maintained virologic response with entecavir, and they have a low risk of virologic breakthrough and drug resistance.[9,22] A recent multicenter European study involving 372 entecavir-treated patients (26% were cirrhotic) followed up for a median of 20 months showed that a virologic response to entecavir (defined as a serum HBV DNA level <80 IU/mL) reduced the probability of clinical events in cirrhotic patients as compared with those without a virologic response.[16] Therefore, it seems that HBV DNA still has a role in predicting the risk of HCC among patients on antiviral therapy, and the use of HBV DNA in the HCC risk scores may still be feasible.

There have been concerns about the heavy weighting assigned to cirrhosis in the CU-HCC and GAG-HCC risk scores. It is well known that early cirrhosis may be missed by ultrasonography and liver biopsy is not feasible as a screening tool. This limitation may lead to substantial errors of the predicted risk of HCC by these scores if the presence or absence of cirrhosis is misclassified.[23] The role of noninvasive liver fibrosis assessments, namely transient elastography and/or serum markers, in the HCC risk scores remains to be defined.[24] Some preliminary data concerning the use of platelet count alone, or transient elastography in a subgroup of 670 patients who underwent the investigation, showed that the performance of the risk scores remained comparable (but less satisfactory in the REACH-B score) (Supplementary Table 2). Nonetheless, based on the clinical criteria of cirrhosis in this study, the performance of the CU-HCC and GAG-HCC risk scores remained satisfactory in patients treated with entecavir. The AUCs for 3-year and 5-year risk of HCC were comparable to those in the original studies.[4,7] The cutoff value of 5 proposed for the CU-HCC score tended to detect most patients who developed HCC, but only approximately half of the patients with no HCC could be identified. In other words, many low-risk patients had the risk of HCC exaggerated. On the contrary, the proposed cutoff value (101) for the GAG-HCC score could identify most patients with a low risk of HCC, but it might miss almost 50% of the HCC cases. Because the GAG-HCC score did not include serum albumin and bilirubin as did the CU-HCC score, it might compensate less well for the misclassification of cirrhosis by clinical criteria alone. If the GAG-HCC score were used to predict HCC in entecavir-treated patients, a lower cutoff value should probably be adopted. A point of note is that there was a small overlap (83 of 1531 patients) between the patients in the current study and the original cohorts for the development of the CU-HCC scores, but this should only pose a minimal effect on the superior performance of the CU-HCC score to other risk scores.

The REACH-B score was originally derived from noncirrhotic patients.[6] Unfortunately, the inaccurate classification of cirrhosis was again inevitable, because ultrasonography remained as the tool to exclude cirrhosis. At a cutoff value of 8, the REACH-B score could detect almost all entecavir-treated patients who developed HCC in 3 and 5 years. The key drawback was a false-positive value, and it could not accurately identify low-risk patients. In other words, most patients might have an inconclusive score and the risk of HCC could not be clearly defined. On the other hand, the performance of the 3 models was slightly inferior, represented by lower specificities, in the subset of previously treatment-naïve patients. The same cutoff values of the models generated more false-positive results. One possible explanation was that this subset of patients had more advanced liver disease (as evidenced by lower baseline albumin level) yet a comparable incidence rate of HCC.

The HBsAg level reflects the amount and transcriptional activity of covalently closed circular DNA inside the liver.[19] Recent data from a large-scale longitudinal study in Taiwan showed that a low serum HBsAg level of <1000 IU/mL in HBeAg-negative noncirrhotic patients with an HBV DNA level <2000 IU/mL had a very low risk of HCC.[23,25] In this study, we could not show HBsAg level as a predictor of HCC. The probable reason was that all our patients had indications for antiviral treatment. Because these patients had active disease, those who had a lower HBsAg level were more likely to be cirrhotic. In other words, there were no "inactive HBV carriers" at very low risk for HCC in our cohort.[23]

There are several implications of HCC risk prediction in patients receiving antiviral therapy. First, entecavir cannot completely eliminate the risk of HCC. Patients at high risk should still undergo regular HCC surveillance.[26,27] Patients with HCC detected at an early stage via a surveillance program have a greater chance of curative treatment with improved survival.[26] Furthermore, patients who failed to achieve maintained viral suppression should consider alternative treatment regimens to reduce the risk of HCC. The optimal treatment regimens for these patients remain controversial. Possible options include combining entecavir with tenofovir disoproxil fumarate[28] and high-dose entecavir (1.0 mg daily).[9] Another point to highlight is the effect of the dynamic change of risk scores. Although a reduction in CU-HCC risk score is associated with lower risk of HCC, the risk is not yet eliminated and HCC surveillance is still warranted.

Our study has the strength of a large sample size and long follow-up, which increased the statistical power and reliability of the results. Nonetheless, our study also has a few limitations. The retrospective nature of certain clinical information might be biased by incomplete data collection. Patient inclusion and identification through the database of HBV DNA testing might miss those not adherent to follow-up. Fortunately, the compliance of HBV DNA monitoring every 6 months was high in entecavir-treated patients (>98%) because the test was free for the patients. Moreover, patients who started taking entecavir after October 2009 had all the clinical information prospectively collected, which also minimized the chance of incomplete data collection. Second, the diagnosis of cirrhosis was based on radiologic and clinical information. Patients with early cirrhosis might be missed. However, ultrasonography is operator dependent and inaccurate in diagnosing early cirrhosis. The use of a more stringent definition of cirrhosis in this study makes our findings more reproducible and more relevant to clinicians in real-life practice. The wide CI secondary to the small number of events, even in such a large cohort, and short duration of follow-up was another major issue. The low event rate was also related to treatment with entecavir. A longer duration of follow-up would allow more events and hence a more precise estimation of the accuracy of risk scores. Lastly, almost one-third of patients received antiviral therapy before treatment with entecavir. This might create a confounding effect on the performance of the risk scores, but the effect should be modest only as reflected by similar results in the entire cohort and the subset of patients who were previously treatment naïve.

In conclusion, the CU-HCC, GAG-HCC, and REACH-B scores can accurately predict subsequent development of HCC in patients treated with entecavir. Lack of maintained virologic response is an independent factor associated with HCC in patients with cirrhosis. Therefore, patients at risk for HCC should undergo regular HCC surveillance even when they are receiving antiviral treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.02.002.

References

1. Chan HL, Sung JJ. Hepatocellular carcinoma and hepatitis B virus. Semin Liver Dis 2006;26:153–161.
2. Chan HL, Tse CH, Mo F, et al. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. J Clin Oncol 2008;26:177–182.
3. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73.
4. Wong VW, Chan SL, Mo F, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol 2010;28:1660–1665.
5. Yang HI, Sherman M, Su J, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol 2010;28:2437–2444.
6. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011; 12:568–574.
7. Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol 2009;50:80–88.
8. Sung JJ, Tsoi KK, Wong VW, et al. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2008;28:1067–1077.
9. Wong GL, Wong VW, Chan HY, et al. Undetectable HBV DNA at month 12 of entecavir treatment predicts maintained viral suppression and HBeAg-seroconversion in chronic hepatitis B patients at 3 years. Aliment Pharmacol Ther 2012;35:1326–1335.
10. Chang TT, Lai CL, Kew Yoon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. Hepatology 2010;51:422–430.
11. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–185.
12. Liaw YF, Leung N, Kao JH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2008;2:263–283.
13. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–662.
14. Schiff E, Simsek H, Lee WM, et al. Efficacy and safety of entecavir in patients with chronic hepatitis B and advanced hepatic fibrosis or cirrhosis. Am J Gastroenterol 2008;103:2776–2783.
15. Shim JH, Lee HC, Kim KM, et al. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. J Hepatol 2010;52:176–182.
16. Zoutendijk R, Reijnders JG, Zoulim F, et al. Virological response to entecavir is associated with a better clinical outcome in chronic hepatitis B patients with cirrhosis. Gut 2012 Apr 5 [Epub ahead of print].
17. Jin YJ, Shim JH, Lee HC, et al. Suppressive effects of entecavir on hepatitis B virus and hepatocellular carcinoma. J Gastroenterol Hepatol 2011;26:1380–1388.
18. Chan HL, Chui AK, Lau WY, et al. Factors associated with viral breakthrough in lamivudine monoprophylaxis of hepatitis B virus recurrence after liver transplantation. J Med Virol 2002;68:182–187.
19. Chan HL, Thompson A, Martinot-Peignoux M, et al. Hepatitis B surface antigen quantification: why and how to use it in 2011—a core group report. J Hepatol 2011;55:1121–1131.
20. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.
21. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000; 56:337–344.
22. Wong GL. Who will have the best response to entecavir? J Gastroenterol Hepatol 2013;28:5–7.
23. Chan HL. Identifying hepatitis B carriers at low risk for hepatocellular carcinoma. Gastroenterology 2012;142:1057–1060.
24. Wong GL, Wong VW, Choi PC, et al. Development of a non-invasive algorithm with transient elastography (Fibroscan) and serum test formula for advanced liver fibrosis in chronic hepatitis B. Aliment Pharmacol Ther 2010;31:1095–1103.
25. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with

low HBV load. Gastroenterology 2012;142:1140–1149 e3; quiz e13–14.
26. Wong GL, Wong VW, Tan GM, et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. Liver Int 2008;28:79–87.
27. Wong VW, Chan HL. Prevention of hepatocellular carcinoma: a concise review of contemporary issues. Ann Hepatol 2012;11: 284–293.
28. Lok AS, Trinh H, Carosi G, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naive patients with chronic hepatitis B. Gastroenterology 2012;143:619–628 e1.

Received November 5, 2012. Accepted February 1, 2013.

Reprint requests

Address requests for reprints to: Vincent W. S. Wong, MD, Department of Medicine and Therapeutics, 9/F Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong. e-mail: wongv@cuhk.edu.hk; fax: (852) 2637-3852.

Conflicts of interest

The authors disclose the following: Grace L. H. Wong has served as an advisory committee member for Otsuka and a speaker for Echosens. Henry L. Y. Chan is a consultant for Abbott, Bristol-Myers Squibb, Gilead, Merck, Novartis, and Roche; has received honorarium for lectures for Abbott, Bristol-Myers Squibb, Echosens, Gilead, GlaxoSmithKline, Merck, Novartis, and Roche; and has received an unrestricted grant from Roche for hepatitis B research. Vincent W. S. Wong has served as an advisory committee member for Roche, Novartis, Gilead, and Otsuka and has served as a speaker for Bristol-Myers Squibb, Roche, Novartis, Abbott Diagnostics, and Echosens. The remaining authors disclose no conflicts.

Funding

Supported in part by the Direct Grant of The Chinese University of Hong Kong (project reference number 2041703 to G.L.-H.W.).