MAJOR ARTICLE

Real-World Effectiveness From the Asia Pacific Rim Liver Consortium for HBV Risk Score for the Prediction of Hepatocellular Carcinoma in Chronic Hepatitis B Patients Treated With Oral Antiviral Therapy

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Background. Patients on oral antiviral (OAV) therapy remain at hepatocellular carcinoma (HCC) risk. Risk prediction tools distinguishing treated patients with residual HCC risk are limited. The aim of this study was to develop an accurate, precise, simple-to-use HCC risk score using routine clinical variables among a treated Asian cohort.

Methods. Adult Asian chronic hepatitis B (CHB) patients on OAV were recruited from 25 centers in the United States and the Asia-Pacific region. Excluded persons were coinfected with hepatitis C, D, or human immunodeficiency virus, had HCC before or within 1 year of study entry, or their follow-up was <1 year. Patients were randomized to derivation and validation cohorts on a 2:1 ratio. Statistically significant predictors from multivariate modeling formed the Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV (REAL-B) score.

Results. A total of 8048 patients were randomized to the derivation (n = 5365) or validation group (n = 2683). The REAL-B model included 7 variables (male gender, age, alcohol use, diabetes, baseline cirrhosis, platelet count, and alpha fetoprotein), and scores were categorized as follows: 0–3 low risk, 4–7 moderate risk, and 8–13 high risk. Area under receiver operating characteristics were >0.80 for HCC risk at 3, 5, and 10 years, and these were significantly higher than other risk models (*p* < .001).

Conclusions. The REAL-B score provides 3 distinct risk categories for HCC development in Asian CHB patients on OAV guiding HCC surveillance strategy.

Keywords. Asian; liver cancer; treatment; viral hepatitis; viral suppression.

In 2017, the World Health Organization recognized that there were 257 million people affected with chronic hepatitis B (CHB) globally. There were 887 000 CHB-related deaths in 2015, with the majority attributed to cirrhosis and hepatocellular carcinoma (HCC) and occurring mainly in the Far East [1–3]. Because there is no cure for CHB, oral viral suppressants are the main therapeutic strategy to decrease HCC risk and slow down the disease, because HCC is now the second leading cause (n = 788 000 deaths) of cancer-related mortality worldwide [4].

Currently, several professional organizations recommend antiviral therapy and HCC surveillance imaging every 6 months for patients at high risk for HCC and disease progression, which can be costly and hard to maintain [5–7]. In addition, despite undergoing treatment, CHB patients remain at risk for HCC

development [8], although it is unclear whether some treated patients may be at lower risk for HCC such that HCC surveillance recommendations can be modified to potentially reduce costs and facilitate maintenance of the surveillance recommendations [9, 10].

Although HCC risk assessment tools have been developed to identify high-risk patients for treatment and surveillance [11], data are limited for HCC risk prediction in treated CHB patients. Therefore, the aim of our study was to develop and validate a noninvasive, easy-to-use, and accurate risk score (Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV [REAL-B] score) to predict HCC risk in a large consort of CHB-treated Asian Americans and Asians residing in Asia. Our secondary aim was to compare the performance of the REAL-B score to previously developed tools based on clinical parameters [12–16].

METHODS

Study Population
A total of 9770 adult CHB patients who initiated oral antiviral therapy at any time before study entry were recruited from 6 United States and 19 Asia-Pacific centers from 1997 to 2016 (5 from Mainland China, 1 from New Zealand, 1 from South Korea, 2 from Hong Kong, 6 from Japan, and 4 from Taiwan), representing the REAL-B study group (Supplemental Figure 1). Patients were identified via *International Classification of Diseases, Ninth Revision* code query for CHB (nos. 070.2–070.3) and/or clinic records, and the diagnosis was verified by individual chart review. Additional demographic, clinical, laboratory, imaging, and treatment data were recorded at all centers using the same structured data collection form, which included standardized definitions of data variables.

The primary study endpoint was the development of HCC. Inclusion criteria for this study consisted of adult (≥18 years) CHB patients treated with an oral antiviral for at least 1 year, no evidence of hepatitis C, D, or human immunodeficiency virus coinfection, as well as no posttransplant or immunosuppressive treatment. Patients were also excluded if they had a prior history of HCC before study entry, developed HCC within 1 year of follow-up, or had a total follow-up time of less than 1 year. A total of 8048 eligible Asian patients were included in study analyses (Figure 1). Definitions of CHB, antiviral therapy, cirrhosis, and HCC are described in Supplemental Table 1. The study was approved by the Institutional Review Boards of Stanford University and participating institutions.

Statistical Analysis
Study patients were randomly assigned to either the derivation or validation cohort in a 2:1 ratio. Standard descriptive and comparative statistics were performed for all demographic and clinical data with missing values in less than 800 patients (~10% of all patients). A 2-sided $p < .05$ was defined as being statistically significant.

We used 2 approaches to identify factors that were significantly associated with the development of HCC. One was to assemble a multivariate Cox proportional hazards regression model that included parameters that were significant in the univariate Cox regression analysis, and then leaving those parameters that were statistically significant to construct the final multivariate Cox proportional hazards model. The other also included all significant factors in the univariate analysis, but it used 3 selection procedures (forward, backward, and stepwise) to determine the final predictors. In this study, the 2 approaches yielded the same final risk factor set.

Regression coefficients from the final Cox proportional hazards model were transformed into scores by dividing each predictor's coefficient by the regression coefficient of 10-year increments in age and rounding to an integer value. The projected HCC risk of a given score was estimated by using the following equation: $1 - P_0 \ e^{(\beta_{age10} \times \sum Score - \sum \beta_i \times \mu_i)}$, where P_0 is the baseline HCC-free probability, β_{age10} is the regression coefficient for a 10-year increase in age, *Score* represents the score for which HCC risk to be estimated, β_i is the regression coefficient for the ith predictor, and μ_i denotes the mean level of the ith predictor. Cumulative risk scores were calculated for each patient and time-varying receiver operating characteristic (ROC) curves and the area under ROC (AUROC) assessed the discrimination of the risk score. The test of AUROC between REAL-B and other scores was performed using a nonparametric approach [17]. Two cutoff points were chosen based on an estimated 3-year risk: <1% for the low-risk group, 1–5% for the intermediate-risk group, and >5% for the high-risk group. Calibration plots by quintiles of predicted 3-, 5-, and 10-year HCC risk were generated with the Hosmer-Lemeshow tests for assessing the calibration of the risk score. The Kaplan-Meier method was used to estimate cumulative HCC incidence. Statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics
After random allocation, there were 5365 patients in the derivation group and 2683 in the validation group (Figure 1). There were no significant differences between the groups except for a slight difference in the history of significant alcohol use. The majority of patients were Chinese (82%) and male (69%), with a mean age of 48.4 years, and over 21% had cirrhosis, 11% had diabetes, and at least 38% had hepatitis B e-antigen (HBeAg) seropositivity. At baseline, 20% of patients were treatment experienced, ie, the baseline laboratory data for these patients were on-treatment values (Table 1).

A total of 378 (7.0%) and 202 (7.5%) newly developed HCC cases occurred during 29571.84 and 14945.27 person-years, respectively, in the model derivation and validation groups, which corresponded to an HCC incidence rate of 1278.2 and 1351.6 per 10^5 person-years, respectively (Figure 1).
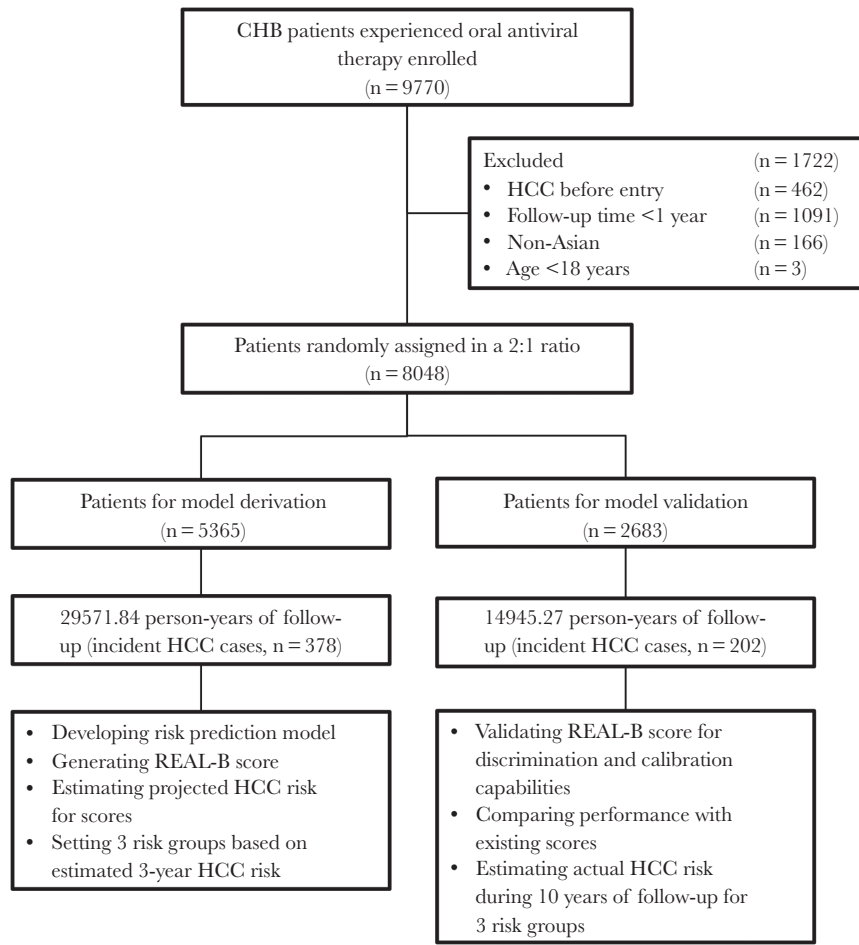
Figure 1. Flow chart of the study. CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; REAL-B, Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV.

Model Development

On univariate analysis, male gender, increasing age, significant alcohol use, cirrhosis at baseline, ascites or hepatic encephalopathy, and diabetes were significantly associated with HCC (Table 2). The laboratory results found to be potential predictors for HCC were baseline HBeAg, baseline values for ALT at the upper limit of normal (ULN) but <2 × ULN, platelet counts of <150 × 10³/μL, albumin <3.0 g/dL, total bilirubin >1.05 mg/dL, and alpha fetoprotein (AFP) >10 ng/mL. Although a few categories of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) were statistically significant, there were no consistent trends across HBV DNA levels. Therefore, this variable was not included in the subsequent multivariate analyses. Model 1 was developed from the univariate significant predictors noted above. After multivariate analysis, significant predictors were male gender (aHR: 1.65, $P = .0015$), age per 10 years (adjusted hazard ratio [aHR] = 1.76, $p < .0001$), alcohol use (aHR = 1.53, $P = .0032$), cirrhosis at baseline (aHR = 2.76, $p < .0001$), diabetes (aHR = 1.71, $p = .0004$), baseline platelet count <150 × 10³/μL (aHR = 1.61, $p = .0011$), and baseline AFP >10 ng/mL

(aHR = 1.46, $p = .0068$) (Table 3). When applying the 3 selection procedures on the same variable set as shown in Model 1, the same 7 parameters were selected. Model 2 was then constructed using the same 7 variables listed above with results as described in Table 3.

Derivation of REAL-B Prediction Score for Hepatocellular Carcinoma

Table 4 provides the regression coefficients for the 7 variables identified in Model 2. Cirrhosis had the largest coefficient at 1.13, and its corresponding score for the composite REAL-B score was 2 vs 0 for no cirrhosis. Age was divided into 7 groups, but the other variables had respective scores of 1 or 0, depending upon whether the condition was present or not (Table 4).

As a result, the total REAL-B score can range from 0 to 13 with 3-year, 5-year, and 10-year risks of developing HCC projected for each as shown in Table 5. For example, a total score of 0 has a projected HCC risk of 0.14%, 0.30%, and 0.71% at 3, 5, and 10 years, respectively, whereas the corresponding risk for a score of 13 was 65.60%, 90.37%, and 99.63%, respectively.

Table 1. Baseline Characteristics of Derivation and Validation Sets

Characteristics	Derivation Set (n = 5365)	Validation Set (n = 2683)	P Value
	No. (%)	No. (%)	
Male gender	3710 (69.2)	1854 (69.1)	.96
Age, mean (SD)	48.4 (12.7)	48.3 (12.5)	.85
Ethnicity			.17
Vietnamese	608 (11.3)	322 (12.0)	
Chinese	4384 (81.7)	2198 (81.9)	
Korean	97 (1.8)	55 (2.1)	
Japanese	247 (4.6)	89 (3.3)	
Cambodian	0 (0.0)	1 (0.0)	
Thai	0 (0.0)	1 (0.0)	
Filipino	24 (0.5)	12 (0.5)	
Asian Indian	5 (0.1)	5 (0.2)	
Alcohol drinking	967 (19.4)	533 (21.5)	.037
Cirrhosis at baseline	1085 (20.2)	592 (22.1)	.053
Ascites	175 (3.5)	101 (4.0)	.24
Encephalopathy	29 (0.6)	13 (0.5)	.74
Diabetes	544 (10.9)	268 (10.7)	.80
Hypercholesterolemia	785 (16.1)	394 (16.1)	.94
Treatment History (Can Be Multiple Courses)			
LAM	939 (17.7)	452 (17.0)	.41
ADV	439 (8.3)	248 (9.3)	.12
Peg-IFN	0 (0.0)	0 (0.0)	
LDT	229 (4.3)	104 (3.9)	.38
ETV	3683 (69.4)	1827 (68.6)	.43
TDF	593 (11.2)	326 (12.3)	.16
Combination treatment	147 (2.7)	86 (3.2)	.24
Sequential treatment	469 (8.7)	254 (9.5)	.28
Viral resistance	309 (6.0)	156 (6.1)	.92
HBeAg seropositivity	1886 (37.4)	954 (37.9)	.68
Baseline ALT, median (IQR)	69 (38–171)	67 (38–156)	.26
Baseline HBV DNA, median (IQR)	1.58×10^5 (2.36×10^3–7.30×10^6)	1.96×10^5 (3.60×10^3–5.48×10^6)	.27
Baseline platelet, mean (SD)[a]	172.8 (71.3)	171.5 (73.0)	.49
Baseline ALB, mean (SD)	4.1 (0.56)	4.1 (0.58)	.81
Baseline TB, median (IQR)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	.48
Baseline AFP, median (IQR)	4.6 (3.0–10.0)	4.5 (3.0–9.0)	.42
Baseline CR, median (IQR)	0.90 (0.70–1.04)	0.90 (0.71–1.06)	.24

Abbreviations: ADV, adefovir disoproxil; AFP, alpha fetoprotein (ng/mL); ALB, albumin (g/dL); ALT, alanine aminotransferase (U/L); CR, creatinine (mg/dL); ETV, entecavir; HBeAg, hepatitis B e-antigen; HBV DNA, hepatitis B viral deoxyribonucleic acid (IU/mL); IQR, interquartile range; LAM, lamivudine; LDT, telbivudine; Peg-IFN, pegylated interferon; SD, standard deviation; TB, total bilirubin (mg/dL); TDF, tenofovir disoproxil fumarate

[a]Platelets (1×10^3/μL).

The AUROC for the prediction of HCC at 3, 5, and 10 years in the derivation cohort was 0.81 (95% confidence interval [CI], .78–.84), 0.80 (95% CI, .78–.83), and 0.80 (95% CI, .78–.82), respectively.

Finally, the Hosmer-Lemeshow tests to validate the calibration capability of REAL-B score (Supplemental Figure 2a–c) demonstrated that the predicted risk calibrated well with the observed risk (P values for Hosmer and Lemeshow goodness-of-fit test, 0.13, 0.21, and 0.25, respectively, for 3, 5, and 10 years prediction).

Validation of the REAL-B Score

Using the validation cohort, we produced AUROCs for the prediction of HCC risk at 3 years (AUROC, 0.83; 95% CI, .78–.87),

5 years (AUROC, 0.81; 95% CI, .77–.85), and 10 years (AUROC, 0.81; 95% CI, .78–.84). In the same validation cohort, the REAL-B scores performed significantly better than the PAGE-B scores [7], across all prediction years ($p < .0001$) (Table 6), and other risk scores developed for untreated patients (REACH-B [18], GAG-HCC [15]) or partially treated patients (CU-HCC score [19]) ($p = .010$ to <.0001) (Supplemental Table 2).

In addition, we performed a subgroup analysis of patients who were treatment experienced (n = 541) and treatment naive (n = 2093) at the time of their study entry (baseline). The AUROCs remained greater than 0.80 across all year groups regardless of prior treatment status or when treatment was initiated for the treatment naive (Supplemental Table 3).

Table 2. Incidence Rate and Univariate Analysis for Potential Predictors of HCC in the Derivation set (n = 5365)

Variable	Category	No. of HCC Cases	Person-Years of Follow-up	Incidence Rate of HCC, per 10^5 Person-Years	Hazard Ratio (95% CI)	P Value
Gender	Female	77	8906.45	864.5	Referent	
	Male	301	20 665.39	1456.5	1.67 (1.30–2.15)	<.0001
Age	Per 1 year				1.06 (1.05–1.07)	<.0001
Alcohol use	No	253	22 356.67	1131.7	Referent	
	Yes	101	5217.28	1935.9	1.72 (1.37–2.17)	<.0001
Cirrhosis at baseline	No	177	24 009.48	737.2	Referent	
	Yes	201	5549.15	3622.2	5.02 (4.09–6.15)	<.0001
Ascites or encephalopathy	No	335	27 553.88	1215.8	Referent	
	Yes	30	824.77	3637.4	3.15 (2.17–4.58)	<.0001
Diabetes	No	267	24 636.74	1083.7	Referent	
	Yes	78	2843.07	2743.5	2.58 (2.01–3.33)	<.0001
Hypercholesterolemia	No	296	22 382.88	1322.4	Referent	
	Yes	43	4466.78	962.7	.73 (.53–1.00)	.058
Viral resistance	No	342	26 409.31	1295.0	Referent	
	Yes	31	2306.84	1343.8	1.00 (.69–1.45)	.99
Baseline HBeAg	Negative	244	17 229.92	1416.1	Referent	
	Positive	105	10 647.12	986.2	.69 (.55–.87)	.0017
Baseline ALT level	<ULN	30	3132.41	957.7	Referent	
	ULN-<2 × ULN	131	8385.30	1562.3	1.61 (1.08–2.40)	.019
	≥2 × ULN	214	17 757.79	1205.1	1.25 (.85–1.83)	.25
Baseline HBV DNA	<20	21	1951.04	1076.3	Referent	
	20–2 × 10^3	56	4713.28	1188.1	1.06 (.64–1.75)	.82
	2 × 10^3–2 × 10^4	33	3033.21	1088.0	.96 (.56–1.67)	.89
	2 × 10^4–2 × 10^5	65	4694.18	1384.7	1.22 (.74–1.99)	.44
	2 × 10^5–2 × 10^6	93	4864.40	1911.8	1.67 (1.04–2.68)	.034
	2 × 10^6–2 × 10^7	60	4113.06	1458.8	1.28 (.78–2.10)	.34
	2 × 10^7–2 × 10^8	31	3934.54	787.9	.70 (.40–1.21)	.20
	≥2 × 10^8	5	1268.07	394.3	.34 (.13–.91)	.032
Baseline platelet count[a]	≥150	128	17 528.39	730.2	Referent	
	<150	235	9693.39	2424.3	3.34 (2.69–4.14)	<.0001
Baseline ALB	≥3.0	313	26 231.82	1193.2	Referent	
	<3.0	36	1118.88	3217.5	2.82 (2.00–3.99)	<.0001
Baseline TB	≤1.05	252	22 242.75	1133.0	Referent	
	>1.05	114	6520.23	1748.4	1.54 (1.24–1.93)	.0001
Baseline AFP	≤10	205	20 758.24	987.6	Referent	
	>10	157	6591.63	2381.8	2.43 (1.97–2.99)	<.0001
Baseline CR	≤1.4	340	25 843.65	1315.6	Referent	
	>1.4	22	1851.02	1188.5	.93 (.61–1.44)	.75

Abbreviations: AFP, alpha fetoprotein (ng/mL); ALB, albumin (g/dL); ALT, alanine aminotransferase (U/L); CI, confidence interval; CR, creatinine (mg/dL); HBeAg, hepatitis B e-antigen; HBV DNA, hepatitis B viral deoxyribonucleic acid (IU/mL); HCC, hepatocellular carcinoma; TB, total bilirubin (mg/dL); ULN, upper limits of normal.

[a]Platelet count (1 × 10^3/μL).

Risk Stratification Using the REAL-B Score

We set group cutoffs based on the estimated 3-year risk as <1% (0–3 points), 1%–5% (4–7 points), and >5% (8–13 points) for the low-risk, intermediate-risk and high-risk groups, respectively. A total of 715 (35.2%), 1092 (53.8%), and 223 (11.0%) patients were classified as low-risk, intermediate-risk, and high-risk groups in the validation cohort, with 7, 90, and 70 HCC cases occurring during 10 years of follow-up, respectively. We examined the cumulative HCC incidence in the validation cohort based on the 3 REAL-B score groups. The cumulative HCC incidence for low-, intermediate-, and high-risk groups is noted in Supplemental Table 4. Our estimated annual incidence rate

by risk group using 3-years data was 0.091% (95% CI, .016%–.32%), 0.90% (95% CI, .59%–1.27%), and 5.82% (95% CI, 4.11%–8.09%), respectively. The model performed well when the estimated risk of HCC was compared with the observed risk as seen in Supplemental Table 4.

Low-Risk Patients With Hepatocellular Carcinoma

During follow-up of the low-risk group, a total of 15 and 7 HCC cases developed in the training and validation cohort, respectively (Supplemental Table 5). The cumulative incidence of HCC increased to 2% by 8 years of follow-up in both the training and validation cohorts (0.0203, 95% CI = .0116–.0334

Table 3. Multivariate Cox Regression Analysis for Independent Predictors of HCC in the Derivation Cohort (n = 5365)

Variables	Model 1[a]		Model 2[b]	
	Multivariate-Adjusted Hazard Ratio (95% CI)	*P* Value	Multivariate-Adjusted Hazard Ratio (95% CI)	*P* Value
Gender: male vs female	1.65 (1.21–2.26)	.0015	1.61 (1.22–2.14)	.0009
Age, per 10 year	1.76 (1.56–1.98)	<.0001	1.67 (1.50–1.85)	<.0001
Alcohol use	1.53 (1.15–2.02)	.0032	1.48 (1.14–1.92)	.0029
Cirrhosis at baseline	2.76 (2.11–3.61)	<.0001	3.10 (2.42–3.97)	<.0001
Ascites or encephalopathy	.99 (.59–1.66)	.96		
Diabetes	1.71 (1.27–2.31)	.0004	1.69 (1.28–2.22)	.0002
Baseline HBeAg seropositivity	1.12 (.84–1.49)	.46		
Baseline ALT (ref: <ULN)				
ULN-<2 × ULN	1.45 (.90–2.32)	.13		
≥2 × ULN	1.32 (.82–2.12)	.25		
Baseline platelet count <150[c]	1.61 (1.21–2.14)	.0011	1.42 (1.10–1.85)	.0083
Baseline ALB <3.0	1.01 (.63–1.60)	.98		
Baseline TB >1.05	1.20 (.93–1.57)	.17		
Baseline AFP >10	1.46 (1.11–1.93)	.0068	1.61 (1.27–2.04)	<.0001

Abbreviations: AFP, alpha fetoprotein (ng/mL); ALB, albumin (g/dL); ALT, alanine aminotransferase (U/L); CI, confidence interval; HBeAg, hepatitis B e-antigen; HCC, hepatocellular carcinoma; ULN, upper limit of normal; TB, total bilirubin (mg/dL).

[a]All significant variables in the univariate analysis with missing data <800 were included.

[b]Only those variables significant in Model 1 were included. Using 3 selection procedures (forward, backward, and stepwise) resulted in the same model with 7 parameters.

[c]Platelets (1 × 10^3/μL).

for training and 0.0206, 95% CI = .0086–.0430 for validation cohort). The mean age of these HCC patients was 41.9 years at baseline, and more than half were male (54.5%). In addition, most of these HCC patients did not have cirrhosis and/or diabetes at baseline or have a history of alcohol abuse. All patients had platelet counts >150 × 10^3/μL. The majority of these patients had AFP <10 ng/mL.

DISCUSSION

In this international collaborative study of over 8000 adult Asian patients treated for CHB, we found the REAL-B model to be a valid, precise, and reliable tool to determine the risk of developing HCC over time. In our model derivation, we found that 7 variables (age in 10-year increments, male gender, alcohol use, cirrhosis status at baseline, presence of diabetes mellitus, baseline platelet count <150 × 10^3/μL, and baseline AFP >10 ng/mL) accounted for 90% of the variance in developing HCC during 10 years of follow-up.

By combining these 7 variables, we were able to develop the REAL-B score, a continuous score that ranges from 0 to 13 to determine projected HCC risk at 3, 5, and 10 years. In the derivation group, a score of zero carried a 0.14%, 0.30%, and 0.71% risk for HCC, respectively, compared with a score of 13, which carried a risk of 65.60%, 90.37%, and 99.63% for developing HCC, respectively. The low-risk group consisted of scores 0–3 (<1% risk of HCC), the intermediate-risk group was 4–7 (1–5% risk of HCC), and the high-risk group was 8–12 (>5% risk for HCC).

We then validated these groups using the cumulative incidence of HCC in the validation group and found that our results closely tracked to the projected risk of developing HCC

as noted in our risk scoring. This fact was even evident when looking at the projected 10-year cumulative incidence of HCC, which was approximately 2% for the low-risk group, 19% for the intermediate, and 61% for the high-risk group—all scores closely tracking to the projected risk of developing HCC as noted in our risk scoring.

To further validate our model, we compared the REAL-B to the PAGE-B [14] model, which was originally developed to estimate the 5-year risk for HCC in white patients who received treatment for CHB with entecavir (ETV) or tenofovir. The PAGE-B is based on baseline patients' age, gender, and platelet count, which has now been validated in Asian cohorts by Kim et al [20] and Brouwer et al [14] [21]. We found that the REAL-B 3-year AUROC was significantly better than that of PAGE-B (0.83 vs 0.74, *p* < .0001), and this significant trend carried out to 10 years. The REAL-B score also performed better when compared with the 3- and 5-year results Kim et al [20] obtained when they tested PAGE-B in a treated Asian population (0.82 vs 0.78) [20]. Other studies showed a consistent AUROC of less than 0.75 for PAGE-B in HCC prediction for up to 7 years in Asian patients who received treatment for CHB [21–23].

One reason for the differences in AUROCs may be that the risk scores developed in Asian populations do not perform well in white populations or visa versa [24–26]. Therefore, it has been argued that the scores should only be applied to patients from populations similar to those in which the scores were originally developed [27].

However, Kim et al [28] recently developed the modified PAGE-B (mPAGE-B) to better capture the HCC risk in the treated Asian population. Their model contains 4 variables (age, gender, albumin, and platelet count). Although the mPAGE-B

Table 4.   Derivation of REAL-B Prediction Score for HCC Using The Derivation Cohort (n = 5365)

Parameter	Regression Coefficient	REAL-B Score
Male gender	0.48	Female: 0
		Male: 1
Age, per 10 years	0.51	18–29: 0
		30–39: 1
		40–49: 2
		50–59: 3
		60–69: 4
		70–79: 5
		≥80: 6
Alcohol use	0.39	No alcohol drinking: 0
		Alcohol drinking: 1
Cirrhosis at baseline	1.13	No cirrhosis: 0
		Cirrhosis: 2
Diabetes	0.52	No diabetes: 0
		Diabetes: 1
Baseline platelet count <150[a]	0.35	Platelet ≥150: 0
		Platelet <150: 1
Baseline AFP >10	0.48	AFP <10: 0
		AFP ≥10: 1

Abbreviations: AFP, alpha fetoprotein (ng/mL); HCC, hepatocellular carcinoma; REAL-B, Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV.

[a]Platelets (1×10^3/μL).

performed better than the PAGE-B (AUROC = 0.82 vs 0.72, respectively) in the original paper, the REAL-B still performed better than the mPAGE-B. The REAL-B AUROCs were significantly higher and greater than 0.81 at 3, 5, and 10 years compared with mPAGE B AUROCs of 0.77 at 3, 5, and 10 years ($P < .0001$). The better performance of REAL-B score may be attributed to the more diverse population used to develop the REAL-B model because the sample was obtained from 25 centers throughout Asia and the United States, and the sample size was 3 times the size of the mPAGE-B. In addition, randomization was used to generate the derivation and validation risk models.

Furthermore, our results do indicate that other parameters (alcohol use, cirrhosis, diabetes mellitus, and AFP) may have a greater impact on the accuracy of HCC risk prediction in Asian patients who received treatment for CHB. We found that patients with diabetes mellitus were 69% more likely to develop HCC compared with those without diabetes mellitus.

In fact, our findings are in line with a recent population-based study of CHB patients in Hong Kong that reported diabetes was an independent risk factor for HCC, even after hepatitis B surface antigen (HBsAg) seroclearance [29]. The fact that diabetes still has an impact even with treatment also helps to explain why the REAL-B model is a stronger prediction model [30–40]. When we compared the REAL-B with the GAG-HCC [15], a risk prediction model comprising similar variables except for diabetes mellitus, we found that the REAL-B performed significantly better. A finding suggested that diabetes is associated with the progression of severe liver outcomes in adults

with CHB, possibly through delaying HBsAg seroclearance or oncogenic effect of diabetes and metabolic syndrome, leading to a faster progression to cirrhosis, HCC, and death [30–40]. Therefore, the importance of the inclusion of alcohol use and diabetes mellitus cannot be overemphasized for the Asian population, because this population is markedly affected by the presence of these factors and may better capture the state of liver disease than albumin because many other factors influence serum albumin levels [41].

Table 5.   Projected HCC Risk for REAL-B Scores

Score	HCC Risk		
	3-Year	5-Year	10-Year
0	0.14%	0.30%	0.71%
1	0.23%	0.50%	1.19%
2	0.38%	0.83%	1.98%
3	0.63%	1.38%	3.28%
4	1.05%	2.29%	5.41%
5	1.75%	3.80%	8.87%
6	2.91%	6.26%	14.37%
7	4.81%	10.24%	22.82%
8	7.89%	16.50%	35.11%
9	12.83%	26.00%	51.42%
10	20.49%	39.51%	70.05%
11	31.80%	56.80%	86.64%
12	47.22%	75.37%	96.53%
13	65.60%	90.37%	99.63%

Abbreviations: HCC, hepatocellular carcinoma; REAL-B, Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV.

Table 6. Areas Under ROC Curves of Predicting 3-, 5-, and 10-Year HCC Risk Using REAL-B and PAGE-B Scores in the Validation Set (n = 2683)

	Area Under ROC Curve (95% Confidence Interval)		
Year of Prediction	REAL-B	PAGE-B	*P* Value
3 year	.83 (.78–.87)	.74 (.68–.79)	<.0001
5 year	.81 (.77–.85)	.73 (.69–.78)	<.0001
10 year	.81 (.78–.84)	.74 (.70–.78)	<.0001

Abbreviations: HCC, hepatocellular carcinoma; REAL-B, Real-world Effectiveness from the Asia Pacific Rim Liver Consortium for HBV; ROC, receive operating characteristics.

Our results may also appear somewhat similar to the recently published study by Hsu et al [21] on the development of a 3-year HCC prediction tool for Asians treated with ETV or tenofovir disoproxil fumarate based on the variables of cirrhosis, age, male gender, and diabetes mellitus (CAMD) using data derived from an insurance claims database. The c indices for HCC development in year 1, 2, and 3 of therapy were 0.83, 0.83, and 0.82, respectively, which dropped to 0.74, 0.75, and 0.75, respectively, in the validation cohort of patients from Hong Kong. However, the REAL-B outperformed the CAMD in several significant areas including a higher c index, better prediction up to 10 years, and being simpler to use. These differences should be considered when evaluating prediction scores for use in practice.

Although surprising, no viral factors were found to be HCC predictors so they were not included in the REAL-B risk score. We surmise that viral replication may have a lesser effect on predicting HCC because antiviral therapy is expected to change the natural history of CHB by inducing viral suppression. This distinction is an important difference, and another strength of this study compared with others—meaning that traditional risk factors may not be significant compared with other factors such as diabetes when determining risk of HCC in treated patients [30–40]. Therefore, we suggest that the predictors of HCC that may be most important in treated and virally suppressed patients are cirrhosis, platelet count, AFP (associated with necroinflammation and hepatocarcinogenesis), and diabetes mellitus, rather than HBeAg, HBV viral load, and ALT [42]. Some studies showed that HBsAg titer or HBV core-related antigen (HBcrAg) titer were associated with HCC development in patients with low HBV DNA levels [23, 27, 43, 44]. Unfortunately, because many study sites did not use these as routine clinical markers, we were unable to investigate HBsAg and HBcrAg titers on HCC development in this study. Their predictability deserves further investigation.

Finally, antiviral therapy decreases the risk of HCC, but it does not eliminate it, so surveillance remains essential for treated patients, even those who are at a low risk of developing HCC. We recognize the burden that implementing a surveillance system on all patients at risk for HCC may place on caretakers, patients, and the healthcare system. However, we do believe that the REAL-B score provides a rationale for individualized care such that for patients whose REAL-B score places them in the low-risk category,

the clinician and patient can discuss the best approach for their care, potentially improving adherence and effectiveness of HCC surveillance [4, 9]. Thus, we recommend further clinical trials on the use of risk scores for guiding HCC surveillance to understand how risk score stratification benefits patients. The analysis on cost effectiveness in such trials would also be important for clinical and health policy decision making. In addition, patients in the high-risk group based on a REAL-B score (score ≥8) carried an extremely high observed rate of HCC development despite antiviral therapy (cumulative HCC incidence at 3, 5, and 10 years: 17%, 25%, and 61%, respectively), warranting further studies focused on reducing HCC risk for this group of patients.

One limitation of this study is that we were unable to determine a treatment duration, which may impact outcomes. However, as noted in a study by Kim et al [45], duration of treatment may not be an issue, because in their multivariate analyses, it was cirrhosis that was independently associated with the risk of HCC. Another potential limitation of our study was that we were unable to determine the influence of HBV genotype and patient ethnicity on patient outcomes. However, because the REAL-B score discriminated HCC risk well, probably due to viral suppression, these factors may not be as important in determining outcomes. Family history of HCC may also play a role, but these data were not available in our study. Finally, the current model used only baseline predictors and not other on-treatment parameters to evaluate effectiveness of therapy; however, because some of our patients were treatment experienced at study entry, their on-treatment profiles could be used. Thus, we were able to demonstrate that, despite when treatment began, the REAL-B score had good discriminatory capability when used with baseline or on-treatment parameters.

CONCLUSIONS

The REAL-B score is an updated model based on 7 variables widely available clinically and ranges only from 0 to 13, with most variables categorized as 0 or 1, thus making it easily calculated in routine clinical settings. In predicting the risk for HCC, the REAL-B score in the validation cohort had very high AUROCs (>0.80) and performed significantly better than several previously developed models for treated and untreated CHB patients. In addition, the REAL-B score provided 3 distinct risk classification groups for the 10-year cumulative incidence of HCC, unlike other scores; however, we did find that even those considered

low risk carry some risk for HCC, and, therefore, they may still need surveillance, albeit less intensive such as once a year, but this awaits prospective validation. Thus, we suggest that the REAL-B score is a useful tool for determining a surveillance strategy for Asian patients who received treatment for CHB. Further research is needed for the REAL-B score and its performance in the non-Asian population that received treatment.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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