Research Article
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Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B

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Background & Aims: The risk of HCC during antiviral therapy in patients with chronic hepatitis B (CHB) is inadequately predicted by the scores built from untreated patients. We aimed at developing and validating a risk score to predict HCC in patients with CHB on entecavir or tenofovir treatment.

Methods: This study analysed population-wide data from the healthcare databases in Taiwan and Hong Kong to identify patients with CHB continuously receiving entecavir or tenofovir. The development cohort included 23,851 patients from Taiwan; 596 (2.50%) of them developed HCC with a three-year cumulative incidence of 3.56% (95% CI 3.26–3.86%). The multivariable Cox proportional hazards model found that cirrhosis, age (cirrhosis and age interacted with each other), male sex, and diabetes mellitus were the risk determinants. These variables were weighted to develop the cirrhosis, age, male sex, and diabetes mellitus (CAMD) score ranging from 0 to 19 points. The score was externally validated in 19,321 patients from Hong Kong.

Results: The *c* indices for HCC in the development cohort were 0.83 (95% CI 0.81–0.84), 0.82 (95% CI 0.81–0.84), and 0.82 (95% CI 0.80–0.83) at the first, second, and third years of therapy, respectively. In the validation cohort, the *c* indices were 0.74 (95% CI 0.71–0.77), 0.75 (95% CI 0.73–0.78), and 0.75 (95% CI 0.72–0.77) during the first three years, and 0.76 (95% CI 0.74–0.78) and 0.76 (95% CI 0.74–0.77) in the extrapolated fourth and fifth years, respectively. The predicted and observed probabilities of HCC were calibrated in both cohorts. A score <8 and >13 points identified patients at distinctly low and high risks.

Conclusions: The easily calculable CAMD score can predict HCC and may inform surveillance policy in patients with CHB during oral antiviral therapy.

Lay summary: This study analyses population-wide data from the healthcare systems in Taiwan and Hong Kong to develop and validate a risk score that predicts HCC during oral antiviral therapy in patients with CHB. The easily calculable CAMD score requires only simple information (*i.e.* cirrhosis, age, male sex, and diabetes mellitus) at the baseline of treatment initiation. With a scoring range from 0 to 19 points, the CAMD score discriminates the risk of HCC with a concordance rate around 75–80% during the first three years on therapy. The risk prediction can be extrapolated to five years on treatment with similar accuracy. Patients with a score <8 and >13 points were exposed to distinctly lower and higher risks, respectively.

Introduction

Hepatitis B virus (HBV) infection is the leading aetiology of hepatocellular carcinoma (HCC) around the globe.[1,2] The risk of HCC is a lifelong threat to patients with chronic hepatitis B (CHB).[3] Antiviral therapy using nucleos(t)ide analogues (NAs) inhibits HBV replication,[4–6] ameliorates hepatic inflammation,[7] reverses liver fibrosis,[8] and may attenuate hepatocellular carcinogenesis. We and others have shown that NA treatment is associated with risk reduction of HCC in patients with CHB.[9–12] In addition, the incidences of HCC decreased over the years while on therapies.[13–15] However, antiviral treatment does not completely eliminate the risk of HCC.[16] Beyond viral suppression, it remains unclear how to lower the risk further.

Prior to the current era of antiviral therapy, several scoring systems, such as CU-HCC, GAG-HCC, and REACH-B, have been built to predict the occurrence of HCC in the natural history of

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CHB.[17–19] Although these systems were externally validated and could attain a fairly good performance in untreated patients, they do not adequately predict HCC in patients on NAs.[20–22] Because long-term suppressive treatment with potent NA currently remains the therapeutic strategy of choice, there is a need for an accurate tool to stratify patients at different risks of HCC during antiviral treatment. Such knowledge is pivotal to inform clinical practice and to direct resource allocation.

Previous studies have shown that age, cirrhosis, male sex, platelet count, liver stiffness, and diabetes mellitus (DM) are risk factors of HCC in patients with CHB receiving NAs.[23–25] In contrast, pretreatment viral load, HBeAg status, HBsAg quantity, and aminotransferase level are not predictive for treated patients, in contrast to their roles established in untreated populations.[26–28] Recently, we analysed the national healthcare database in Taiwan to uncover the HCC risk factors in patients continuously receiving entecavir or tenofovir for CHB. The relative impact of these factors and their interaction were quantified through an analysis of the population-level data.[15] On the basis of these instrumental findings, the present study aimed at developing a simple scoring tool for risk prediction during continuous NA treatment in patients with CHB. External validation was carried out also using the population-wide data extracted from the state-run healthcare database in Hong Kong.

Materials and methods

Data source

This study analysed the National Health Insurance Research Database (NHIRD) in Taiwan and the Hospital Authority (HA) database in Hong Kong. Both databases contained data collected from in- and outpatient services in the respective healthcare systems. Their characteristics have been detailed in prior researches.[10,29] In brief, the NHIRD covers 99% of the 23.5 million Taiwan residents and the HA covers 70–80% of the 7.3 million Hong Kong citizens. They both applied the International Classification of Diseases, Ninth Revision, Clinical Modification codes, and their coding accuracy for major diseases has been validated.[30,31] Of note, the NHIRD exclusively consists of claim data, whereas the HA includes laboratory results as well. Data retrieval and analysis were approved by the research ethics committee of the National Health Research Institutes in Taiwan (EC-1030705-E) and the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee in Hong Kong (reference number 2016.595). The conduction of this study conformed to the Declaration of Helsinki.

Study populations

Data in a nationwide cohort of 23,851 adult (age >18 years) patients from Taiwan were used to construct the risk score (the development cohort). They were identified from all (N = 65,426) patients with CHB who received entecavir or tenofovir from 1 August 2008 through the end of 2013 (Fig. S1). Eligible patients needed to fill prescriptions of entecavir or tenofovir continuously (defined as gaps between fills <7 days) for at least three months. Patients were excluded if they had an existing diagnosis of any malignancy, decompensated cirrhosis, other viral hepatitis, or end-stage renal failure; developed HCC or passed way within three months of starting antiviral treatment; or had used lamivudine, adefovir, or telbivudine for ≥3 months.

Reimbursement for NA was tightly regulated in Taiwan.[10] Briefly, serum HBV DNA >2,000 IU/ml was mandatory in patients without hepatic decompensation, organ transplantation, or malignancy. Serum alanine aminotransferase (ALT) needed to exceed twofold the upper limit of the normal range (ULN) in those without cirrhosis. During the study period, the reimbursement continuously lasted for a maximum of three years unless a particularly serious condition was present.[32]

Through analysis of the territory-wide HA database, 19,321 Hong Kong patients were identified to serve as the validation cohort (Fig. S2). They fulfilled the same eligibility criteria, except for the enrolment period starting on 24 February 2004 and ending on 26 December 2016. In Hong Kong, reimbursement for NA also required HBV DNA >2,000 IU/ml and ALT more than twofold ULN in those without cirrhosis and detectable HBV DNA in those with cirrhosis.

Definitions of co-morbidity and potential risk factors

In principle, a disease was defined based on the International Classification of Diseases, Ninth Revision, Clinical Modification code in conjunction with a specific pharmacotherapy or intervention if applicable (Tables S1–S3). For instance, DM was defined by the prescription of anti-diabetes agents for at least three months in addition to the code. Drug exposure was defined by a filled prescription of at least three months. Because cirrhosis was incompletely coded in the HA database,[29] we supplemented the definition by fibrosis indices based on blood tests. In the Hong Kong cohort, red-blood-cell-distribution-width-to-platelet ratio >0.16.[33,34] Fibrosis-4 (FIB-4)>3.25[35] and aspartate-transaminase-to-platelet-ratio index >1 also defined the presence of cirrhosis.[36] This study excluded patients with decompensated cirrhosis, defined by the related clinical complications, including hepatic encephalopathy, acute variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome.[37]

Observation for the occurrence of HCC during antiviral therapy

Outcome observation commenced after the 'washout' period of the initial three months of antiviral therapy. Patients were followed up thereafter until HCC, death, cessation of the therapy (treatment interruption for ≥3 months), or the end of the study period, whichever occurred first. The data set for the development cohort ended on 1 January 2014, whereas the last day was 26 December 2016 in the validation cohort.

Both in Taiwan and Hong Kong, surveillance for HCC was performed using liver sonography with or without serum alpha-fetoprotein. The interval of sonography was six months in general and usually shorter for those with liver cirrhosis. Our prior studies have documented the validity of HCC diagnosis in both databases. In short, the accuracy of the HCC diagnosis was certified by the Registry for Catastrophic Illness Patient Database in the Taiwan cohort.[10,30] In the Hong Kong cohort, the accuracy and completeness of data collection, including the diagnosis of HCC, have been confirmed after the implementation of the clinical data framework.[31]

Data analysis and statistical tests

The incidence of HCC was estimated both by accounting for competing mortality and by the Kaplan–Meier method treating death as censoring. Given that the estimates were nearly identical between the two approaches (Fig. S3), we kept the latter. A Cox proportional hazards model was built to identify the risk predictors of HCC. The process of model building has been pre-

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viously detailed.[15] In brief, the model started with all variables available at the baseline of NA initiation. The final model was determined by the Akaike information criterion with backward elimination. We applied bootstrapping with the samples of 5,000, 10,000, 15,000, 20,000, and 25,000 patients. Each sample size was repeated for 1,000 times. We then calculated the shrinkage factor by averaging the calibration slopes of bootstrap samples in the original data to correct over-optimism in using the model selected by the whole development cohort.[38]

From a nomogram based on the regression coefficients, we developed the risk score by simplifying the assigned points to integers. The performance in discrimination was assessed by the time-varying receiver-operating-characteristic (ROC) curves for censored survival data.[39] The area under the ROC curve was computed to generate Harrell's *c* index. For the evaluation of calibration, the expected probability as predicted by the Cox model was plotted against the observed probability as estimated by the Kaplan–Meier method. We also compared our score with the well-established platelet, age, and gender-B (PAGE-B) score in the ROC curves. The PAGE-B score was calculated according to the published scoring formula.[40]

We performed two steps of the 'optimal cut-off approach' according to Youden's index to find the two cut-off points for risk stratification. In the first step, the entire development cohort was dichotomised by Youden's index. In the second step, the respective optimal cut-off point in each dichotomy was used to categorise patients into high-risk (above the upper cut-off), intermediate-risk (between the upper and lower cut-offs), and low-risk (below the lower cut-off) subgroups. The cumulative incidences of HCC among the three risk subgroups were compared.

The statistical tests were carried out by SAS (version 9.4; SAS Institute, Cary, NC, USA) and the R software programs (version 3.3.3). Continuous variables were expressed by the medians and the interquartile ranges (IQRs). Categorical variables were summarised by the percentage. Point estimates were accompanied with the 95% CIs. All tests were two tailed, and $p < 0.05$ defined the statistical significance.

For further details regarding the materials used, please refer to the CTAT table.

Results

Characteristics of the study populations

The two cohorts differed in the baseline characteristics from demographics, co-morbidity, to drug exposure (Table 1). The Taiwan cohort had more patients with cirrhosis, while the Hong Kong cohort was older. During a median follow-up of 25.8 (IQR 12.7–35.7) months, 596 (2.50%) patients in the Taiwan cohort developed HCC with a cumulative incidence of 3.56 (95% CI 3.26–3.86) at three years (Fig. 1A). The annual incidences in the first, second, and third years were 1.40%, 0.94%, and 0.72%, respectively. The validation Hong Kong cohort was followed up for a median of 33.3 (IQR 13.4–36.0) months, and 383 (1.98%) patients developed HCC within three years (Fig. 1B). During the first three years, the annual incidences of HCC were 1.03%, 0.74%, and 0.64%, respectively, with a cumulative incidence of 2.66% (95% CI 2.39–2.93%). The observation was extrapolated to five years in the Hong Kong cohort for external validation (Fig. S4). With a total of 478 cases, the cumulative incidence of HCC was 3.91% (95% CI 3.54–4.28%) at five years.

Regression models and the risk score to predict HCC occurrence

The final Cox proportional hazards model revealed that cirrhosis, age, male sex, and DM were the independent risk factors. Besides, cirrhosis and age significantly interacted with each other in the association with HCC. These variables, including the interaction between age and cirrhosis, were weighted to construct the cirrhosis, age, male sex, and diabetes mellitus (CAMD) score (Table 2). The weighted scores in the original model were not amended by the results of bootstrapping given that the shrinkage factor was found to be 0.990 (Table S4). The score ranged from 0 to 19 points.

Discrimination and calibration of the risk score

In the development cohort, the *c* indices of the CAMD score for HCC occurrence were 0.83 (95% CI 0.81–0.84), 0.82 (95% CI 0.81–0.84), and 0.82 (95% CI 0.80–0.83) at one, two, and three years, respectively (Fig. 2A). In the validation cohort, the *c* indices were 0.74 (95% CI 0.71–0.77), 0.75 (95% CI 0.73–0.78), and 0.75 (95% CI 0.72–0.77), respectively (Fig. 2B). We also extrapolated the CAMD score beyond three years with the *c*

Table 1. Baseline characteristics of the study participants with chronic hepatitis B on continuous entecavir or tenofovir therapy.

	Development, Taiwan (23,851)	Validation, Hong Kong (19,321)	*p* value
Baseline features			
Age (years)	47.5 (37.8–56.5)	52.1 (41.8–59.9)	<0.001
Male sex, n (%)	17,649 (74.00)	12,762 (66.05)	<0.001
Compensated cirrhosis	6,308 (26.45)	1,371 (7.10)	<0.001
Entecavir user, n (%)	22,971 (96.31)	18,403 (95.25)	<0.001
Tenofovir user, n (%)	880 (3.69)	918 (4.75)	<0.001
Diabetes mellitus	2,950 (12.37)	3,090 (15.99)	<0.001
Insulin independent, n (%)	1,715 (7.19)	2,392 (12.38)	<0.001
Insulin dependent, n (%)	1,235 (5.18)	698 (3.61)	<0.001
Hyperlipidaemia, n (%)	1,881 (7.89)	2,904 (15.03)	<0.001
Hypertension, n (%)	6,055 (25.39)	7,132 (36.91)	<0.001
Interferon exposure, n (%)	747 (3.13)	341 (1.76)	<0.001
Metformin exposure, n (%)	2,578 (10.81)	2,576 (13.33)	<0.001
Statin exposure, n (%)	2,413 (10.12)	2,604 (13.48)	<0.001

Observation for outcomes commenced after the 'washout period' (no HCC within the first three months of therapy in the study cohort), and continued until interruption of antiviral therapy (no filled prescription >3 months), death, or end of the study period. Continuous variables were expressed with the median along with the interquartile range and the categorical variables summarised with the exact number and the percentage. The between-cohort difference was examined by the Mann–Whitney *U* test for the continuous variables and the Chi-square test for the categorical ones.

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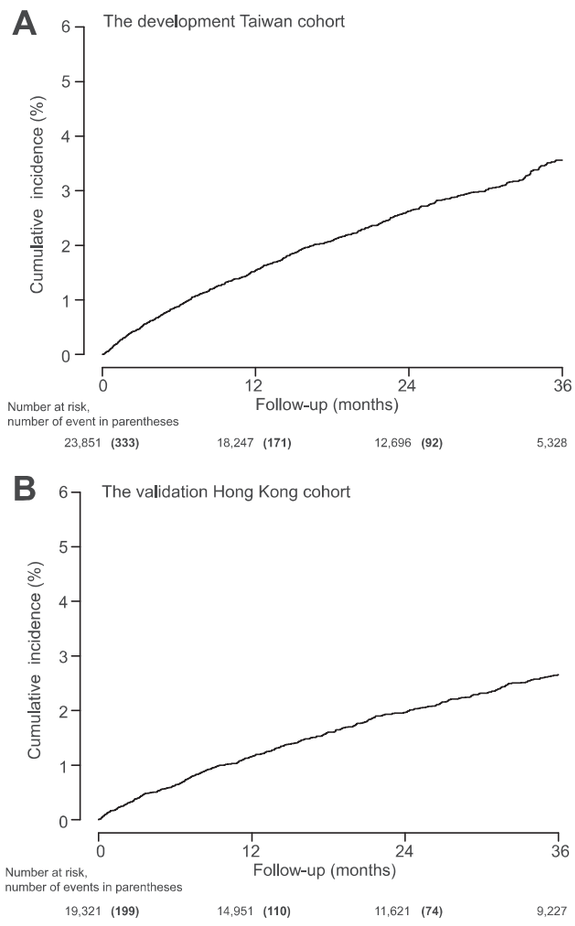

Fig. 1. The cumulative incidences of hepatocellular carcinoma. (A) Development Taiwan cohort. (B) Validation Hong Kong cohort.

Table 2. Multivariable Cox model for HCC occurrence and the CAMD score.

Variables	Adjusted hazard	CAMD score
Cirrhosis		
No cirrhosis	Reference	0
Cirrhosis with age <40 years	18.8 (95% CI 9.2–38.7)	10
Cirrhosis with age ≥40 years	4.6 (95% CI 3.8–5.6)	6
Age (years)		
<40	Reference	0
40–49	4.5 (95% CI 2.4–8.5)	5
50–59	9.0 (95% CI 4.8–16.8)	8
≥60	15.9 (95% CI 8.5–29.7)	10
Male sex		
Female sex	Reference	0
Male sex	1.8 (95% CI 1.4–2.2)	2
Diabetes mellitus		
Not diabetic	Reference	0
Diabetic	1.3 (95% CI 1.1–1.6)	1

The regression coefficients in the multivariable Cox model were weighted to generate the risk score. CAMD, cirrhosis, age, male sex, and diabetes mellitus; HCC, hepatocellular carcinoma.

indices of 0.76 (95% CI 0.74–0.78) and 0.76 (95% CI 0.74–0.77) at four and five years, respectively (Fig. 2B).

The calibration chart illustrated the predicted *vs.* the observed incidences of HCC (Fig. 3). It was well calibrated during the three-year treatment period in the development cohort (Fig. 3A). In the validation cohort, the calibration was illustrated during the first three years and could also be extrapolated to five years (Fig. 3B). The predicted HCC incidences according to each point of the CAMD score were detailed in the first three years on therapy (Table 3).

The ROC curve of the CAMD score was plotted against that of the PAGE-B score in 17,984 Hong Kong patients who had the baseline platelet data (Fig. 4). In these patients, the *c* indices of the CAMD and PAGE-B scores were 0.74 (95% CI 71–0.76) *vs.* 0.73 (95% CI 0.70–0.75) at three years ($p = 0.33$; Fig. 4A), and 0.75 (95% CI 0.73–0.77) *vs.* 0.74 (95% CI 0.72–0.76) at five years ($p = 0.26$, Fig. 4B), respectively.

Application of the CAMD score for risk stratification

The two cut-off points were set at 8 and 13 points to stratify patients into low-, intermediate-, or high-risk subgroups (Fig. 5). In the development cohort, the three-year cumulative incidences of HCC in patients with a CAMD score <8, 8–13, and >13 points were 0.27% (95% CI 0.12–0.42%), 2.40% (95% CI 2.03–2.78%), and 10.75% (95% CI 9.68–11.81%), respectively (Fig. 5A). The average annual incidences among the three risk subgroups during the first three years on therapy were 0.09% (95% CI 0.05–0.16%), 0.85% (95% CI 0.73–0.99%), and 4.06% (95% CI 3.69–4.47%), respectively ($p < 0.0001$).

In the validation cohort, the three-year cumulative incidences of HCC with a CAMD score <8, 8–13, and >13 points were 0.72% (95% CI 0.49–0.94%), 3.35% (95% CI 2.93–3.76%), and 9.17% (95% CI 7.29–11.05%), respectively (Fig. 5B). The corresponding average annual incidences were 0.25% (95% CI 0.18–0.34%), 1.21% (95% CI 1.07–1.37%), and 3.30% (95% CI 2.66–4.08%), respectively. The CAMD score was externally validated to show the five-year cumulative incidences of 0.91% (95% CI 0.64–1.19%), 4.95% (95% CI 4.37–5.52%), and 13.62% (95% CI 11.21–16.04%) among the low-, intermediate-, and high-risk subgroups, respectively (Fig. S5).

Discussion

Through an analysis of population-wide data from the independent healthcare systems in Taiwan and Hong Kong, we develop and validate a risk score to predict the risk of HCC in patients with CHB on entecavir or tenofovir therapy. On the basis of simple information (*i.e.* the status of cirrhosis, age, biological sex, and DM) that is readily available in everyday practice, the developed CAMD score accurately stratifies patients into distinct risk subgroups with a scoring range from 0 to 19 points. A score lower than 8 points that predicts an average annual incidence below 0.3% may spare the patients from HCC surveillance while on therapies; this might obviate diagnostic workup that is potentially harmful and hardly cost-effective.[41] In contrast, a score higher than 13 points not only heralds the necessity of intensive surveillance to detect HCC at an early stage, but also indicates the unmet need of novel strategies beyond viral suppression to reduce the risk further.[42]

Our risk score was developed using data from all eligible patients in the entire Taiwan population, and therefore, mitigated the concern of sampling bias commonly seen in researches that were confined to selected samples. Furthermore, the CAMD score was externally validated in a totally independent Hong Kong population to confirm its generalisability. The two cohorts were dissimilar in the baseline demographics and comorbidities, probably reflecting differences in the population

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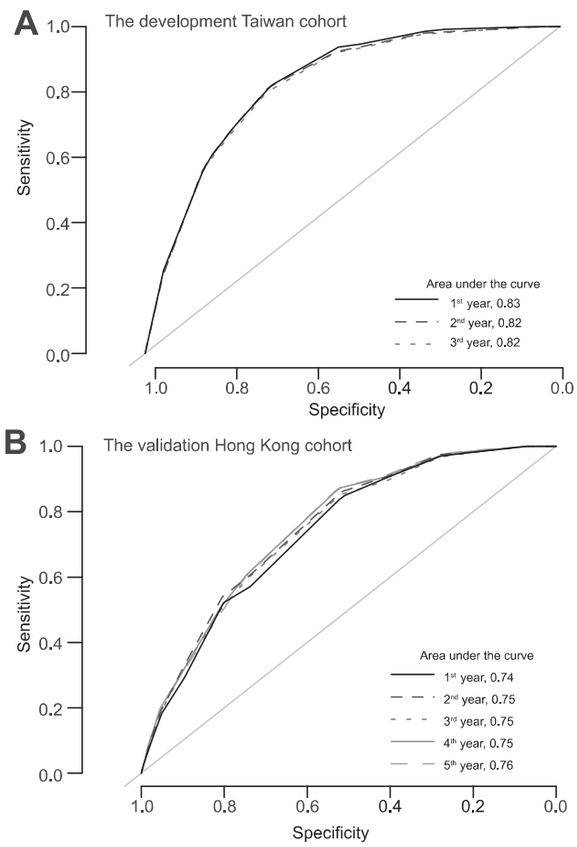

Fig. 2. Receiver-operating-characteristic curves of the CAMD score to predict hepatocellular carcinoma during the first three years on therapy. (A) Development Taiwan cohort. (B) Validation Hong Kong cohort, in which the prediction was extrapolated to five years. CAMD, cirrhosis, age, male sex, and diabetes mellitus.

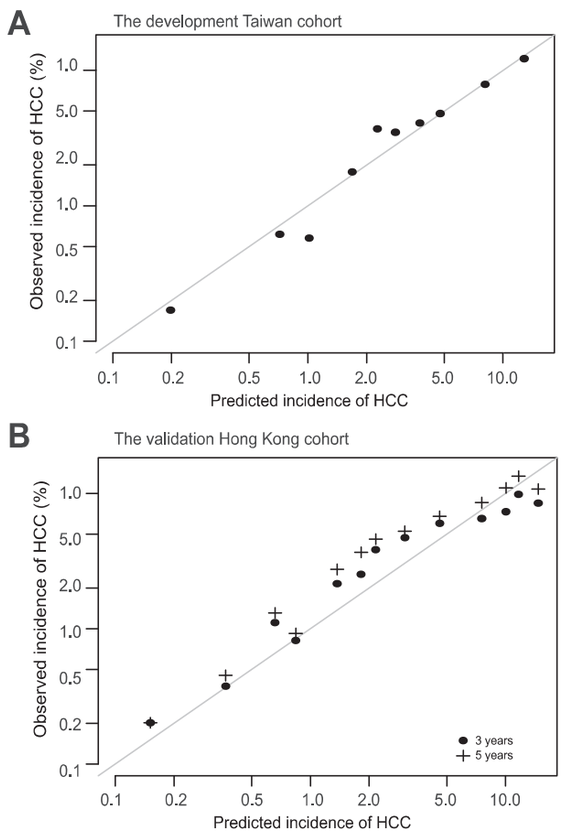

Fig. 3. Predicted incidence of hepatocellular carcinoma according to the CAMD score was calibrated with the observed incidence as estimated by the Kaplan–Meier method. (A) Development Taiwan cohort. (B) Validation Hong Kong cohort, in which the calibration was externally validated to five years. CAMD, cirrhosis, age, male sex, and diabetes mellitus.

composition, healthcare policy, diagnostic definition, disease pattern, or care-seeking behaviour between the two countries. Notably, the proportion of liver cirrhosis in the Hong Kong cohort (7.10%) was significantly lower than that in the Taiwan counterpart (26.45%). This might, at least in part, result from the insufficient coding of cirrhosis in the HA database.[29] Regardless, the concordance indices of 0.74–0.76 in the validation cohort confirm that the CAMD score is generalisable to different populations of previously untreated patients with CHB during the NA treatment.[43]

Older age, liver cirrhosis, male sex, and DM have all been reported as the risk factors of HCC in patients with CHB with or without oral antiviral therapy.[16,21–23] Nonetheless, their relative impact was less clear. Thanks to the statistical power as a result of a large sample size, our model was able to weigh in each risk factor and quantify the interaction among them. Such quantitative knowledge is essential for an accurate prediction. In daily practice, the diagnosis of cirrhosis is usually made by typical sonographic features, and may be complemented with radiographic, endoscopic, or laboratory data.[44] Pathological confirmation is seldom available. Given that our study extracted data from the real-world practice, cirrhosis was clinically defined without tissue proof in most patients. Although a clinical diagnosis could be subjective and misclassification was possible, a distinctly higher HCC risk in patients with cirrhosis defined in the study conferred additional convergent validity to the definition. In light of our results along with the existent literature,[16] a clinical diagnosis of cirrhosis remains informative for the risk prediction of HCC in the present era of antiviral therapy.

Our CAMD score is uniquely free of any specific laboratory test, as compared with other risk scores for patients with NA-treated CHB.[40,45–48] In fact, it relies on baseline information so readily available that few patients had to be excluded because of missing data, which is a common source of bias in retrospective analyses. This may be regarded as an advantage because the score is hence applicable to literally every patient on NA treatment for CHB. In everyday practice, not all patients were routinely tested for platelet count, serum alpha-fetoprotein, ALT levels, HBeAg status, HBsAg quantity, viral genotype, and HBV DNA at exact time points along the course of treatment. Despite lacking laboratory components, our CAMD score appeared to be similarly accurate with the well-established PAGE-B score that has been validated in Caucasian and Asian populations.[49]

The risk of HCC in patients with CHB is not static during the antiviral therapy. We and others have shown that the HCC incidence significantly decreased over the years on treatment.[13–15] However, it remains elusive whether a prolonged therapy can eventually eliminate the risk, and if so, how long the regimen should be. Recently, Papatheodoridis *et al.*[14] reported that a substantial risk of HCC still lingered after the first five years of

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Table 3. Predicted incidence of HCC according to each point of the CAMD score in the first three years on continuous entecavir or tenofovir therapy.

Score	First year (%) (95% CI)	Second year (%) (95% CI)	Third year (%) (95% CI)
1	0.075 (0.052–0.099)	0.131 (0.090–0.172)	0.181 (0.125–0.237)
2	0.098 (0.069–0.127)	0.170 (0.121–0.220)	0.236 (0.168–0.304)
3	0.128 (0.092–0.163)	0.222 (0.162–0.282)	0.307 (0.225–0.389)
4	0.166 (0.123–0.209)	0.289 (0.217–0.361)	0.399 (0.300–0.498)
5	0.216 (0.164–0.268)	0.376 (0.289–0.462)	0.520 (0.401–0.638)
6	0.281 (0.219–0.343)	0.489 (0.386–0.592)	0.676 (0.535–0.818)
7	0.366 (0.292–0.440)	0.636 (0.514–0.758)	0.880 (0.713–1.047)
8	0.476 (0.388–0.564)	0.828 (0.684–0.972)	1.145 (0.948–1.342)
9	0.620 (0.515–0.724)	1.077 (0.909–1.245)	1.490 (1.261–1.720)
10	0.806 (0.683–0.930)	1.402 (1.206–1.597)	1.939 (1.673–2.205)
11	1.049 (0.904–1.195)	1.824 (1.598–2.050)	2.523 (2.217–2.830)
12	1.366 (1.193–1.538)	2.374 (2.112–2.636)	3.284 (2.930–3.638)
13	1.777 (1.569–1.985)	3.089 (2.782–3.397)	4.273 (3.860–4.687)
14	2.313 (2.057–2.568)	4.020 (3.650–4.391)	5.561 (5.064–6.058)
15	3.009 (2.685–3.334)	5.231 (4.765–5.698)	7.237 (6.610–7.864)
16	3.916 (3.488–4.345)	6.808 (6.187–7.429)	9.417 (8.580–10.255)
17	5.096 (4.512–5.681)	8.859 (7.993–9.725)	12.255 (11.081–13.429)
18	6.632 (5.813–7.451)	11.529 (10.282–12.775)	15.948 (14.249–17.646)
19	8.630 (7.466–9.795)	15.002 (13.184–16.821)	20.753 (18.264–23.242)

CAMD, cirrhosis, age, male sex, and diabetes mellitus; HCC, hepatocellular carcinoma.

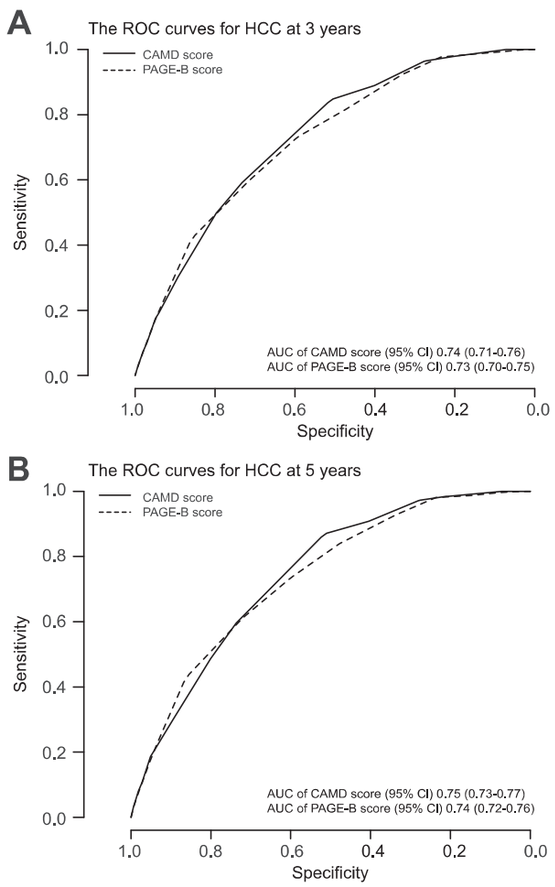

Fig. 4. Receiver-operating-characteristic curves of the CAMD and PAGE-B scores to predict HCC during the entecavir or tenofovir therapy in 17,984 Hong Kong patients with platelet data available at baseline. (A) Three years. (B) Five years. CAMD, cirrhosis, age, male sex, and diabetes mellitus; PAGE-B, platelet, age, and gender-B.

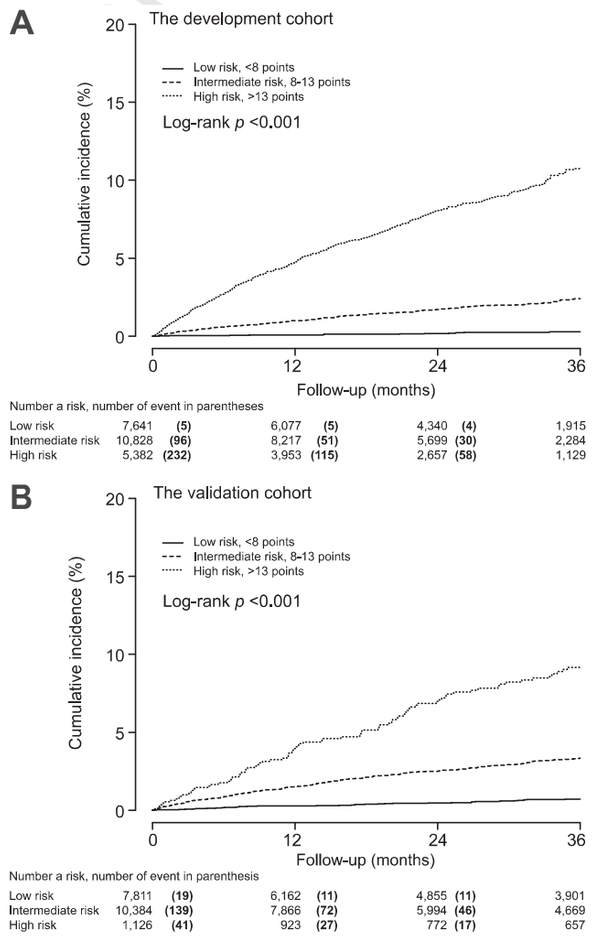

Fig. 5. CAMD score stratified patients into distinct subgroups at a low, intermediate, or high risk of hepatocellular carcinoma during entecavir or tenofovir therapy. (A) Development cohort. (B) Validation cohort. The log-rank test was used for statistical comparison. CAMD, cirrhosis, age, male sex, and diabetes mellitus.

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entecavir or tenofovir treatment in patients with liver cirrhosis or aged above 50 years at baseline. They further demonstrated that age, platelet count at baseline and Year 5, and liver stiffness at Year five were associated with HCC development in the 5–10 years of treatment. Therefore, the excessive risks predicted by old age and liver cirrhosis will probably persist throughout the first decade on therapy. Our study validated that the CAMD score could predict HCC risk in the first five years of therapy. Its performance for late HCC after a longer period of treatment warrants further research.

How the risk of HCC may change following NA cessation in patients with CHB is currently unknown. The risk prediction after cessation of oral antiviral therapies may differ from that during the treatment, insomuch as the reactivation of viral replication almost always follows treatment discontinuation,[50,51] and viral remission most likely underlies the mechanism through which NA therapies prevent hepatocellular carcinogenesis.[52,53] Therefore, we explicitly censored the observation when the treatment was discontinued. Exclusion of the off-NA periods avoided an erroneous message that the risk prediction should have remained the same whether or not patients stopped the treatment. Novel knowledge is urgently needed to elucidate how cessation of NA therapies may influence the risk and risk estimation of HCC.

We recognise the following limitations in our study. First, patient management might vary among physicians or institutions. Nonetheless, the study cohorts reflect the daily practice for treated patients with CHB to receive HCC surveillance in the real world. Second, the healthcare policy in Taiwan limited the observation duration in the development cohort. Extending the observation beyond three years in Taiwan patients would have introduced a selection bias, because only those with particularly serious conditions were reimbursed for longer than three years of NA treatment.[32] Third, the Taiwan database did not contain laboratory results, and not all Hong Kong patients had comprehensive blood tests. We cannot rule out the possibility that adding certain laboratory parameters might improve the CAMD score. Although previous studies have shown that baseline HBV features, such as viral genotype, viral load, and HBeAg status, were not predictive of HCC in patients on continuous NA therapy,[23,24] whether the current scoring system may be augmented by the additional laboratory data require future research. Finally, both cohorts enrolled Asian patients with serum viral load higher than 2,000 IU/ml and ALT elevation above twofold of ULN or those with liver cirrhosis. Caution is needed before extrapolation to Caucasian patients or those with a milder disease.

In summary, this study analyses the healthcare databases covering Taiwan and Hong Kong populations to develop and validate the CAMD score to predict HCC in patients with CHB on continuous entecavir or tenofovir treatment. The score requires simple information that is readily available in all treated patients. By stratifying patients at different risks of HCC, the easily applicable score may inform the clinical practice and healthcare policy in the era of antiviral treatment for CHB.

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Conflict of interest

Y-CH has served as an advisory committee member for Gilead Sciences. He also reported having received lecture fees from AbbVie, Bristol-Myers Squibb, and Gilead Sciences. VW-SW has served as an advisory committee member for AbbVie, Roche, Novartis, Gilead Sciences, and Otsuka. He has also served as a speaker for AbbVie, Bristol-Myers Squibb, Roche, Novartis, Abbott Diagnostics, and Echosens. GL-HW has served as an advisory committee member for Gilead Sciences. She has also served as a speaker for Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Furui, Gilead Sciences, Janssen, Otsuka, and Roche. All other authors have nothing to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Concept: Y-CH, M-SW, J-TL, C-YW. Design: Y-CH, TC-FY, VW-SW, HBE, GL-HW, C-YW. Data analysis: SJH, TC-FY. Data interpretation: Y-CH, SJH, VW-SW, YTH, HBE, TYL, GL-HW, C-YW. Manuscript drafting: Y-CH, TC-FY. Manuscript edition and final approval: all authors. Guarantor of the article: Y-CH

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.02.032.

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