



# Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score

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## Summary

**Background** Therapy for chronic hepatitis B reduces the risk of progressing to hepatocellular carcinoma (HCC); however, there is no suitable and accurate means to assess risk. This study aimed to develop and validate a simple scoring system to predict HCC risk in patients with chronic hepatitis B.

**Methods** The development cohort consisted of 3584 patients without cirrhosis from the community-based Taiwanese REVEAL-HBV study (of whom 131 developed HCC during follow-up), and a validation cohort of 1505 patients from three hospitals in Hong Kong and South Korea (of whom 111 developed HCC during follow-up). We used Cox multivariate proportional hazards model to predict risk of HCC at 3, 5, and 10 years. Variables included in the risk score were sex, age, serum alanine aminotransferase concentration, HBeAg status, and serum HBV DNA level. We calculated the area under receiver operating curve (AUROC) and calibration of predicted and observed HCC risk.

**Findings** A 17-point risk score was developed, with HCC risk ranging from 0·0% to 23·6% at 3 years, 0·0% to 47·4% at 5 years, and 0·0% to 81·6% at 10 years for patients with the lowest and highest HCC risk, respectively. AUROCs to predict risk were 0·811 (95% CI 0·790–0·831) at 3 years, 0·796 (0·775–0·816) at 5 years, and 0·769 (0·747–0·790) at 10 years in the validation cohort, and 0·902 (0·884–0·918), 0·783 (0·759–0·806), and 0·806 (0·783–0·828), respectively, after exclusion of 277 patients in the validation cohort with cirrhosis. Predicted risk was well calibrated with Kaplan-Meier observed HCC risk.

**Interpretation** A simple-to-use risk score that uses baseline clinical variables was developed and validated. The score accurately estimates the risk of developing HCC at 3, 5, and 10 years in patients with chronic hepatitis B. Clinicians can use this score to assess risk of HCC in patients with chronic hepatitis B and subsequently make evidence-based decisions about their clinical management.

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## Introduction

Chronic hepatitis B is a major cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide, accounting for around 1 million deaths every year.<sup>1</sup> The risk of chronic hepatitis B progression to HCC can be reduced by hepatitis B virus (HBV) therapy, as suggested by a meta-analysis.<sup>2</sup> The identification and classification of patients who are at high risk of developing HCC is therefore important, and will allow timely intervention in those who will most benefit.<sup>3</sup>

Known risk factors for disease progression in chronic hepatitis B can be broadly divided into host, viral, and environmental factors.<sup>4</sup> Host factors include age, sex, genetic susceptibility, family history, obesity, and immune status. Findings from a Korean study<sup>3</sup> showed that age, male sex, and raised alanine aminotransferase (ALT) concentration were prognostic for HCC development. Viral factors can include HBeAg status, HBV DNA level, genotype, mutants, and co-infection. HBsAg seropositivity is an important risk factor for HCC, and HBeAg seropositivity has been associated with an increased risk of developing HCC.<sup>4,5</sup> Increasing HBV DNA levels have

been associated with a stepwise increase in HCC risk, with high HBV DNA associated with an increased risk of HCC.<sup>6–8</sup> Findings from several studies have shown that the risk of liver-related mortality is increased with even slight increases in serum ALT.<sup>9,10</sup> Gradual and cumulative liver damage caused by low level viraemia, and indicated by small rises in ALT concentrations, could be the pathway for severe complications and disease progression in Asian patients with chronic hepatitis B.<sup>10</sup> HBV genotype is a contentious risk factor for HCC. A previously reported risk between HCC and HBV genotype C<sup>11,12</sup> could be attributable to close associations with genotype C and core promoter mutations,<sup>7</sup> which are an independent risk factor.<sup>13</sup> Furthermore, a meta-analysis<sup>14</sup> has suggested that basal core promoter mutants might be an important risk factor. Environmental factors are the most difficult to quantify clinically, and include alcohol use, cigarette smoking, chemical carcinogens, and aflatoxin exposure.

The primary aim of therapy for chronic hepatitis B is to prevent disease progression to liver cirrhosis, HCC, and death.<sup>15</sup> Although there is general consensus in guidelines

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about when and how to treat this disease and who should be treated, several other areas of management are controversial.<sup>16</sup> Definitions for normal ALT, appropriate serum HBV DNA cutoff points, and the suitability of liver biopsy differ between guidelines.<sup>15,17–19</sup> There is no standardised and accurate guidance about assessment of HCC risk in chronic hepatitis B. Several HBV risk scores have been published; however, most are limited by population size.<sup>3,7,20,21</sup> A published nomogram had high potential to be adapted into a simplified clinical instrument, but it has not been externally validated.<sup>20</sup>

The successful development and use of risk calculators in cardiovascular disease have shown the benefits of such instruments to both patients and physicians.<sup>22,23</sup> All reliable, easily accessible, and accurate clinical factors predicting complications from chronic hepatitis B need to be identified and consolidated. This process could facilitate the timely identification of high-risk patients for whom treatment is still viable. The REACH-B (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B) study aimed to develop and validate a simple, clinically useful long-term prediction score, to identify the risk of progression to HCC in patients with chronic hepatitis B by use of a snapshot risk profile consisting of currently used non-invasive parameters.

## Methods

### Study populations for model derivation

The patient population used to develop the risk score (development cohort) consisted of patients from the population-based prospective REVEAL-HBV database, which has been described previously.<sup>8</sup> Briefly, 3584 patients aged 30–65 years who were HBsAg seropositive, were anti-HCV seronegative, did not have cirrhosis, and had serum HBV DNA measured at study entry were used for this study. Patients did not receive antiviral treatment during the median follow-up of 12.0 years (IQR 11.5–12.4), during which time 131 developed HCC.

The population used to validate the risk score (validation cohort) was a hospital-based composite international cohort. This cohort consisted of 1505 patients from three independent university hospital databases, with a mean follow-up of 7.3 years. Patients from the University of Hong Kong (UHK; n=820) were aged 14–83 years and were followed up for a mean of 6.3 years; those from the Chinese University of Hong Kong (CUHK; n=426) were aged 12–80 years and followed up for a mean of 9.4 years; and those from Yonsei University Hospital (YUH; n=259) were aged 24–70 years and followed up for a median of 7.0 years (IQR 5.0–10.3). 111 patients from the validation cohort developed HCC during follow-up (46 at CUHK; 40 at UHK; 25 at YUH). No patients received antiviral therapy throughout the follow-up period for this study.

	Development cohort (n=3584)	Validation cohort (n=1505)	p value
HCC	131 (3.7%)	111 (7.4%)	..
Median duration of follow-up (years; IQR)	12.0 (11.5–12.4)	7.0 (5.0–10.3)	..
Men	2198 (61.3%)	1016 (67.5%)	<0.0001
Age (years)			
Mean (SD)	45.7 (9.8)	41.9 (13.5)	<0.0001
Range	30–65	12–83	..
<30	0	298 (19.8%)	<0.0001
30–39	1204 (33.6%)	361 (24.0%)	..
40–49	997 (27.8%)	470 (31.2%)	..
50–59	1032 (28.8%)	205 (13.6%)	..
60–64	351 (9.8%)	71 (4.7%)	..
≥65	0	100 (6.6%)	..
HBeAg negative	3039 (84.8%)	919 (61.1%)	<0.0001
ALT concentration			
Mean (SD) of log(ALT)	1.10 (0.34)	1.70 (0.37)	<0.0001
Range (U/L)	1–765	4–1251	..
<15 U/L	2182 (60.9%)	56 (3.7%)	<0.0001
15–44 U/L	1199 (33.5%)	679 (45.1%)	..
≥45 U/L	203 (5.7%)	770 (51.2%)	..
<0.5×ULN*	2822 (78.7%)	293 (19.5%)	<0.0001
0.5–1×ULN*	566 (15.8%)	568 (37.7%)	..
>1×ULN*	196 (5.5%)	644 (42.8%)	..
HBV DNA level (copies per mL)			
<300	869 (24.3%)	218 (14.5%)	<0.0001
300–9999	1151 (32.1%)	184 (12.2%)	..
10 000–99 999	629 (17.6%)	178 (11.8%)	..
100 000–999 999	333 (9.3%)	250 (16.6%)	..
≥10 <sup>6</sup>	602 (16.8%)	674 (44.8%)	..
No liver cirrhosis at entry	3584 (100.0%)	1228 (81.6%)	<0.0001

Data are number (%) unless otherwise indicated. HCC=hepatocellular carcinoma. ALT=alanine aminotransferase. ULN=upper limit of normal. HBV=hepatitis B virus. \*ULN=45 U/L in datasets from REVEAL, 58 U/L in datasets from Chinese University of Hong Kong, 45 U/L in datasets from Yonsei University Hospital, and 58 U/L (men) and 36 U/L (women) in datasets from the University of Hong Kong.

**Table 1:** Baseline characteristics of development and validation cohorts

All validation centres used ultrasonographic evidence plus other clinical and serological data including ascites, varices, hypersplenism, hypoalbuminaemia, and the ratio of aspartate aminotransferase to platelet count to define patients with cirrhosis. HCC was identified in the development cohort by histopathological confirmation; detection of a positive lesion with at least two imaging techniques (abdominal ultrasound, angiogram, or CT); or detection with one imaging technique coupled with an  $\alpha$ -fetoprotein concentration greater than 400  $\mu$ g/L. Identification of HCC cases in centres comprising the validation cohort was by positive histology or increased  $\alpha$ -fetoprotein (>50  $\mu$ g/L or a rising trend >20  $\mu$ g/L), combined with identification of HCC features by CT, MRI, or hepatic angiogram.

This study was approved by the institutional review board of the College of Public Health, National Taiwan

	Hazard ratio (95% CI)	β coefficient	p value	Risk score
<b>Sex</b>				
Female	1.00	1.00	..	0
Male	2.2 (1.4-3.4)	0.78798	0.0004	2
<b>Age (years)</b>				
Per 5 years	1.64 (1.48-1.81)	0.49295	<0.0001	1
30-34	..	..	..	0
35-39	..	..	..	1
40-44	..	..	..	2
45-49	..	..	..	3
50-54	..	..	..	4
55-59	..	..	..	5
60-65	..	..	..	6
<b>ALT (U/L)</b>				
<15	1.00	1.00	..	0
15-44	1.5 (1.0-2.2)	0.38823	0.0559	1
≥45	2.6 (1.5-4.4)	0.96311	0.0003	2
<b>HBeAg</b>				
Negative	1.00	1.00	..	0
Positive	2.3 (1.3-3.8)	0.81308	0.0026	2
<b>HBV DNA level (copies per mL)</b>				
<300 (undetectable)	1.00	1.00	..	0
300-9999	1.1 (0.4-2.9)	0.11648	0.8063	0
10 000-99 999	3.7 (1.6-8.5)	1.31467	0.0017	3
100 000-999 999	9.7 (4.4-21.3)	2.27028	<0.0001	5
≥10 <sup>6</sup>	8.1 (3.5-19.0)	2.09258	<0.0001	4*

ALT=alanine aminotransferase. HBV=hepatitis B virus. \*The risk score attributed to HBV DNA ≥10<sup>6</sup> copies per mL was less than that for HBV DNA of 100 000-999 999 copies per mL because most patients with HBV DNA ≥10<sup>6</sup> copies per mL were also HBeAg positive, thus sharing the associated higher score for this category.

**Table 2: β coefficient and hazard ratio estimation from development cohort with multivariate Cox proportional hazards model and corresponding risk score**

University in Taipei, Taiwan. All patients provided written informed consent.

**Rationale for risk factor inclusion**

Risk factors identified for inclusion were those previously shown to be contributing factors and important long-term risk predictors in the development of HCC.<sup>8</sup> Factors chosen were those easily measured by widely available, non-invasive clinical tests. Risk factors that met these criteria and were common to all databases comprising the development and validation cohorts were sex, age, serum ALT concentration, HBeAg status, and serum HBV DNA level (by PCR assay).

**Statistical analyses**

All statistical analyses were done with SAS (version 9.1). Development of the risk score had three steps. First, a Cox proportional hazards model was used to estimate the β regression coefficient, p value, and hazard ratio and its 95% CI for each of the selected risk predictors. We also estimated baseline disease-free probabilities at 3, 5, and 10 years. Second, the regression coefficient in the Cox

proportional hazards model of each risk predictor was divided by the regression coefficient for 5-year increase of age, and was rounded into an integer value to generate the risk score. Third, the projected HCC risk was estimated with the equation:

$$1 - P_0^{\exp(\Sigma \beta_{age} \times score - \Sigma \beta_i \times M_i)}$$

where P<sub>0</sub> is the baseline disease-free probability; β<sub>age</sub> is the β regression coefficient for 5-year increment of age; score is the cumulative risk score to be projected; β<sub>i</sub> is the β regression coefficient for the ith covariate; and M<sub>i</sub> is the mean level of the ith covariate. Projected HCC risk was calculated for three timepoints (3, 5, and 10 years) for all cumulative risk scores possible with this method (range 0-17).

Model validation had two steps: discrimination and calibration. Discrimination was assessed with the receiver operating characteristic (ROC) curve, area under ROC (AUROC) curves, sensitivity, and specificity. A cumulative risk score was calculated for every patient in the validation cohort. ROC curves were plotted with 1-specificity and sensitivity measured along the horizontal and vertical axes, respectively, with all possible cumulative risk scores in the validation cohort as cutoff points for the prediction of HCC events within 3, 5, and 10 years of follow-up. For the assessment of calibration, we calculated observed HCC risk with the Kaplan-Meier method for patients in the validation cohort with the same cumulative risk scores. When the number of HCC cases in a group with the same cumulative risk score was sparse, this group was combined with the neighbouring group of cumulative risk score to secure a stable estimate of HCC risk observed by the Kaplan-Meier method. Kaplan-Meier estimates were plotted against the mean predicted risk in the group to form a calibration chart.

**Role of the funding source**

The sponsors of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

Table 1 shows the baseline characteristics of the development and validation cohorts. In both cohorts, most patients were men and HBeAg negative. As per the entry criteria, all patients in the development cohort did not have cirrhosis at baseline, compared with 82% (1228 of 1505) of patients in the hospital-based validation cohort. Patients in the development cohort differed from those in the validation cohort in terms of the distribution of sex, age, viral load, HBeAg status, and ALT and HBV DNA levels (table 1).

Table 2 shows  $\beta$  regression coefficient estimation with the multivariate Cox proportional hazards model. Table 3 shows the cumulative risk score and associated 3-year, 5-year, and 10-year risk of developing HCC; for example, a male patient (risk score=2), aged 59 years (5), who was HBeAg positive (2), with ALT concentration of 47 IU/L (2), and HBV DNA viral load of 10000–99999 copies per mL (3) would have a cumulative risk score of 14, with a projected HCC risk of 6% at 3 years, 14% at 5 years, and 32% at 10 years of follow-up. The webappendix shows the risk function used to estimate the risk of developing HCC.

We plotted ROC curves for 3-year, 5-year, and 10-year risk with the 1505 patients from the validation cohort. We also plotted a calibration chart for predicted and observed risk (figure 1). The overall model showed a fairly good discrimination capability, with AUROC of 0.811 (95% CI 0.790–0.831) for risk at 3 years, 0.796 (0.775–0.816) at 5 years, and 0.769 (0.747–0.790) at 10 years (figure 1). The predicted HCC risk calibrated well with the observed risk, with a correlation coefficient of 0.973 for 3-year risk, 0.942 for 5-year risk, and 0.994 for 10-year risk (figure 1). In an analysis stratified by age, the AUROC for patients aged 30–65 years was 0.782 (0.756–0.806) at 3 years, 0.771 (0.746–0.796) at 5 years, and 0.751 (0.725–0.776) at 10 years. For patients younger than 30 years or older than 65 years the AUROC was 0.922 (0.891–0.946) at 3 years, 0.904 (0.871–0.931) at 5 years, and 0.854 (0.816–0.888) at 10 years. In patients from each of the three validation datasets, the AUROCs for risk at 3, 5, and 10 years were: 0.857 (0.821–0.889), 0.832 (0.793–0.866), and 0.785 (0.743–0.824), respectively, in the CUHK cohort; 0.881 (0.857–0.902), 0.859 (0.833–0.882), and 0.838 (0.811–0.862), respectively, in the UHK cohort; and 0.703 (0.644–0.758), 0.707 (0.648–0.762), and 0.717 (0.657–0.771), respectively, in the YUH cohort.

We also plotted ROC curves for risk at 3, 5, and 10 years in 1228 patients from the validation cohort who did not have cirrhosis at study entry. The non-cirrhotic model showed good sensitivity and specificity, with AUROC of 0.902 (0.884–0.918) for risk at 3 years, 0.783 (0.759–0.806) at 5 years, and 0.806 (0.783–0.828) at 10 years in patients without cirrhosis (figure 2), compared with 0.671 (0.612–0.726), 0.698 (0.640–0.752), and 0.647 (0.588–0.704), respectively, in patients with cirrhosis. We also plotted a calibration chart for predicted HCC risk and observed risk, showing a good correlation in the non-cirrhotic model (figure 2). The correlation coefficient was 0.975 for HCC risk at 3 years, 0.991 at 5 years, and 0.999 at 10 years.

## Discussion

This study was undertaken to develop a clinically useful HCC risk-prediction score in patients with chronic hepatitis B, with use of a community-based natural history cohort from Taiwan. The resulting predictive risk score was validated in a hospital-based composite cohort

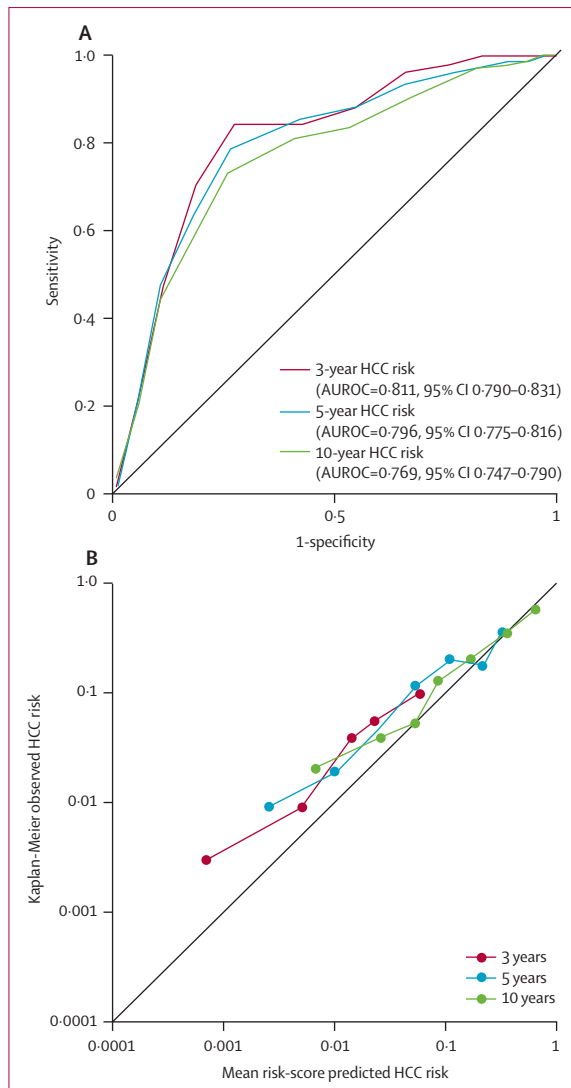
	3 years	5 years	10 years
0	0.0%	0.0%	0.0%
1	0.0%	0.0%	0.1%
2	0.0%	0.0%	0.1%
3	0.0%	0.1%	0.2%
4	0.0%	0.1%	0.3%
5	0.1%	0.2%	0.5%
6	0.1%	0.3%	0.7%
7	0.2%	0.5%	1.2%
8	0.3%	0.8%	2.0%
9	0.5%	1.2%	3.2%
10	0.9%	2.0%	5.2%
11	1.4%	3.3%	8.4%
12	2.3%	5.3%	13.4%
13	3.7%	8.5%	21.0%
14	6.0%	13.6%	32.0%
15	9.6%	21.3%	46.8%
16	15.2%	32.4%	64.4%
17	23.6%	47.4%	81.6%

**Table 3: Cumulative risk score and associated 3-year, 5-year, and 10-year risk of developing hepatocellular carcinoma in patients with chronic hepatitis B**

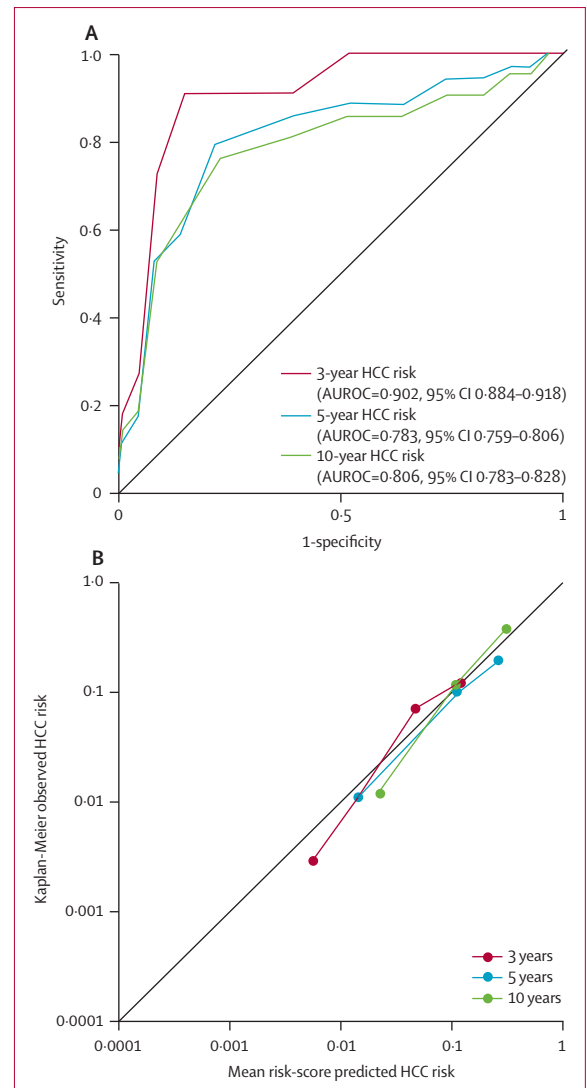
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from several centres in Hong Kong and South Korea. To maximise clinical use, this risk calculator was designed to include simple, non-invasive, and routinely measured factors. Factors predictive of HCC in this study—sex, age, serum ALT concentration, HBeAg status, and serum HBV DNA level—were consistent with those identified in previous studies.<sup>3–5,8,9</sup> A 17-point risk-score was developed and validated with these clinical factors. The resulting risk score was accurate and reliable, with predicted risk correlating well with observed risk.

The risk score developed in this study can provide guidance about treatment by focusing on the long-term outcomes in chronic hepatitis B, which are not covered in treatment recommendations. This risk score is of particular benefit for patients who do not meet existing treatment initiation recommendations—a group who are not addressed in current treatment guidelines. Another conceivably useful application would be to assess the change in risk after initiation of therapy; however, further verification would be needed before recommendation of the risk score for this purpose. This risk-prediction instrument could be used by a wide range of health-care professionals, from general practitioners to experienced hepatologists. It might also provide valuable insights for health authorities needing information for long-term resource planning. Another opportunity for this risk calculator is in communication of risk to patients, which could lead to better treatment acceptance and compliance in patients needing therapy. For patients assessed as having a high risk score, several management strategies might be considered, including more intensive follow-up, more frequent HCC



**Figure 1:** ROC curves for 3-year, 5-year, and 10-year risk of developing HCC (A), and calibration chart for predicted versus observed risk in the overall validation cohort (including patients with cirrhosis at study entry; B) ROC=receiver operating characteristics. HCC=hepatocellular carcinoma. AUROC=area under receiver operating characteristic curve.



**Figure 2:** ROC curves for 3-year, 5-year, and 10-year risk of developing HCC (A), and calibration chart for predicted versus observed risk in the non-cirrhotic validation cohort (patients without cirrhosis at study entry; B) ROC=receiver operating characteristics. HCC=hepatocellular carcinoma. AUROC=area under receiver operating characteristic curve.

surveillance with use of sensitive imaging techniques such as CT and MRI, and the initiation of antiviral therapy when appropriate. By contrast, patients with low risk scores might be managed with less vigorous follow-up or surveillance, and delay treatment until more effective antiviral therapies are available.

This study used the largest cohort of patients so far to develop a risk score predictive of HCC in chronic hepatitis B. The datasets used provide not only tangible data, but also allow the determination of risk at different timepoints. This risk score also takes into account factors such as age and sex, which are known to be important but not addressed in present guidelines.<sup>4</sup> Selection bias in the development cohort was minimised

because the cohort was taken from a population-based natural history study. The validation cohort was large and diverse and, importantly, independent from the development cohort.

The risk factors included in this study are not exhaustive, and we omitted several known and suggested risk factors to instead use widely available and easily measurable data. We did not include  $\alpha$ -fetoprotein because testing has variable sensitivity and specificity,<sup>24</sup> which is poor for prediction of HCC occurrence in the long term. The absence of a standardised definition of heavy alcohol use between countries means that appropriate cutoffs remain contentious, and such data are difficult to collect. Although genotype and core promoter or precore mutations might

be important risk factors, they are not widely available. The potential for underestimation of HCC cases in the cohorts might be a weakness of this study. Although we excluded patients with overt cirrhosis, the proportion of patients with subclinical cirrhosis was assumed to be similar between datasets. This issue could be addressed by non-invasive measurement of liver stiffness in clinical practice. Some existing clinical scores are associated with fibrosis stages, but these scores are not widely validated. Therefore, clinicians have to judge further risk in patients whom they suspect have cirrhosis.

This risk score was developed and validated in Asian patients. Because the clinical characteristics included are common to clinical guidelines prepared by the Asia-Pacific Association for the Study of the Liver, the American Association for the Study of Liver Diseases, and the European Association for the Study of Liver, this risk score might be applicable to non-Asian patients. However, further validation is needed for patients of other ethnic origins, and might need to take into account diversities in age at infection (perinatal *vs* adulthood), genetic background, HBV genotype or species, and exposure to environmental factors such as aflatoxin and alcohol. Although these additional characteristics have not been included in our risk score, it can realistically be modified and validated with use of long-term follow-up data from non-Asian patients with chronic hepatitis B.

Further caution in use of this risk calculator should be given for patients who are co-infected with HIV or hepatitis C virus, or those with ALT flares that could be indicative of several factors. Calculation of risk in immune-tolerant patients might be inappropriate, because antiviral treatment is not indicated for these patients. To include immune-stable patients only, an age cutoff of 30 years was used for this risk score. Similarly, patients with evidence of cirrhosis need immediate antiviral therapy, so this risk calculator would not apply to this patient group. Treatment with antiviral agents, resulting in a lowering of HBV DNA viral load and ALT concentrations and accelerating of HBeAg seroclearance and seroconversion, has the potential to substantially change the risk profile of an individual patient. However, because responses are not durable in many patients, the risk profile could be highly dynamic both during and after treatment. Further analysis is recommended, with application of the current risk score in a treated cohort to establish whether the treatment-modified risk profile actually corresponds to reduced HCC risk.

The results of this study represent a simple-to-use risk score combining widely available clinical variables for the estimation of HCC risk within a specific timeframe for Asian patients with chronic hepatitis B. This risk score needs to be validated in patients of other ethnic origins. Further investigation and validation of risk calculation and the change of risk in patients undergoing therapy would also be beneficial. International consensus

### Panel: Research in context

#### Systematic review

We searched PubMed for relevant articles up to June 30, 2010, with the search terms “risk prediction AND hepatocellular carcinoma AND hepatitis B”. The resulting references were reviewed, and only English language articles associated with prospective estimation of the risk for developing hepatocellular carcinoma (HCC) with risk functions were considered. To the best of our knowledge, four HCC risk prediction models have been published.<sup>3,7,20,21</sup> Most of them were hospital-based studies with small sample sizes for model derivation and validation. The studies included a diverse set of risk predictors, some of which were difficult to standardise because of varied definitions (eg, cirrhosis and alcohol use). Most importantly, these studies were validated with samples drawn from the same cohort as the derivation sets, or had similar characteristics to the derivation sets. Therefore external validation was urgently needed for HCC prediction models in chronic hepatitis B, because the most stringent test of a risk prediction score is applying it to populations with very different characteristics from those from which it was derived.

#### Interpretation

Previously published studies established that long-term HCC risk is predictable with clinical parameters, but they were limited by inadequate external validation. The risk score presented here was developed with data from a population-based natural history cohort and validated in a large, independent multicentre cohort. The findings of our study are much less affected by selection bias than the previous studies, and the robustness of the method for HCC prediction was much improved. Our study provides a useful and accurate instrument for prediction of long-term HCC risk in patients with chronic hepatitis B on the basis of their age, sex, serum alanine aminotransferase concentrations, hepatitis B virus (HBV) DNA levels, and HBeAg serostatus. Clinicians could use this score to assess the risk of progressing to HCC in patients with chronic hepatitis B, and subsequently make evidence-based decisions about the clinical management of choice for these patients.

on what constitutes high risk of developing HCC in chronic hepatitis B is also needed. Although further validation of this risk score with use of data from a prospective study is desirable, it is unrealistic, because a large cohort of patients with untreated disease is unlikely to be recruited. The developed risk score has the potential to be incorporated into a clinical risk-prediction instrument that could improve patient management through appropriate and timely intervention (panel).

#### Contributors

Datasets used in this report were collected and analysed by M-FY and W-KS of the University of Hong Kong on behalf of their respective study groups; HL-YC and VW-SW of the Chinese University of Hong Kong on

behalf of their respective study groups; D-YK, S-HA, and K-HH of Yonsei University College of Medicine on behalf of their respective study groups; and C-JC on behalf of the REVEAL-HBV Study Group. H-IY did statistical analyses. All authors contributed equally to the content of this report.

#### Conflicts of interest

H-IY and C-JC have received speakers' honoraria and travel expenses from Bristol-Myers Squibb in relation to the REACH-B working group meeting. C-JC has received research grant support from the Department of Health, Academia Sinica and National Health Research Institute, Taiwan; and Bristol-Myers Squibb. M-FY's institution has received a grant from Research Grants Council and Research Fund for Clinical Infectious Diseases, Hong Kong. M-FY has received payment for lectures from GlaxoSmithKline and Bristol-Myers Squibb for work unrelated to this study. HL-YC has received paid consultancy from Bristol-Myers Squibb, Novartis, Roche, and Merck. P-JC's institution has received a grant for the HCC BRIDGE study. P-JC has received speakers' honoraria, travel expenses, and payment for development of educational presentation from Bristol-Myers Squibb. VW-SW is a paid advisory board member of Novartis, Roche, and Gilead; and has received lecture fees from Novartis, Abbott, and Echosens. K-HH, D-YK, S-HA, and W-KS declare that they have no conflicts of interest.

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