

Risk and Risk Score Performance of Hepatocellular Carcinoma Development in Patients With Hepatitis B Surface Antigen Seroclearance

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INTRODUCTION: Hepatocellular carcinoma (HCC) can develop among chronic hepatitis B patients after hepatitis B surface antigen (HBsAg) seroclearance. However, whether HCC risk after HBsAg seroclearance differs between antiviral therapy (AVT)-induced or spontaneous seroclearance cases and ways to identify at-risk populations remain unclear.

METHODS: A retrospective cohort of 1,200 adult chronic hepatitis B patients who achieved HBsAg seroclearance (median age: 56 years; 824 men; 165 with cirrhosis; 216 AVT-induced cases) were analyzed. The risk of HCC after HBsAg seroclearance and the performance of 6 HCC prediction models were assessed.

RESULTS: During a median of 4.8 years of follow-up (range: 0.5–17.8 years), HCC developed in 23 patients (1.9%). The HCC incidence rate was higher in the AVT-induced cases than that in the spontaneous cases (3.9% vs 0.9% at 5 years). AVT and cirrhosis were independent factors associated with HCC, with HCC incidence rates of 0.5%, 1.2%, 4.0%, and 10.5% at 5 years for spontaneous/no-cirrhosis, AVT-induced/no-cirrhosis, spontaneous/cirrhosis, and AVT-induced/cirrhosis patients, respectively. Among the 6 predictive HCC models tested, Chinese University-HCC score (0.82) showed the highest C-statistics, which was followed by guide with age, gender, HBV DNA, core promoter mutations and cirrhosis (0.81).

DISCUSSION: AVT-induced HBsAg seroclearance was associated with higher HCC risk, especially for patients with cirrhosis, indicating that they need careful monitoring for HCC risk. The HCC risk models were able to stratify the HCC risk in patients with HBsAg seroclearance.

Clinical and Translational Gastroenterology 2021;12:e00290. <https://doi.org/10.14309/ctg.000000000000290>

INTRODUCTION

Chronic hepatitis B virus (HBV) infection, defined as the persistence of serum hepatitis B surface antigen (HBsAg) for more than 6 months, is a major cause of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide (1,2). During the natural course of chronic HBV infection, some patients show the spontaneous loss or clearance of HBsAg (3–5). The risk of disease progression is very low among chronic hepatitis B (CHB) patients with spontaneous HBsAg seroclearance (6,7) and is considered a state of functional cure (4). HBsAg seroclearance also occurs in CHB patients who received or are receiving antiviral therapy (AVT) (8,9). AVT-induced HBsAg seroclearance is known to be as durable as spontaneous HBsAg seroclearance (10) and is also

associated with favorable clinical outcomes (8,11). Therefore, HBsAg seroclearance is considered the ideal endpoint of AVT in HBV guidelines (3,4). However, it is also known that some CHB patients with HBsAg seroclearance still develop HCC (12).

To date, limited information is available to indicate whether AVT-induced HBsAg seroclearance shows the same favorable clinical outcome as spontaneously induced HBsAg seroclearance. In a recent systemic review of 28 studies involving 8,904 CHB patients with HBsAg seroclearance, the incidence of HCC was very low (1.86%), and the risk factors of HCC included cirrhosis, male sex, and age at HBsAg seroclearance (13). However, limited information is available whether the risk of HCC is comparable between patients with AVT-induced and spontaneous-induced

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Received July 9, 2020; accepted November 10, 2020; published online January 11, 2021

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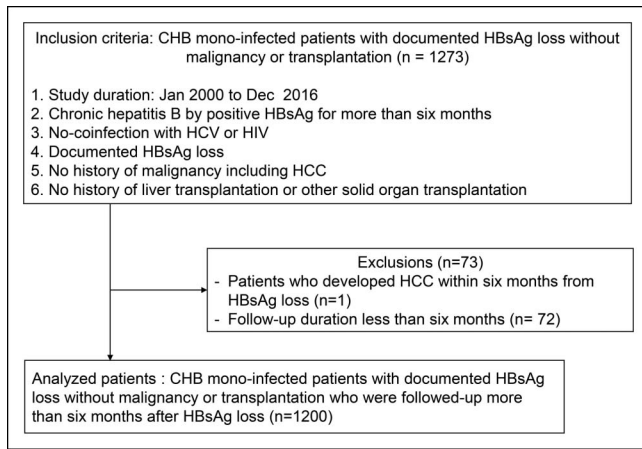


Figure 1. Study participants. A total of 1,200 patients were analyzed in this study. CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

HBsAg seroclearance. In addition, because the HCC incidence rate after HBsAg seroclearance is low, risk stratification is needed to guide future follow-up plans, especially regarding HCC surveillance. Yet, there is limited information on the ways to stratify the HCC risk in CHB patients who have achieved HBsAg seroclearance. In this study, we compared the HCC risk between AVT-induced and spontaneously induced HBsAg seroclearance to determine whether AVT-induced HBsAg seroclearance was as safe as spontaneously induced HBsAg seroclearance. We also assessed the performance of several HCC prediction scores developed for CHB patients to determine whether these HCC risk scores could be applied to patients with HBsAg seroclearance.

METHODS

Study design, setting, and participants

This study was a hospital-based, retrospective, multicenter cohort study performed at 3 academic institutions in South Korea. The electronic medical records were screened for patients to include in the study. We included a total of 1,273 adults aged 18 years or older who met all inclusion criteria between January 1, 2000 and December 31, 2016 from each site. The inclusion criteria were as follows: (i) chronic HBV infection, defined by the presence of serum HBsAg for more than 6 months; (ii) no coinfection with

hepatitis C virus or HIV; (iii) no history of cancer, including HCC; (iv) no history of liver transplantation or other solid organ transplantation, and (v) patients with documented HBsAg loss. Among them, we excluded 73 patients who met the following exclusion criteria: (i) 1 patient developed HCC within 6 months of HBsAg loss and (ii) 72 patients with follow-up durations less than 6 months from HBsAg loss. Finally, 1,200 chronic HBV mono-infected patients with documented HBsAg loss, without malignancy or transplantation at baseline, and with more than 6 months of follow-up after HBsAg loss were analyzed in this study (Figure 1). The study protocol was reviewed and approved by the Institutional Review Board of each participating site. The requirement for informed consent from the patients was waived because only deidentified data routinely collected during hospital visits were used.

Study outcomes, variables, and measurements

The primary outcome was incident HCC during follow-up. HCC was diagnosed according to the regional HCC diagnostic guidelines during the study period (14,15). In brief, HCC was diagnosed either by pathology or clinical criteria showing typical features of HCC in imaging studies. The index date was defined as the first date of documented HBsAg loss. The patients were followed up from the index visit to the date of the diagnosis of HCC or to the last clinic visit (reference date: December 31, 2019).

The variables collected were age, sex, and serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bilirubin, and platelet levels measured closest to the index date. Imaging findings on ultrasonography, computed tomography or magnetic resonance imaging, and information on AVT use (interferon, pegylated interferon, lamivudine, adefovir, telbivudine, clevudine, entecavir, and tenofovir) were also collected.

AVT was defined for patients with a history or current use of AVT at HBsAg loss. Liver cirrhosis was defined by radiological evaluation when imaging findings suggestive of cirrhosis, a blunted, nodular liver edge, and/or splenomegaly (16) were identified. For 53 patients (0.4%), imaging studies within a year of the index visit were missing. For them, the fibrosis (FIB)-4 index ($\text{age in years} \times \text{AST level in U/L} / ([\text{platelet count} \times 10^9/\text{L}] \times [\text{ALT level in U/L}])$) was calculated and was used to define cirrhosis (because cirrhosis was defined when the FIB-4 index was >3.25) (17,18). Elevated ALT levels were defined as ALT >34 in men or >30 in women (19). In addition, we also calculated the

Table 1. Baseline characteristics of patients

	All (n = 1,200)	Spontaneous (n = 984)	AVT-induced (n = 216)	P	HCC (+) (n = 23)	HCC (-) (n = 1,177)	P
Age, yr	56 (50–62)	57 (51–63)	52 (45–58)	<0.001	58 (55–63)	56 (50–62)	0.23
Men	824 (68.7%)	662 (67.3%)	162 (75.0%)	0.029	20 (87.0%)	804 (68.3%)	0.068
Liver cirrhosis	165 (13.8%)	107 (10.9%)	58 (26.9%)	<0.001	14 (60.9%)	151 (12.8%)	<0.001
AST, U/L	22 (19–27)	22 (19–27)	22 (18–26)	0.07	26 (22–36)	22 (19–27)	0.005
ALT, U/L	20 (15–28)	20 (15–27)	20 (14–28)	0.28	27 (20–34)	20 (15–27)	0.002
Albumin, g/dL	4.5 (4.3–4.6)	4.4 (4.3–4.6)	4.5 (4.3–4.7)	0.020	4.5 (4.1–4.6)	4.5 (4.3–4.6)	0.90
Bilirubin, mg/dL	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.77	0.9 (0.7–1.3)	0.8 (0.6–1.1)	0.22
Platelet count, $10^3/\mu\text{L}$	193 (158–229)	195 (160–231)	180 (143–220)	<0.001	153 (132–217)	193 (159–230)	0.019

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVT, antiviral therapy; HCC, hepatocellular carcinoma.

AST-to-platelet ratio index (20) and the risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) (21), guide with age, gender, HBV DNA, core promoter mutations and cirrhosis (GAG-HCC) (22), Chinese University-HCC (CU-HCC) (23), platelets, age, gender hepatitis B (PAGE-B) (24), modified PAGE-B (25), and age-male-ALBI-platelets (aMAP) (26) scores using baseline variables.

Statistical analysis

Descriptive statistics for the continuous variables and the categorical variables are presented by median (interquartile range) and frequency (%), respectively. Cox regression models were used to identify the factors associated with incident HCC. AVT, age, sex, liver cirrhosis, and serum AST, ALT, albumin, bilirubin levels, and platelet counts were tested in univariable analysis for HCC development. We included the variables with *P* values <0.1 on univariable analysis in a multivariable analysis. Age was

included in the multivariable analysis, regardless of the *P* value on univariable analysis. The cumulative HCC incidence rate was estimated using a Kaplan-Meier method, and differences between the groups were compared with the log-rank test.

To assess the prognostic performance of the HCC prediction models in patients with HBsAg loss, the area under the receiver operating characteristic curves (AUROCs) was calculated to predict HCC development at 3 and 5 years, respectively. After calculating the AUROC, one with the highest C-index was used as a reference to test performance of other model. AUROC was compared with test statistical difference between models with the cutoff *P* value of 0.05. Comparison was performed using the open source statistics software R (version 3.5.1) in conjunction with pROC package (27) that used DeLong method (28).

RESULTS

Baseline characteristics

The baseline characteristics at HBsAg loss are summarized in Table 1. The median patient age was 56 years, 68.7% were men, and 13.8% of the analyzed patients had cirrhosis. Of 1,200 patients, 984 patients (82%) were spontaneously induced cases, whereas 216 patients (18%) were AVT-induced cases. Among the 216 AVT-induced cases, the types of AVT used were nucleoside or nucleotide analogs, interferon/pegylated interferon, and both nucleoside or nucleotide analogs and interferon/pegylated interferon for 186 (86.1%), 10 (4.6%), and 17 (7.9%) patients, respectively.

When compared, the AVT-induced cases were younger, comprised more men, had cirrhosis, and showed higher albumin levels and lower platelet counts than those of spontaneous-induced cases (Table 1). When compared between those who developed and those who did not, those who developed HCC comprised more cirrhosis and showed higher AST and ALT levels and lower platelet count (Table 1).

Incidence and risk factors of HCC

During a median of 4.8 years of follow-up (range: 0.5–17.8 years), HCC developed in 23 patients (1.9%). The cumulative incidence rate of HCC was 1.0%, 1.4%, and 3.2% at 3, 5, and 7 years, respectively. The HCC incidence according to baseline characteristics is summarized in Table 2. The HCC incidence was lower for young adults, women, those without cirrhosis, and those with low FIB-4 or AST-to-platelet ratio index scores. No significant difference was found according to baseline ALT levels. In the multivariable adjusted analysis, AVT (hazard ratio = 3.10, 95% confidence interval: 1.26–7.65) and cirrhosis (hazard ratio = 6.23, 95% confidence interval: 2.37–16.40) were independent factors associated with HCC (Table 3). When stratified according to cirrhosis and AVT use, the 5-year cumulative HCC incidence rate was 0.5%, 1.2%, 4.0%, and 10.5% for patients without cirrhosis/spontaneous cases (*n* = 877), patients without cirrhosis/AVT-induced cases (*n* = 158), patients with cirrhosis/spontaneous cases (*n* = 107), and patients with cirrhosis/AVT-induced cases (*n* = 58), respectively (Figure 2, *P* < 0.001).

Role of HCC prediction models for patients with HBsAg loss

The performance of the HCC prediction models for predicting HCC development at 5 years is summarized in Table 4. Notably, HBV DNA levels, which contribute to the CU-HCC, GAG-

Table 2. Risk of hepatocellular carcinoma according to baseline characteristics

	Number	HCC	Cumulative HCC incidence rate (%)			<i>P</i>
			3-yr	5-yr	7-yr	
Age, yr						0.06
<50	298	1	0.0	0.0	0.9	
50–59	520	12	1.5	2.0	3.1	
≥60	422	10	1.0	1.5	4.8	
Sex						0.07
Women	376	3	0.6	0.9	0.9	
Men	824	20	1.2	1.6	4.1	
Cirrhosis ^a						<0.001
No	1,035	9	0.4	0.6	1.6	
Yes	165	14	4.6	6.5	13.3	
ALT levels						0.35
Normal	1,015	18	1.0	1.3	2.9	
Elevated ^b	185	5	1.2	1.9	5.0	
FIB-4						0.02
<1.45	603	9	0.4	0.9	3	
1.45–3.25	525	10	1.4	1.4	2.5	
>3.25	75	4	3.4	5.3	9.6	
APRI						<0.001
<1	1,162	19	0.8	1.1	1.9	
≥1	38	4	6.7	10.4	19.4	
AVT						<0.001
No	984	12	0.7	0.9	2.2	
Yes	216	11	2.5	3.9	8.1	

^aCirrhosis was defined by radiologic evaluation for 1,147 patients and by elevated FIB-4 score (>3.25) for 53 patients.

^bElevated ALT levels were defined as ALT >34 in men or >30 in women. ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AVT, antiviral therapy; FIB-4, fibrosis 4; HCC, hepatocellular carcinoma.

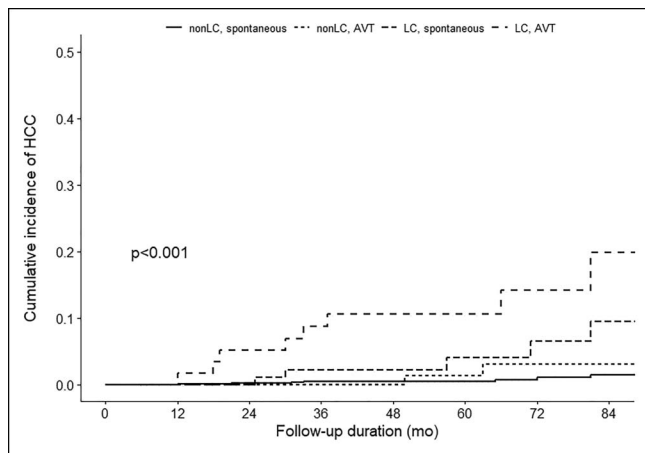


Figure 2. Cumulative incidence of hepatocellular carcinoma according to cirrhosis and antiviral treatment. AVT, antiviral therapy; HCC, hepatocellular carcinoma; LC, liver cirrhosis.

HCC, and REACH-B scores, did not contribute to participants with HBsAg loss. Of the 6 models tested, CU-HCC scores showed the highest AUROC in the overall population, which was better than the REACH-B or PAGE-B scores. The GAG-HCC scores showed the highest AUROC in the spontaneously induced cases, and the CU-HCC scores showed the highest AUROC in the AVT-induced cases.

The HCC incidence according to risk scores cutoffs is summarized in Table 5. The HCC incidence was high for those with medium or high CU-HCC scores (5.3% or 14.3% at 5 years, respectively) and those with high GAG-HCC scores (7.9% at 5 years), but the HCC risk was not null for those with low CU-HCC scores (0.6% at 5 years) and those with low GAG-HCC scores (0.8% at 5 years). By contrast, the HCC incidence rate was not high even for high PAGE-B scores (2.1% at 5 years) and high modified PAGE-B scores (2.8% at 5 years), but no HCC developed in patients with low PAGE-B scores (0% at 5 years), low modified PAGE-B scores (0% at 5 years), or low aMAP score (0% at 5 years). When stratified according to AVT use, the HCC incidence rate was higher for AVT-induced cases compared with that of spontaneously induced cases, within the same category of risk scores (Table 5).

DISCUSSION

In this study, the incidence of HCC among patients with HBsAg seroclearance was low (1.9%), with a cumulative HCC incidence rate of 1.4% at 5 years, during a median follow-up duration of 4.8 years. The patients with AVT-induced seroclearance patients showed a higher risk of HCC compared with the patients with spontaneously induced seroclearance and was an independent risk factor associated with HCC, along with cirrhosis. CU-HCC and GAG-HCC scores, which include cirrhosis as a variable, showed better performance than REACH-B, PAGE-B, modified PAGE-B, or aMAP scores. When the patients were grouped according to the proposed cutoff values, CU-HCC and GAG-HCC showed higher performance in identifying the high-risk group, whereas PAGE-B, modified PAGE-B, and aMAP scores were able to identify patients who were at *null* risk of developing HCC within 5 years.

In this study, cirrhosis was an independent factor associated with HCC development. Similarly, several studies, including a meta-analysis, have identified the presence of cirrhosis as a key factor associated with future HCC risk in patients with HBsAg seroclearance (12,13,29). Male sex and age at HBsAg seroclearance were also suggested as important risk factors of HCC (29,30). Although age and sex were not independent risk factors in this study, the HCC incidence rate was higher in men compared with that in women and was higher for older patients in this study (Table 2). Notably, the HCC risk was higher for patients with AVT-induced HBsAg seroclearance than that for patients with spontaneously induced (0.9% and 3.9% at 5 years, respectively). AVT is usually considered for patients with persistent inflammation (3–5). Hence, the AVT-induced group might have experienced prolonged inflammation in the liver before HBsAg seroclearance than that by the spontaneous group. Indeed, when the baseline characteristics were compared, the prevalence of cirrhosis was higher in the AVT-induced group (Table 1). HBV DNA persists in the liver and might show very-low-level HBV replication after HBsAg seroclearance (31). Those who achieved spontaneous HBsAg seroclearance through host immune control might have stronger immune control of HBV. In a study by Kim et al. (29), the HCC risk was not higher for patients with AVT-induced HBsAg seroclearance than that for the spontaneously induced group. However, the number of AVT-induced cases was relatively small ($n = 105$) with shorter follow-up intervals (median 3.2 years) than that in this study. To our knowledge, no other studies have directly compared HCC risk

Table 3. Factors associated with hepatocellular carcinoma development

	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
AVT yes (vs no)	4.97 (2.17–11.4)	<0.001	3.10 (1.26–7.65)	0.014
Age (per year)	1.03 (0.98–1.07)	0.24	1.03 (0.99–1.09)	0.14
Men (vs women)	2.88 (0.85–9.68)	0.09	2.39 (0.69–8.24)	0.17
Cirrhosis (vs no)	10.5 (4.51–24.3)	<0.001	6.23 (2.37–16.40)	<0.001
AST, U/L	1.00 (0.99–1.01)	0.19		
ALT, U/L	1.00 (1.00–1.01)	0.28		
Albumin, g/dL	0.55 (0.18–1.64)	0.28		
Bilirubin, mg/dL	1.65 (0.92–2.94)	0.09	1.22 (0.56–2.66)	0.61
Platelet count, $10^3/\mu\text{L}$	0.99 (0.98–0.99)	0.003	1.00 (0.99–1.01)	0.71

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVT, antiviral therapy; CI, confidence interval; HR, hazard ratio.

Table 4. Performance of risk prediction models for hepatocellular carcinoma development at 5 years

	CU-HCC score	GAG-HCC score	<i>P</i> ^a	REACH-B score	<i>P</i> ^a	PAGE-B score	<i>P</i> ^a	Modified PAGE-B score	<i>P</i> ^a	aMAP score	<i>P</i> ^a
Original components	Age, albumin, bilirubin, HBV DNA, cirrhosis	Age, sex, BCP mutation, HBV DNA levels, cirrhosis		Age, sex, ALT, HBV DNA, HBeAg		Age, sex, platelet counts		Age, sex, platelet count, albumin		Age, sex, bilirubin, albumin, platelet count	
Components used in this study	Age, albumin, bilirubin, cirrhosis	Age, sex, cirrhosis		Age, sex, ALT		Age, sex, platelet counts		Age, sex, platelet count, albumin		Age, sex, bilirubin, albumin, platelet count	
Overall (n = 1,200)											
AUROC (95% CI)	0.82 (0.70–0.93)	0.81 (0.70–0.93)	0.60	0.64 (0.52–0.75)	0.03	0.62 (0.49–0.75)	0.01	0.72 (0.61–0.82)	0.08	0.73 (0.63–0.84)	0.03
Spontaneous (n = 984)											
AUROC (95% CI)	0.79 (0.62–0.96)	0.82 (0.65–0.98)	0.92	0.66 (0.49–0.83)	0.20	0.65 (0.49–0.81)	0.26	0.77 (0.64–0.90)	0.81	0.71 (0.59–0.83)	0.31
AVT induced (n = 216)											
AUROC (95% CI)	0.81 (0.632–0.98)	0.74 (0.58–0.90)	0.19	0.70 (0.56–0.84)	0.48	0.53 (0.31–0.76)	0.007	0.67 (0.51–0.82)	0.06	0.73 (0.53–0.93)	0.08

^a*P* value, compared with CU-HCC score. For CU-HCC score, 0 point was given for HBV DNA score. For GAG-HCC score, 0 point was given for HBV DNA and BCP mutation. For REACH-B score, 0 point was given for HBV DNA and HBeAg. aMAP, age-male-ALBI-platelets; AUROC, area under the receiver operating characteristic curve; ALT, alanine aminotransferase; AVT, antiviral therapy; BCP, basal core promoter; CI, confidence interval; CU-HCC, Chinese University-HCC; GAG-HCC, guide with age, gender, HBV DNA, core promoter mutations and cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PAGE-B, platelets, age, gender hepatitis B; REACH-B, risk estimation for hepatocellular carcinoma in chronic hepatitis B.

between AVT-induced cases and spontaneously induced cases. Further data are needed to validate our observations. However, our findings indicate that patients with AVT-induced seroclearance warrant more careful attention to increased HCC risk. In addition, when stratified according to cirrhosis, the 5-year cumulative HCC incidence rate was 0.5% and 1.2% for patients with spontaneous- and AVT-induced seroclearance without cirrhosis and 4.0% and 10.5% for patients with spontaneous- and AVT-induced seroclearance with cirrhosis, respectively (Figure 2). This suggests that the ideal AVT endpoint should be HBsAg seroclearance before cirrhosis. The clinical benefit of AVT-induced HBsAg seroclearance might be low when cirrhosis is present.

In this study, the risk of HCC was low (1.4% at 5 years). Consistently, the reported HCC incidence rate after HBsAg seroclearance is (0.86%–3.7%) (29,30,32,33). Hence, risk-stratification is needed to provide individualized care, especially in HCC surveillance. Cirrhosis is a strong risk of HCC in patients with HBsAg seroclearance (12,13,29) and warrants HCC surveillance after HBsAg seroclearance. Yet, HCC was also observed in noncirrhotic patients indicating cirrhosis alone might not be optimal factor to identify individual who need HCC surveillance for HBsAg seroclearance. In this study, 6 predictive models for HBV-related HCC were assessed. Among these models, CU-HCC showed the highest predictive ability (AUROC 0.82), followed by GAG-HCC (0.81). Liver cirrhosis was the most important predictor for HCC in HBsAg seroclearance patients (13). The integral components of CU-HCC and GAG-HCC include liver cirrhosis, whereas those of REACH-B, PAGE-B, modified PAGE-B, and aMAP do not. CU-HCC and GAG-HCC, which include liver cirrhosis as a variable,

showed highest AUROC and observed that HCC risk was high (14.3%–7.9% at 5 years) for those classified as a high risk group. However, although the incidence was low, HCC development was observed for patients classified as a low-risk group by CU-HCC and GAG-HCC (0.6%–0.8% at 5 years). For REACH-B, PAGE-B, and modified PAGE-B score, HCC risk was not very high (0.2%–2.8% at 5 years) for those classified as a high risk group. However, HCC risk was null (0% at 5 years) for those classified as a low-risk group by PAGE-B or modified PAGE-B score. For aMAP scores, HCC risk was comparably high (6.3% at 5 years) for those classified as a high-risk group, and HCC risk was null (0% at 5 years) for those classified as a low-risk group. These different risk models warrant further validation but might be used as an initial step to identify high-risk patient who need HCC surveillance (CU-HCC, GAG-HCC, and aMAP) and to identify very-low-risk patients who might be exempted from HCC surveillance (PAGE-B, modified PAGE-B, and aMAP). Among risk scores, aMAP score was able to triage both high- and very-low-risk patients. Notably, the HCC risk was, especially, higher for patients with AVT-induced seroclearance with higher scores, indicated by HCC risk models (Table 5).

This study had some limitations. The study had the inherent limitations of a retrospective cohort study. Because HBsAg was not systematically evaluated at regular intervals, the age at seroclearance might be earlier than the date of documentation of HBsAg seroclearance in this study. Liver cirrhosis was defined radiologically, which has interobserver and intraobserver variability and was assessed by many radiologists in 3 centers. However, the radiologists were unaware of the study's aim, and the direction of bias was nondifferential. There were 53 patients (0.4%) with missing imaging

Table 5. Risk of hepatocellular carcinoma (HCC) according to HCC risk scores

	No. with HCC/at risk (overall)	Cumulative HCC incidence rate (%) at 5 yr (overall)	No. with HCC/ at risk (spontaneous)	Cumulative HCC incidence rate (%) at 5 yr (spontaneous)	No. with HCC/ at risk (AVT-induced)	Cumulative HCC incidence rate (%) at 5 yr (AVT-induced)
CU-HCC						
Low (<5)	9/1,026	0.6	7/869	0.5	2/157	1.3
Medium (5–19)	12/158	5.3	3/101	2.0	9/57	10.7
High (≥20)	2/16	14.3	2/14	16.7	0/2	
GAG-HCC						
Low (<100)	12/1,093	0.8	7/905	0.5	5/188	2.3
High (≥100)	11/107	7.9	5/79	5.6	6/28	14.3
REACH-B						
Low (<8)	8/705	0.1	5/555	0.8	3/150	1.7
High (≥8)	15/495	0.2	7/429	0.9	8/66	8.6
PAGE-B						
Low (≤9)	0/171	0.0	0/146	0.0	0/25	0.0
Intermediate (10–17)	12/616	1.3	6/500	0.8	6/116	3.4
High (≥18)	11/413	2.1	6/338	1.3	5/75	5.6
Modified PAGE-B						
Low (≤8)	0/139	0.0	0/107	0.0	0/32	0.0
Intermediate (9–12)	8/670	0.9	4/542	0.4	4/128	3.1
High (≥13)	15/391	2.8	8/335	1.9	7/56	7.4
aMAP						
Low (<50)	0/300	0.0	0/244	0.0	0/56	0.0
Intermediate (50–60)	14/674	2.4	8/552	1.8	6/122	5.7
High (>60)	9/226	6.3	4/188	2.5	5/38	26.7

aMAP, age-male-ALBI-platelets; AVT, antiviral therapy; CU-HCC, Chinese University-HCC; GAG-HCC, guide with age, gender, HBV DNA, core promoter mutations and cirrhosis; HCC, hepatocellular carcinoma; PAGE-B, platelets, age, gender hepatitis B; REACH-B, risk estimation for hepatocellular carcinoma in chronic hepatitis B.

studies within a year of the index visit, in which we used FIB-4 to define cirrhosis. Hence, more objective measures of fibrosis burden obtained by liver biopsies or fibroscans might provide more accurate information on the future HCC risk. There were several unmeasured factors, including a family history of HCC, alcohol use, smoking, metabolic syndrome, fatty liver, and/or steatohepatitis, which might be associated with HCC development in these patients. The primary outcome incidence was small (HCC, $n = 23$) and had to include strong alleged risk factors and analyze in the model. Studies with larger sample sizes with more events (primary outcome) are needed. Although HBV genotype study was missing for this study, almost all HBV infections found in South Korea were infected with genotype C HBV (1). Hence, the generalizability to other ethnicities and patients infected with other HBV genotypes warrants validation. HCC surveillance requires medical cost and is not harm free. Hence, additional studies, including cost-effective analysis, are required to find out optimal surveillance strategy for patients with HBsAg seroclearance. The strength of these data was the large sample size, careful definition of the study variables, and relatively long follow-up period.

In conclusion, we found that HCC risk was generally low after HBsAg seroclearance but was not *null*. AVT was an independent risk factor, along with cirrhosis, and the HCC risk was considerable, especially for cirrhotic patients who achieved HBsAg seroclearance by AVT. This indicates that AVT-induced HBsAg seroclearance might not be as safe as spontaneous HBsAg seroclearance, especially when cirrhosis is present. The HCC risk models showed acceptable performance in patients with HBsAg seroclearance. The CU-HCC and GAG-HCC scores were useful in identifying high-risk patients, whereas PAGE-B and modified PAGE-B scores were useful in identifying very-low-risk patients. These risk scores might be used together to stratify future HCC risk in patients with HBsAg seroclearance.

CONFLICTS OF INTEREST

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Specific author contributions: Yewan Park, MD, and Jeong-Hoon Lee, MD, PhD, contributed equally to this study. J.-H.L., D.H.S., and J.Y.P.: study design. Y.P. and D.H.S.: drafting of the manuscript. Y.P.,

J.Y.P., J.-H.L., M.A.K., Y.J.K., J.-H.Y., S.H.A., W.K., G.-Y.G., Y.-H.P., M.S.C., J.H.L., K.C.K., and S.W.P.: data collection. Y.P., D.H.S., and J.H.L.: statistical analysis and interpretation of the data. J.Y.P., J.-H.L., Y.J.K., J.-H.Y., S.H.A., G.-Y.G., Y.-H.P., M.S.C., J.H.L., K.C.K., and S.W.P.: critical revision of the manuscript. D.H.S. and J.Y.P.: study supervision. All authors approved the final submission.

Financial support: None to report.

Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Loss or seroclearance of hepatitis B surface antigen (HBsAg) can occur spontaneously or by antiviral therapy.
- ✓ Several hepatocellular carcinoma (HCC) risk models are available to predict HCC risk for chronic hepatitis B patients.

WHAT IS NEW HERE

- ✓ HCC risk was higher in antiviral therapy-induced HBsAg seroclearance than spontaneous case.
- ✓ HCC risk models were able to stratify HCC risk in patients with HBsAg seroclearance.

TRANSLATIONAL IMPACT

- ✓ Patients with antiviral therapy-induced HBsAg seroclearance warrants more close attention for HCC risk.
- ✓ HCC risk models can be used to stratify HCC risk in patients with HBsAg seroclearance.

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