Hepatocellular Carcinoma Risk Steadily Persists over Time Despite Long-Term Antiviral Therapy for Hepatitis B: A Multicenter Study

Seung Up Kim[1,2,3], Yeon Seok Seo[4], Han Ah Lee[4], Mi Na Kim[5], Eun Ju Lee[6], Hye Jung Shin[6], Yu Rim Lee[7], Hye Won Lee[1,3], Jun Yong Park[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3], Kwang-Hyub Han[1,2,3], Soon Ho Um[4], Won Young Tak[7], Young Oh Kweon[7], Beom Kyung Kim[1,2,3], and Soo Young Park[7]

ABSTRACT

Background: Long-term antiviral therapy (AVT) for chronic hepatitis B (CHB) reduces the risk of hepatocellular carcinoma (HCC). We assessed the temporal trends in the incidence of HCC over time during long-term AVT among Asian patients with CHB.

Methods: Patients with CHB receiving entecavir/tenofovir (ETV/TDF) as a first-line antiviral were recruited from four academic hospitals in the Republic of Korea. We compared the incidence of HCC during and after the first 5 years of ETV/TDF treatment.

Results: Among 3,156 patients, the median age was 49.6 years and males predominated (62.4%). During the follow-up, 9.0% developed HCC. The annual incidence of HCC per 100 person-years during the first 5 years ($n = 1,671$) and after the first 5 years ($n = 1,485$) was statistically similar (1.93% vs. 2.27%, $P = 0.347$). When the study population was stratified according to HCC prediction model, that is, modified PAGE-B score, the annual incidence of HCC was 0.11% versus 0.39% in the low-risk group (<8 points), 1.26% versus 1.82% in the intermediate-risk group (9–12 points), and 4.63% versus 5.24% in the high-risk group (≥13 points; all $P > 0.05$). A Poisson regression analysis indicated that the duration of AVT did not significantly affect the overall trend of the incidence of HCC (adjusted annual incidence rate ratio = 0.85; 95% confidence interval, 0.66–1.11; $P = 0.232$).

Conclusions: Despite long-term AVT, the risk of HCC steadily persists over time among patients with CHB in the Republic of Korea, in whom HBV genotype C2 predominates.

Impact: Careful HCC surveillance is still essential.

Introduction

Chronic hepatitis B virus (HBV) infection is the major cause of liver cirrhosis as well as hepatocellular carcinoma (HCC; ref. 1). Because active viral replication and the subsequent necro-inflammation and/or fibrosis primarily accelerate hepato-carcinogenesis, an achievement of long-term virologic response by antiviral therapy (AVT) with potent oral nucleos(t)ide analogs (NUC) with high genetic barrier, that is, entecavir (ETV) or tenofovir disoproxil fumarate (TDF), is of paramount importance in terms of prevention of HCC occurrence as well as the progression to cirrhosis (2, 3). Nevertheless, the possibility of HCC cannot be completely eliminated (4, 5), so an effective surveillance strategy that enables early detection of HCC and timely application of curative antitumor therapy is needed (6, 7).

From the similar perspective, stratification of the cumulative probability of HCC occurrence among patients with chronic hepatitis B (CHB) undergoing NUCs has been an important issue. Although prolonged potent AVT improves necro-inflammation, fibrogenesis, and ultimately carcinogenesis in the liver, the pattern of temporal change in the risk of HCC over time during treatment of patients with CHB is still unclear. Indeed, contradictory results have been reported. First, among a cohort of European patients with CHB, in whom HBV genotype D infection acquired horizontally predominates (8), Papatheodoridis and colleagues (9) showed that the risk of HCC development tended to decrease after the first 5 years of AVT. Likewise, in a Taiwanese cohort, the risk of HCC decreased as the duration of AVT increased, even though older patients are more likely to develop HCC (10). In contrast, a prior study conducted in the Republic of Korea (ROK) showed that the incidence of HCC did not significantly change during and after the first 5 years of ETV therapy (11). However, because the baseline characteristics of the patients differed among these studies (9–11), physicians should recognize them for an appropriate interpretation of the study results and further research is needed.

In the ROK, most patients with CHB (>98%) have HBV genotype C2 infection acquired by vertical transmission (8, 12). Here, we conducted a large-scale, multicenter study to assess the temporal trends in the incidence of HCC during long-term NUCs with ETV or TDF among Asian patients with CHB.

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea. [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea. [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea. [4]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea. [5]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea. [6]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea. [7]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea.

Materials and Methods

Patients

Patients with CHB treated with ETV 0.5 mg/day or TDF 300 mg/day between January 2011 and December 2015 in four academic teaching hospitals in the ROK (Yonsei University Severance Hospital, Kyungpook National University Hospital, Korea University Anam Hospital, and CHA Bundang Medical Center) were consecutively screened for eligibility. The inclusion criteria were as follows: (i) age ≥18 years, (ii) NUCs-naïve, and (iii) liver function of Child–Pugh class A or B. The exclusion criteria were: (i) history of HCC at enrollment, (ii) decompensated cirrhosis with Child–Pugh class C at enrollment, (iii) coinfection with other hepatitis virus, (iv) history of organ transplant, (v) HCC development within 4 months of starting ETV or TDF, and (vi) other significant medical illness. Patients considered at risk of HCC development after 5 years of AVT were those who had been followed-up for more than 5 years and did not develop HCC within the first 5 years of AVT.

AVT with NUCs was started based upon the practice guidelines of the Korean Association for the Study of the Liver (13, 14) and the reimbursement guidelines of the National Health Insurance Service of the ROK. Cirrhosis was determined histologically or clinically as follows: (i) platelet count of $<150 \times 10^3/\mu L$ and ultrasonography findings suggestive of cirrhosis, including a blunted, nodular liver edge accompanied by splenomegaly (>12 cm) or (ii) clinical signs of portal hypertension such as gastro-esophageal varices (15).

The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of each institution. The written informed consent was waived owing to its retrospective study design.

Clinical evaluation and follow-up

Routine laboratory tests, serum HBV-DNA level, and other viral markers were assessed every 3 to 6 months according to the physicians' discretion during the follow-up. Furthermore, to detect the development of HCC and other cirrhosis-related complications, abdominal ultrasonography and serum alpha-fetoprotein lev were assessed every 6 months.

The primary end-point of this study was HCC occurrence, which was confirmed on the basis upon either histologic or radiologic results (16–18). The time to HCC occurrence was the interval between the date of starting AVT and that of HCC diagnosis, in the absence of HCC, to the end of the follow-up.

Statistical analysis

The significance of differences among continuous and categorical variables was examined by the Mann–Whitney test and the chi-squared test or Fisher exact test, respectively. The cumulative probability of HCC occurrence was assessed through the Kaplan–Meier method. To evaluate the association between the cumulative HCC risk and each variable and to calculate the hazard ratio (HR) and 95% confidence interval (CI), a Cox regression analysis was used. The cutoffs of continuous variables identified as significant in univariate analyses were selected using the Contal and O'Quigley method based on a log-rank test, an outcome-oriented method (19). Subsequently, a step-wise multivariate Cox regression analysis was performed to assess the associations between the variables and the risk of HCC development.

The incidence of HCC per 100 person-years was estimated by comparison of patients during and after the first 5 years of AVT using the formula of Rothman (20). Finally, to assess the temporal changes in the risk of HCC development according to the AVT duration across a long-term follow-up, a Poisson regression analysis involving significant multivariate predictors identified in the Cox regression analysis was performed and multivariate-adjusted annual incidence rate ratios (IRR) were calculated.

Statistical analyses were performed using SAS (v. 9.4; SAS Institute) and R (v. 3.5.1, http://cran.r-project.org/) software using R packages (e.g., survival, survminer, ggplot2, and rms). Two-sided P values <0.05 were considered to indicate statistical significance.

Results

Baseline clinical characteristics of the study population

The baseline clinical characteristics of the 3,156 patients analyzed are listed in **Table 1**. The median age of the patients was 49.6 (40.5–56.6) years, and males predominated (62.4%). Of the patients, 267 (8.5%) and 320 (10.1%) had diabetes mellitus and hypertension, respectively. As the first-line antiviral regimen, ETV and TDF were initiated in 1,651 (52.3%) and 1,505 (47.7%) patients, respectively. Of the patients, 1,015 (32.2%) had cirrhosis at enrollment and 2,941 (93.2%) had well-preserved liver function (Child–Pugh class A).

Among the patients, 1,671 (52.9%) had a follow-up duration of <5 years under AVT and/or HCC development during the first 5 years of AVT (group 1), whereas 1,485 (47.1%) had a follow-up duration of ≥5 years under ETV or TDF therapy and did not develop HCC during the first 5 years of AVT (group 2). Regarding clinical characteristics (Supplementary Table S1), patients in group 2 were significantly younger (median 49.0 years vs. 50.0 years; $P = 0.011$) and had a lower proportion of cirrhosis (30.0% vs. 34.0%; $P = 0.016$), lower median total bilirubin level (0.63 mg/dL vs. 0.73 mg/dL; $P < 0.001$), and higher median platelet count ($170 \times 10^3 \, \mu L^{-1}$ vs. $154 \times 10^3 \, \mu L^{-1}$; $P < 0.001$) and serum albumin level (4.2 g/dL vs. 4.2 g/dL; $P < 0.001$) than those in group 1.

Factors associated with the risk of HCC development during the follow-up

The baseline characteristics of the patients are listed in Supplementary Table S2. Patients with HCC had a higher median age (55.6 years vs. 48.7 years), frequency of males (75.1% vs. 61.1%), diabetes (16.1% vs. 7.7%), hypertension (16.1% vs. 9.5%), and cirrhosis (73.7% vs. 28.0%), and a higher median total bilirubin level

Table 1. Baseline characteristics of the study population ($n = 3,156$).

Variables	Values
Age, years	49.6 (40.5–56.6)
Male gender	1,969 (62.4)
Diabetes mellitus	267 (8.5)
Hypertension	320 (10.1)
Cirrhosis	1,015 (32.2)
Total bilirubin, mg/dL	0.7 (0.5–1)
Serum albumin, g/dL	4.2 (3.8–4.5)
Platelet count, $\times 10^3 \, \mu L^{-1}$	161 (117–208)
Prothrombin time, INR	1.03 (0.95–1.11)
Positive HBeAg	1,561 (49.5)
ETV/TDF	1,651 (52.6)/1,505 (47.4)

Note: Values are expressed as number (%) or median (interquartile range).
Abbreviations: HBeAg, hepatitis B e antigen; INR, international normalized ratio.

Table 2. Clinical factors associated with the risk of HCC development.

Variables	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age, years				
<40	Reference		Reference	
40–50	4.54 (2.32–8.90)	<0.001	2.76 (1.40–5.44)	0.003
50–60	9.63 (5.07–18.3)	<0.001	4.89 (2.55–9.39)	<0.001
≥60	13.05 (6.78–25.13)	<0.001	6.84 (3.51–13.33)	<0.001
Male gender	1.88 (1.44–2.46)	<0.001	2.23 (1.70–2.92)	<0.001
Diabetes mellitus	2.07 (1.51–2.84)	<0.001	—	—
Hypertension	1.71 (1.24–2.34)	<0.001	—	—
Cirrhosis	6.24 (4.8–8.13)	<0.001	3.30 (2.48–4.39)	<0.001
Total bilirubin ≥0.82 mg/dL	1.96 (1.56–2.48)	<0.001	—	—
Serum albumin <4.0 g/dL	2.59 (2.05–3.27)	<0.001	1.56 (1.22–1.99)	<0.001
Platelet count <131 × 10^3 μL^{-1}	4.36 (3.42–5.56)	<0.001	2.00 (1.53–2.61)	<0.001

(0.80 mg/mL vs. 0.69 mg/dL) and lower median serum albumin level (3.9 g/dL vs. 4.2 g/dL) and platelet count (113×10^3 μL^{-1} vs. 166×10^3 μL^{-1}) compared with those without HCC (all $P < 0.05$).
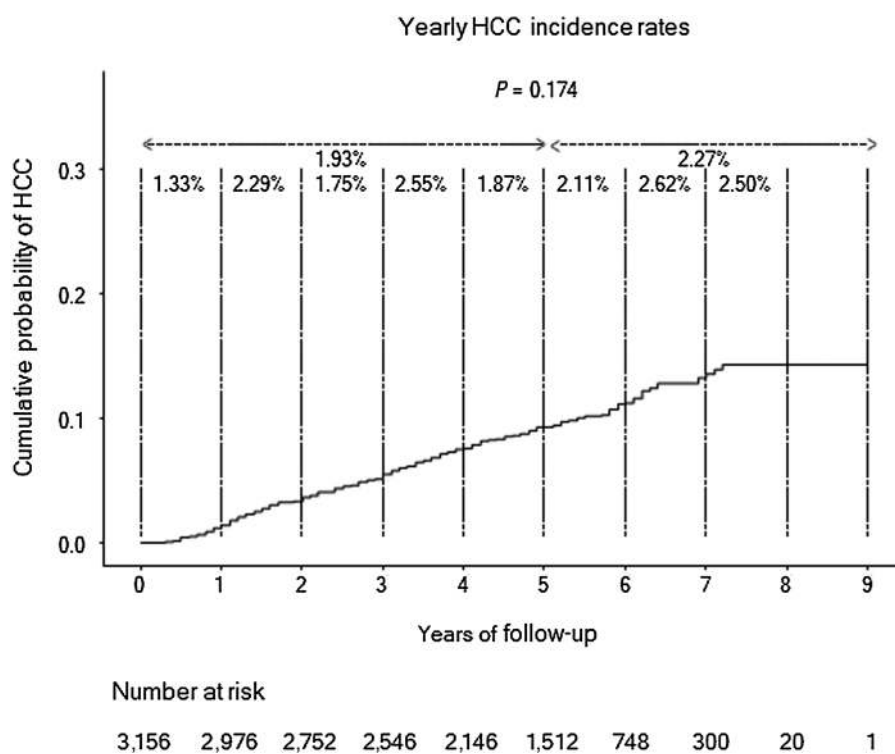
Univariate analyses to identify factors associated with the risk of HCC development during follow-up showed that the total bilirubin and serum albumin levels and the platelet count were significantly predictive of HCC development. Next, these three variables were converted to binary variables using the Contal and O'Quigley method (19). The optimal cutoff points for prediction of HCC were as follows: total bilirubin level of 0.82 mg/dL, serum albumin level of 4.0 g/dL, and platelet count of 131×10^3/μL (**Table 2**). Thus, patients with a total bilirubin level of ≥0.82 mg/dL, serum albumin level of <4.0 g/dL, and platelet count of $<131 \times 10^3$ μL^{-1} have a significantly higher risk of HCC development (HR = 1.96; 95% CI, 1.56–2.48; $P < 0.001$), 2.59 (95% CI, 2.05–3.27; $P < 0.001$), and 4.36

(95% CI, 3.42–5.56; $P < 0.001$), respectively. Male gender (HR = 1.88; 95% CI, 1.44–2.46; $P < 0001$) was also associated with a higher risk of HCC development and the risk of HCC increased stepwise with increasing age.
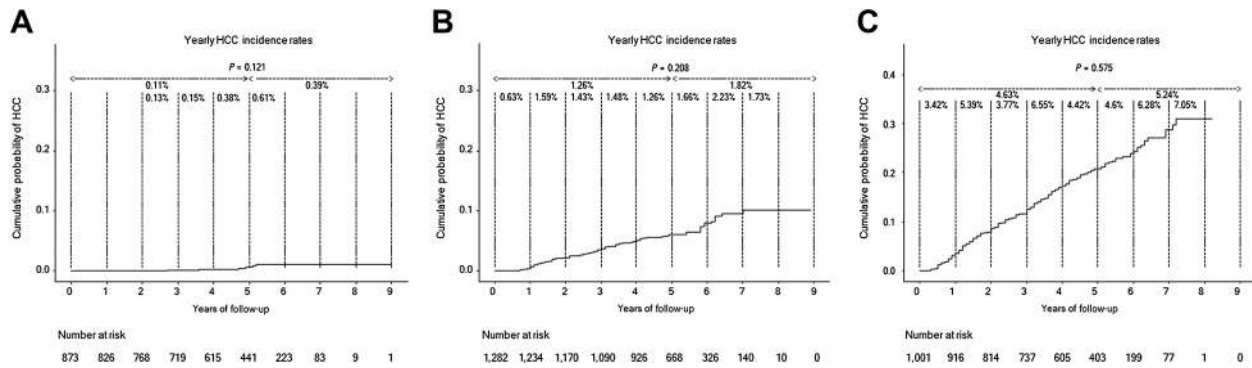
A multivariate Cox-regression analysis (**Table 2**) indicated that cirrhosis (adjusted HR = 3.30, 95% CI, 2.48–4.39; $P < 0.001$), a low serum albumin level (adjusted HR = 1.56; 95% CI, 1.22–1.99; $P < 0.001$), and low platelet count (adjusted HR = 2.00; 95% CI, 1.53–2.61; $P < 0.01$) were independent risk factors for HCC development and the risk of HCC also independently increased stepwise with increasing age.

Incidence of HCC during and after the first 5 years of AVT

The incidence of HCC is shown in **Fig. 1**. During the follow-up (median = 58.3 months; interquartile range = 42.2–70.4 months), 285 (9.0%) patients developed HCC. The overall cumulative probabilities

Yearly HCC incidence rates

$P = 0.174$

1.93%

1.33% | 2.29% | 1.75% | 2.55% | 1.87% | 2.11% | 2.62% | 2.50%

2.27%

Years of follow-up

Number at risk

3,156 2,976 2,752 2,546 2,146 1,512 748 300 20 1

Figure 1.
Annual incidence of HCC during long-term AVT in the entire population.

Figure 2.
Annual incidence of HCC during long-term AVT stratified by the modified PAGE-B score for low-risk (**A**), intermediate-risk (**B**), and high-risk (**C**) groups.

of HCC development at 3, 5, and 7 years were 5.3%, 9.3%, and 13.8%, respectively. The annual incidence of HCC per 100 person-years was 1.93% during the first 5 years of AVT and 2.27% after the first 5 years of AVT ($P = 0.347$; **Fig. 1**).

We analyzed the annual incidence of HCC stratified according to the modified PAGE-B score, an HCC prediction model (21). In the low-risk group (<8 points), the annual incidence per 100 person-years during and after the first 5 years of AVT was 0.11% and 0.39%, respectively ($P = 0.121$; **Fig. 2A**). The equivalent values in the intermediate-risk (9–12 points) and high-risk (≥13 points) groups were 1.26% and 1.82% ($P = 0.208$) and 4.63% and 5.24%, respectively ($P = 0.575$; **Fig. 2B** and **C**).

Multivariate-adjusted analysis for the risk of HCC development during long-term AVT

To assess the temporal changes in the risk of HCC development according to the AVT duration across a long-term follow-up, a Poisson regression analysis was performed (**Table 3**). In the final model, age, male gender, cirrhosis, low platelet count, and low serum albumin level were significantly and independently associated with the adjusted annual IRR (all $P < 0.05$). However, the duration of AVT did not significantly affect the incidence of HCC during long-term AVT (adjusted annual IRR = 0.85; 95% CI, 0.66–1.11; $P = 0.232$).

Discussion

The pattern of temporal changes in the risk of HCC development over time during prolonged NUC therapy in patients with CHB is still

Table 3. Determinants for HCC risk in the final Poisson regression model.

Variables	Adjusted IRR (95% CI)	P value
Years on AVT	0.85 (0.66–1.11)	0.232
Age, years		
<40	Reference	
40–50	2.79 (1.42–5.51)	0.003
50–60	4.95 (2.57–9.53)	<0.001
≥60	6.03 (3.02–12.05)	<0.001
Male gender	1.98 (1.45–2.72)	<0.001
Cirrhosis	3.36 (2.53–4.48)	<0.001
Platelet count <131 × 10^3 μL^{-1}	1.76 (1.27–2.43)	<0.001
Serum albumin <4.0 g/dL	1.4 (1.04–1.88)	0.026

unclear. Because prolonged potent AVT could attenuate the necro-inflammation and consequent fibrogenesis caused by active HBV replication, the risk of HCC development may decrease over time. Conversely, because patients become older as time goes on, the preventive effect of AVT seems to be substantially offset by the host factors. Such information is essential for estimating the HCC risk of patients on AVT and development of a cost-effective surveillance strategy. In this study, we aimed to evaluate the temporal changes in the incidence of HCC during long-term AVT with high-genetic barrier NUCs.

Even though the HCC incidence during the follow-up seemed to gradually increase among nearly 3,000 patients with CHB, it did not significantly increase with increasing treatment duration [annual incidence per 100 person-years 1.93% during the first 5 years and 2.27% after the first 5 years ($P = 0.347$), adjusted IRR 0.85 (95% CI, 0.66–1.11; $P = 0.232$)]. That is, rather than the viral factor, that is duration of AVT, the baseline host factors such as older age, male gender, cirrhosis, and a low platelet count and serum albumin level at the time of AVT were independent determinants of HCC development among NUC-treated patients, which were in accordance with previous reports (11, 21, 22). Furthermore, patients with CHB in the ROK remain at relatively high risk of HCC development for a longer period than those in Western countries. Similarly, the risk of HCC development increased in a step-wise manner according to the modified PAGE-B score (21). However, in all three subgroups (low-, interme-diate-, and high-risk groups), the annual incidence of HCC changed only minimally during the treatment period.

There are several explanations for the discrepancies between ours and previous studies involving Western and Taiwanese cohorts (9, 10). The baseline clinical characteristics of our study population, that is, Asian ethnicity (vs. Caucasian), predominance of HBV genotype C [vs. presumably D in the Caucasian cohort (9) or B and C in the Taiwanese cohort (10)], and a prevalence of liver cirrhosis of nearly 50% (vs. ∼30%; refs. 9, 10) might contribute to the higher risk of HCC despite long-term AVT. As a matter of fact, in the ROK, most patients with CHB (>98%) have HBV genotype C2, which they contracted by vertical transmission. Even though the overall virologic response rates through potent NUCs are similar among HBV genotypes, both HBV genotype C2 itself and the associated longer disease duration might considerably contribute the higher HCC risk (8, 12). Accordingly, patients enrolled in this study might have a more unfavorable natural history compared to cohorts from other countries. HBV-related carcinogenesis is a multifactorial process where the direct oncogenic activity of HBV is enhanced by chronic active inflammation due to

increased oxidative stress, necrosis, regeneration, angiogenesis, and cellular senescence (17, 23). Because NUCs primarily improve liver histologic lesions by inhibiting HBV replication but cannot eradicate HBV from hepatocytes (24), we speculate that some molecular mechanisms of carcinogenesis are not affected by long-term use of potent NUCs (e.g., specific HBV mutants or integration of HBV DNA into the host genome).

This study has some advantages from the methodologic viewpoint. Not only the larger sample size ($n = 3{,}156$) compared with two hospital-based cohort studies [$n = 894$ (11) or 1,951 (9)], but also the longer follow-up duration (median 58.3 months vs. 25.1 months) and the higher rate of HCC occurrence (9.0% vs. 2.9%) compared with a nationwide cohort study (10) might considerably enhance the statistical power and the reliability. Indeed, many previous studies of the risk of HCC during long-term AVT had a mean/median treatment duration of less than 5 years (4, 25) and data on the incidence of HCC after the first 5 years of AVT are sparse. Furthermore, from the statistical viewpoint, the proportional hazard assumption in Cox regression analysis was verified using Grambasch and Therneau test (all $P > 0.05$; Supplementary Table S3; ref. 26) and the value/df for the deviance in Poisson regression analysis was 1.321, which suggests the absence of overdispersion. Finally, the homogeneity of the cohort in terms of ethnicity and HBV genotype (C2) facilitated analysis and interpretation of the data.

In the low-risk group by modified PAGE-B score accounting for approximately 27.7% among the entire study population (21), after 5 years of AVT, the annual incidence of HCC was still very low; 0.39%. Hence, whether the current strategy of biannual abdominal ultrasonography with or without assessment of tumor markers for such a subgroup is beneficial should be evaluated further, in terms of the cost-effectiveness and practical usefulness of the HCC screening (27). Conversely, the intermediate- and high-risk groups (>70% of the population) had significantly higher annual incidences of HCC despite treatment with potent NUCs. Therefore, more sensitive screening methods to detect early-stage HCC, for example magnetic resonance imaging (MRI) with liver-specific contrast (28, 29) or a simplified noncontrast MRI (30, 31), might be helpful and the optimal diagnostic modality and interval between visits need to be determined taking into consideration the risk of HCC. Finally, other risk factors in the environment and life style, such as cigarette smoking, alcohol consumption, and metabolic diseases, should be controlled simultaneously to reduce the HCC risk (32).

We also recognize several limitations of this study. First, because all the participants were from the ROK, the results may not be representative of the whole spectrum of patients with chronic HBV infection. Second, the molecular characteristics of HBV (e.g., mutations of the envelope, core, and X proteins), novel biomarkers (e.g., serum HBsAg, hepatitis B core-related antigen, or HBV-RNA level), and refined fibrosis markers [e.g., elastography, fibrotest (33), or enhanced liver fibrosis test (34)] should be considered to enhance our understanding of the pathogenesis of HCC. Finally, even though our study has a relatively longer follow-up duration, the number of patients with more than 5 to 7 years of follow-up is still rather small, reducing the power of the study in detecting potential longer-term effects of the AVT on hepatocellular carcinoma incidence. Therefore, given that chronic HBV infection can be life-long, further studies involving a longer duration of AVT (>10 years) are needed to assess the beneficial effect of NUC therapy.

In summary, the annual incidence of HCC steadily persists over time during long-term AVT among Asian patients with CHB, in whom HBV genotype C2 predominated. Thus, despite the beneficial effect of long-term AVT, periodic HCC surveillance based on predetermined host factors is needed to improve overall survival.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.U. Kim, Y.S. Seo, B.K. Kim
Development of methodology: S.U. Kim, B.K. Kim, S.Y. Park
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.U. Kim, Y.S. Seo, H.A. Lee, H.W. Lee, J.Y. Park, D.Y. Kim, S.H. Ahn, K.-H. Han, S.H. Um, B.K. Kim, S.Y. Park
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.U. Kim, E.J. Lee, H.J. Shin, K.-H. Han, B.K. Kim
Writing, review, and/or revision of the manuscript: S.U. Kim, H.A. Lee, H.J. Shin, D.Y. Kim, Y.O. Kweon, B.K. Kim
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.U. Kim, M.N. Kim, B.K. Kim, S.Y. Park
Study supervision: Y.S. Seo, S.H. Ahn, W.Y. Tak, Y.O. Kweon, B.K. Kim, Y.R. Lee

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