ORIGINAL RESEARCH

The Prognostic Role of On-Treatment Liver Stiffness for Hepatocellular Carcinoma Development in Patients with Chronic Hepatitis B

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Background: Dynamic changes in fibrosis markers occur under long-term antiviral treatment (AVT) for chronic hepatitis B. We evaluated prognostic values of on-treatment liver stiffness (LS) compared to ultrasonography findings and determined its optimal cutoff.

Methods: The cumulative probability of hepatocellular carcinoma (HCC) was assessed among 880 patients receiving entecavir or tenofovir for ≥2 years. LS was measured using transient elastography.

Results: After ≥2 years' AVT, the proportion of patients with cirrhosis on ultrasonography decreased from 54.7% to 44.9% and the mean LS decreased from 13.6 to 8.2 kPa (both $p<0.001$). However, unlike cirrhosis on ultrasonography before AVT ($p<0.001$), that after ≥2 years' AVT did not discriminate HCC risk ($p=0.792$). Using the Contal and O'Quigley's method, pre-AVT and on-treatment LS of 12.0 and 6.4 kPa, respectively, were chosen as optimal cutoffs to successfully discriminate HCC risk (both $p<0.001$). However, through stratification using both pre-AVT and on-treatment LS, the prognosis was finally determined according to on-treatment LS of 6.4 kPa, regardless of pre-AVT LS of 12.0 kPa. Using on-treatment LS of 12 kPa suggested by Caucasians with CHB receiving long-term AVT, patients with higher LS were more likely to develop HCC than those with lower LS ($p=0.017$); however, there was no significant difference between those with on-treatment LS of 6.4–11.9 and ≥ 12.0 kPa ($p=0.920$).

Conclusion: For HCC risk stratification in patients receiving long-term AVT, on-treatment LS cutoff should be lowered to 6.4 kPa, which is more predictive than 12 kPa or cirrhosis on ultrasonography. Further studies are required for validation.

Keywords: antiviral treatment, hepatitis B, liver stiffness, hepatocellular carcinoma

Introduction

The overall prognosis of chronic hepatitis B virus (HBV) infection has improved primarily owing to long-term antiviral treatment (AVT) with potent oral nucleos(t) ide analogs (NUCs), such as entecavir (ETV) or tenofovir disoproxil fumarate (TDF), to prevent liver-disease progression and achieve to virological and biochemical remission.[1–4] However, as hepato-carcinogenesis is very complex based upon both host and viral factors,[5–10] it is difficult to eradicate, and some patients show HCC development, which remains a major public health problem in HBV-endemic areas.[11] Therefore, in addition to AVT, early detection of HCC by periodic surveillance is of paramount importance to allow timely interventions with a curative intent.[12–19]

Before the era of potent AVT, the serum HBV-DNA level was an important risk factor for HCC development.[20] However, because most patients taking potent NUCs can quickly achieve a complete virological response, its predictive performance had been substantially attenuated, especially in patients undergoing long-term NUC therapy;[21,22] this explains the considerable discrepancies among predictive performances of various HCC risk scores among study populations. Therefore, the remaining fibrotic burden, rather than antiviral regimens and/or intrahepatic inflammatory activity, has become the most crucial factor for determining the risk of HCC development.[23,24] Given that active AVT-induced reversal of liver fibrosis is the key mechanism by which viral suppression induces favorable clinical outcomes, long-term NUC therapy can also reduce the fibrotic burden, as assessed when by liver stiffness (LS).[25] Recently, Papatheodoridis et al[24] showed that patients achieving an LS of <12 kPa in 5 years of AVT had a significantly lower risk of HCC development than those who did not achieve this LS cutoff. However, while gross ultrasonographic findings indicative of liver cirrhosis at baseline are also a strong predictor of HCC development,[26] few studies have evaluated their predictive performances compared to that of on-treatment LS in patients receiving prolonged AVT.

This study assessed the prognostic value of on-treatment LS during long-term NUC therapy compared to those of gross ultrasonographic findings and established an optimal LS value for the prediction of HCC among patients with chronic hepatitis B (CHB).

Methods
Study Subjects
Between 2012 and 2018, treatment-naïve patients with CHB who had been taking ETV or TDF for at least 2 years in Severance Hospital, Seoul, Republic of Korea, were considered eligible for enrollment. The inclusion criteria were 1) age ≥19 years, 2) reliable LS values both before starting AVT and at ≥2 years of AVT, and 3) available ultrasonography results both before starting AVT and at ≥2 years of AVT. LS was measured using transient elastography (TE; FibroScan®, EchoSens, Paris, France) with a standard protocol.[27] Only LS values with at least 10 valid measurements, a success rate of at least 60%, and an interquartile range (IQR)-to-median ratio of <30% were considered reliable. On-treatment LS value was defined as one assessed after ≥ 2 years of AVT. The exclusion criteria

were 1) history of HCC or decompensated liver cirrhosis at enrollment; 2) co-infection with other hepatitis viruses; 3) history of organ transplantation; 4) HCC development, hepatic decompensation, or death within 6 months of enrollment; and 5) other significant medical illnesses.

The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of Severance Hospital, Seoul, Korea. Patient consent was waived because it is a retrospective study design. Patient's information was replaced with research identification codes for patient data confidentiality.

Clinical Evaluation and Follow-Up
During follow-up, NUC therapy was continued, and all patients underwent routine laboratory testing and assays for measuring serum HBV-DNA levels and other viral markers every 3–6 months. Serum alanine aminotransferase (ALT) levels were measured using standard laboratory procedures with the upper limit of normal set at <40 IU/mL. Furthermore, patients also underwent ultrasonography and assays for measuring serum alpha-fetoprotein levels every 6 months to screen for HCC and portal hypertension-related complications.[4,16,28] Liver cirrhosis based on ultrasonographical findings was defined when at least one of the following criteria was fulfilled; the presence of an irregular, nodular liver surface, highly coarse liver echotexture, a blunt liver edge, shrunken liver parenchyma, disturbed vascular architecture, or other findings suggestive of portal hypertension including splenomegaly (size >12 cm) and/or portosystemic collaterals.[29–32]

The primary endpoint of this study was HCC development. HCC was diagnosed based on histological evidence or dynamic computed tomography and/or magnetic resonance imaging findings (a nodule sized >1 cm with arterial hyper-vascularity and portal/delayed-phase washout).[33–35] The index date was the date of enrollment, while the time to HCC development was considered as the period between the index date and the date of HCC diagnosis or the end of follow-up in the absence of HCC development.

Statistical Analysis
Data are expressed as means ± standard deviations, medians (IQRs), or numbers (%), as appropriate. Differences among continuous and categorical variables were examined for statistical significance by the Student's *t*-test (or

the Mann–Whitney test, if appropriate) and chi-squared (or Fisher's exact tests, if appropriate) test. Paired data were analyzed using McNemar's or Wilcoxon signed-rank tests.

The cumulative risk of HCC development was evaluated using the Kaplan–Meier method, with comparisons using the Log rank test. Cox regression analysis was performed to assess the associations between the risk of HCC and each variable and to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Furthermore, Contal and O'Quigley's method based on Log rank tests,[36] an outcome-oriented method, was applied to determine an optimal LS cutoff before and during AVT for prognostication. Then, multivariable Cox-regression analysis was performed to determine the final prognostic factors associated with HCC development.

All statistical analyses were conducted using SAS, version 9.2 (SAS Institute), R (V.3.0, http://cran.r-project.org/), and IBM® SPSS® Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Two-sided p-values < 0.05 were considered to indicate statistical significance.

Results
Clinical Characteristics of the Study Population After ≥2 Years of AVT

A total of 880 treatment-naïve CHB patients were analyzed; of these, 400 and 480 patients were treated with ETV and TDF, respectively. Their clinical characteristics after ≥2 years of AVT are described in Table 1. The mean age was 53.1 years, and the male was predominant (57.6%). Liver cirrhosis was identified by ultrasonography in 44.9% of patients. The mean ALT value and platelet count were 29.0 IU/mL and 170 ×10³/uL, respectively, whereas the mean $\log_{10}$ HBV-DNA value was 1.3 IU/mL. The mean on-treatment LS was 8.2 kPa. All patients had well-preserved liver function (Child-Pugh class A).

Changes in Parameters After ≥2 Years of AVT

Clinical characteristics of the study population before starting AVT are described in Table 2. Liver cirrhosis was detected in 54.7% of patients, and the mean LS was 13.6 kPa. The mean ALT level and platelet count were 114.0 IU/mL and 160 ×10³/uL, respectively.

Table 1 Patients' Clinical Characteristics Before Starting AVT and After ≥ 2 Years of AVT (n=880)

Variables	Before Starting AVT	After ≥ 2 Years of AVT
Age, years	49.9 ± 10.7	53.1± 10.5
Male	373 (42.4)	507 (57.6%)
Diabetes mellitus	112 (12.7)	134 (15.2%)
Liver cirrhosis*	481 (54.7)	395 (44.9%)
ALT, IU/mL	114 ± 269	29.0 ± 34.7
Total bilirubin, mg/dL	1.2 ± 2.0	0.9 ± 0.5
Albumin, mg/dL	4.1 ± 0.5	4.4 ± 0.4
Prothrombn time-INR	1.1 ± 0.2	1.0 ± 0.1
Platelet count, ×10³/uL	160 ± 63	170 ± 64
HBeAg positivity	471 (53.5)	429 (50.6%)
HBV-DNA, $\log_{10}$ IU/mL	4.7 ± 2.5	1.3 ± 0.9
LS, kPa	13.6 ± 11.3	8.2 ± 5.9
Controlled attenuated parameter, dB/m	224 ± 57	240 ± 43
The proportion of normalized ALT after ≥ 2 years of AVT *		761 (85.2%)
The proportion of HBV-DNA < 20 IU/mL after ≥ 2 years of AVT		702 (79.8%)
Δ LS, kPa **	−5.4 ± 9.6	
Δ Controlled attenuation parameter, dB/m **	9.4 ± 41.8	

Notes: Values are expressed as mean ± standard deviation or number (%). The delta is defined as the value after ≥ 2 years of AVT minus that before starting AVT. *P-value<0.001 by McNemar test; **P-value<0.001 by Wilcoxon signed rank test.
Abbreviations: AVT, antiviral treatment; ALT, alanine aminotransferase; INR, international normalized ratio; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LS, liver stiffness.

After ≥2 years of AVT, serum HBV-DNA levels <20 IU/mL were observed in 79.8% of patients. During long-term NUC therapy, the proportion of patients with normal serum ALT levels increased from 39.7% to 85.2% (p<0.001). After ≥2 years of AVT, the LS decreased significantly by 5.4 kPa (p<0.001), and the proportion of patients with liver cirrhosis on ultrasonography also decreased from 54.7% to 44.9% (p<0.001) (Table 1).

Cumulative Probability of HCC Development According to Variables Before Starting AVT

Among 880 patients, 81 (9.2%) developed HCC. Table 2 shows the comparison of variables between those who developed HCC and those who did not. To assess the prognostic significance of dynamic changes in variables through ≥2 years of AVT, we first analyzed the cumulative probability of HCC development according to values recorded before starting AVT. Using Contal and O'Quigley's method, we proposed an optimal cut-off value of pre-AVT LS of 12.0 kPa.[36] The cumulative risk of HCC development was significantly higher in patients with pre-AVT LS of ≥12.0 kPa than in those with pre-AVT LS of <12.0 kPa (p<0.001) (Figure 1). Furthermore, patients with liver cirrhosis on

ultrasonography before AVT were more likely to develop HCC than those without (p<0.001) (Figure 2A).

Cumulative Probability of HCC Development According to On-Treatment Variables After ≥2 Years of AVT and Overall Predictors for HCC Development

We stratified the cumulative risk of HCC development based on the fibrotic burden after ≥2 years of AVT. Likewise, using Contal and O'Quigley's method, we identified an optimal cutoff value of on-treatment LS of 6.4 kPa.[36] The cumulative risk of HCC development was significantly higher in patients with on-treatment LS of ≥6.4 kPa than in those with on-treatment LS of <6.4 kPa (p<0.001; Figure 3). In contrast, liver cirrhosis on ultrasonography after ≥2 years of AVT, a prognostic factor in the previous study, did not have discriminatory ability in terms of HCC risk prediction (p=0.792; Figure 2B), unlike liver cirrhosis on ultrasonography before AVT.

Thereafter, univariate analysis was performed to identify potential factors associated with HCC development. Univariate predictors with p values of < 0.05, including age, ALT levels ≥40 U/L, total bilirubin levels, albumin levels, platelet counts, and on-treatment LS of ≥6.4 kPa,

Table 2 Comparisons of Clinical Characteristics Between Patient with HCC and Those without

Variables After ≥ 2 Years of AVT	Patients with HCC (n=81)	Patients without HCC (n=799)	p-value
Age, years	58.4 ± 8.4	52.6 ± 10.6	<0.001
Male	52 (64.2%)	455 (56.9%)	0.208
Diabetes mellitus	13 (16.0%)	121 (15.1%)	0.829
Liver cirrhosis	36 (44.4%)	359 (44.9%)	0.933
ALT, IU/mL	46.4 ± 80.5	27.2 ± 25.3	0.036
Total bilirubin, mg/dL	1.0 ± 0.7	0.9 ± 0.4	0.094
Albumin, mg/dL	4.2 ± 0.5	4.4 ± 0.3	0.001
Prothrombn time-INR	1.0 ± 0.1	1.0 ±0.1	0.552
Platelet count, ×10^3/uL	129 ± 44	174 ± 64	<0.001
HBeAg positivity	39 (51.3%)	390 (50.5%)	0.894
HBV-DNA, $\log_{10}$ IU/mL	1.1 ± 0.5	1.3 ± 0.9	0.057
LS, kPa	10.1 ± 5.3	8.0 ± 5.9	0.002
Controlled attenuated parameter, dB/m	249 ± 43	239 ± 42	0.033

Note: Values are expressed as mean ± standard deviation or number (%).
Abbreviations: AVT, antiviral treatment; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; INR, international normalized ratio; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LS, liver stiffness.

were entered into a multivariate Cox regression model. Finally, four variables—older age (adjusted HR [aHR] 1.044, 95% CI 1.019–1.070; p<0.001), lower platelet counts (aHR 0.991, 95% CI 0.987–0.996; p<0.001), ALT levels ≥40 U/mL (aHR 1.947, 95% CI 1.158–3.276; p=0.012), and on-treatment LS ≥6.4 kPa (aHR 2.347, 95% CI 1.296–4.250; p=0.005)—were identified as independent prognostic factors for HCC development (Table 3).

Verification of Another Cutoff of On-Treatment LS After ≥2 Years of AVT

We tested the prognostic performance of another cutoff (12 kPa) of on-treatment LS that had been recently suggested by Papatheodoridis et al to be a significant predictor of HCC development among Caucasians with CHB receiving long-term potent AVT.[24] In our study population, patients with on-treatment LS of ≥12 kPa were also
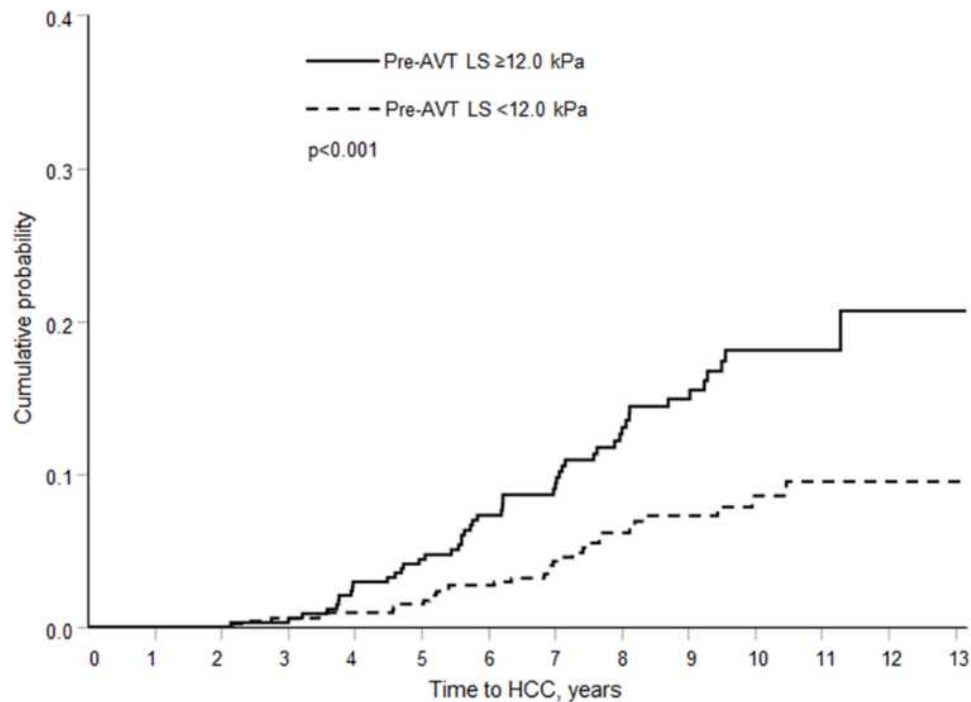

Figure 1 Kaplan–Meier analyses according to pre-AVT LS with a cutoff of 12.0 kPa.
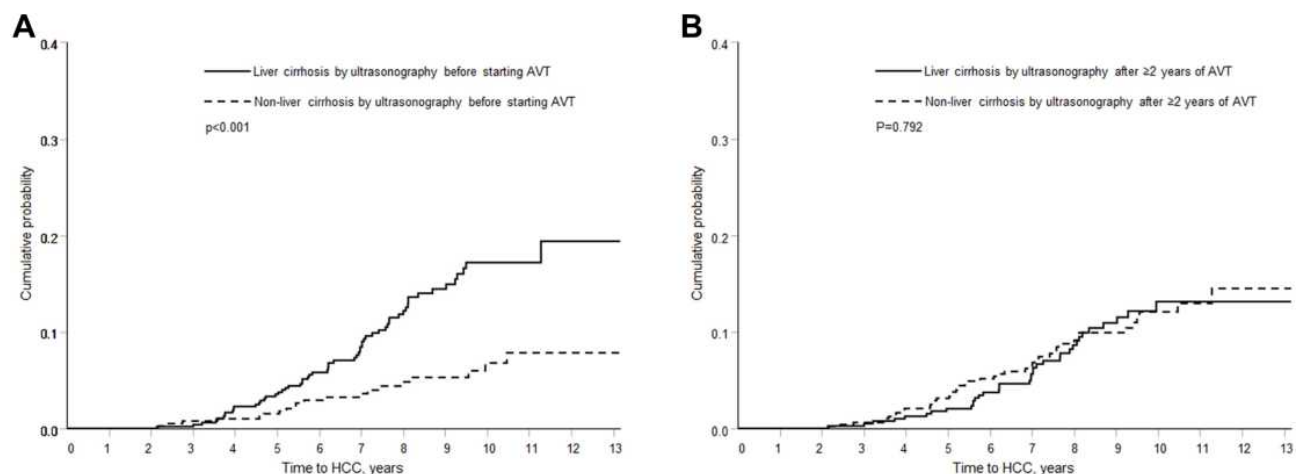**Abbreviations:** AVT, antiviral treatment; LS, liver stiffness; HCC, hepatocellular carcinoma.

Figure 2 Kaplan–Meier analyses according to liver cirrhosis on ultrasonography before starting AVT (**A**) and after ≥ 2 years of AVT (**B**).
Abbreviations: AVT, antiviral treatment; HCC, hepatocellular carcinoma.

significantly more likely to develop HCC than those with on-treatment LS of <12 kPa (p=0.017) ([Supplementary Figure 1A](#)).

However, dividing the patients into three groups by on-treatment LS values (<6.4 kPa vs 6.4–11.9 kPa vs ≥12.0 kPa) showed no significant differences in risk between those with an on-treatment LS of 6.4–11.9 kPa and ≥12.0 kPa (p=0.920; [Supplementary Figure 1B](#)). However, patients with on-treatment LS of <6.4 kPa were still significantly less likely to develop HCC (both p<0.001) than those with an on-treatment LS of 6.4–11.9 kPa or ≥12.0 kPa.

Risk Stratification Based on LS Both Before Starting AVT and After ≥2 Years of AVT

We stratified our study population into four groups based on pre-AVT and on-treatment LS ([Supplementary Figure 2](#)). Regardless of pre-AVT LS (≥12.0 vs <12 kPa), the prognosis was finally determined according to on-treatment LS, ie, ≥6.4 vs <6.4 kPa. Among patients with on-treatment LS≥6.4 kPa, there was no significant difference in the HCC risk according to pre-AVT LS (≥12.0 vs <12 kPa) (p=0.302). Likewise, among patients with on-

treatment LS<6.4 kPa, there was no significant difference in the HCC risk according to pre-AVT LS (≥12.0 vs <12 kPa) (p=0.961).

Furthermore, we tried to validate the prognostic significance of on-treatment LS over pre-AVT LS among the independent cohort from Gangnam Severance Hospital, Seoul, Republic of Korea (n=458), where similar results were reproduced. Among patients with on-treatment LS≥6.4 kPa, there was no significant difference in the HCC risk according to pre-AVT LS (≥12.0 vs <12 kPa) (p=0.527). Likewise, among patients with on-treatment LS<6.4 kPa, there was no significant difference in the HCC risk according to pre-AVT LS (≥12.0 vs <12 kPa) (p=0.643).

Generation of the HCC Risk Prediction Model

We generated the HCC risk prediction model using 4 significant variables shown in [Table 3](#), ie, age, ALT, platelet count, and LS value; the regression coeffcient of each risk predictor from the multivariate Cox proportional hazards model was divided by that of age criteria (≥ 60 vs < 60 years), which was the lowest value among those of 4 variables, and then was rounded to an integer value to generate each score, respectively ([Supplementary Table 1](#)).
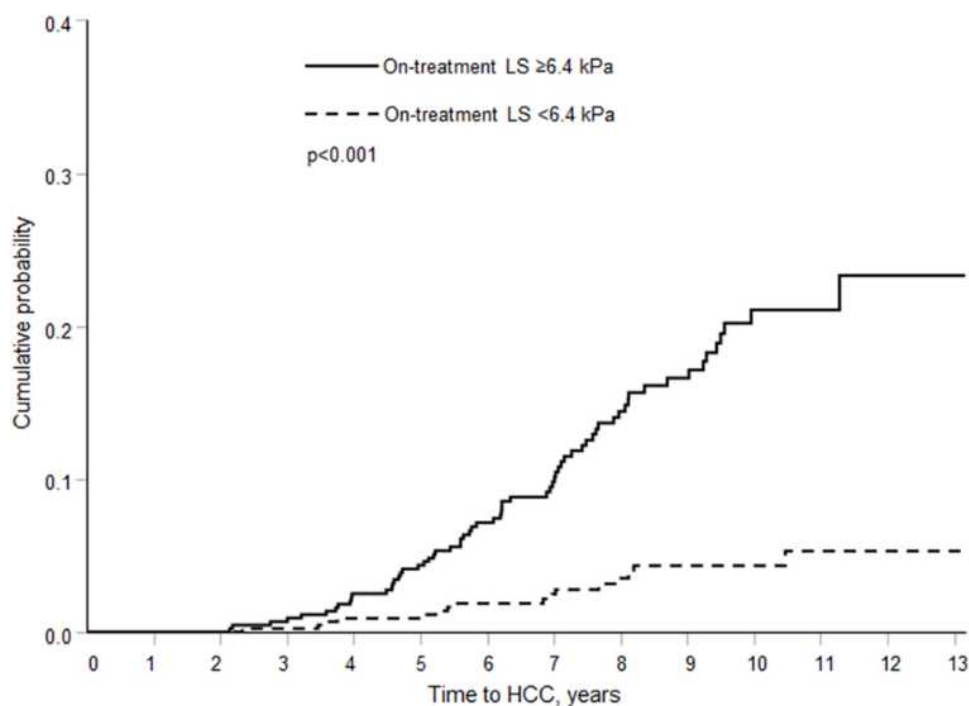

Figure 3 Kaplan–Meier analysis according to on-treatment LS with a cutoff of 6.4 kPa after ≥ 2 years of AVT.
Abbreviations: LS, liver stiffness; AVT, antiviral treatment; HCC, hepatocellular carcinoma.

Table 3 Risk Factors for the Development of Hepatocellular Carcinoma

Variables After ≥ 2 Years of AVT	Univariate Analysis	Multivariate Analysis		
	P-value	Adjusted HR	95% CI	P-value
Age	<0.001	1.044	1.019 ~ 1.070	<0.001
Male	0.241			
Diabetes	0.845			
Liver cirrhosis	0.792			
ALT ≥ 40 U/mL	0.009	1.947	1.158 ~ 3.276	0.012
Total bilirubin	0.029	0.865	0.586 ~ 1.279	0.468
Albumin	<0.001	0.673	0.407 ~ 1.114	0.123
Prothrombin time-INR	0.505			
Platelet count	<0.001	0.991	0.987 ~ 0.996	<0.001
HBeAg positivity	0.998			
HBV-DNA, $\log_{10}$ IU/mL	0.288			
LS ≥ 6.4 kPa	<0.001	2.347	1.296 ~ 4.250	0.005

Abbreviations: AVT, antiviral treatment; HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; INR, international normalized ratio; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LS, liver stiffness.

Then, the risk-scoring model was the sum of each score assigned to each key variable, providing the area under the receiver operating characteristic curve of 0.750 (95% CI 0.670 ~ 0.830) to predict the HCC development at 3 years.

Discussion

Several HCC risk scores have been developed and validated in large cohorts of NUC-treated CHB patients.[21,22] Most models established in the era of potent AVT did not incorporate serum HBV-DNA levels. Conversely, parameters reflecting fibrotic burden, such as serum fibrosis markers, ultrasonography findings, and LS, have been always crucial components. Given that such indices can change dynamically through fibrosis regression during prolonged potent AVT,[37] we aimed to identify an optimal cutoff for on-treatment LS for more accurate prognostication and to compare its usefulness to that of gross ultrasonography findings or other LS cutoffs.

In this study, we proposed a much lower cutoff of 6.4 kPa for on-treatment LS as a sentinel for HCC surveillance, approximately half of the conventional cutoffs (eg, 12 or 13 kPa).[38,39] Kim et al[39] proposed the so-called concept of TE-defined subclinical cirrhosis for 13 kPa, indicative of a higher risk of HCC development among patients with LS ≥13 kPa. However, in that study by Kim et al,[39] approximately 45% of enrolled patients did not receive AVT. Thus, our study provides more reliable data optimized for patients receiving long-term potent NUC therapy. In contrast, Papatheodoridis et al[24] suggested an on-treatment LS cutoff of 12 kPa for patients who had been receiving potent NUC therapy for 5 years.

Stratification of the population showed that the prediction of HCC risk might also be feasible with an on-treatment LS cutoff of 12 kPa (p=0.017). However, as seen in Supplementary Figure 1B, when patients were stratified into three categories of on-treatment LS (6.3 kPa vs 6.4–11.9 kPa vs ≥12.0 kPa), stepwise discrimination of HCC risk was no longer observed as patients with high vs intermediate levels of on-treatment LS had similar HCC risks. Thus, because the identification of patients with negligible risk of HCC development is one of the primary goals of risk scoring systems, we propose that a lower on-treatment LS cutoff of 6.4 ka would be more appropriate for effective HCC surveillance.

Liver cirrhosis on ultrasonography before AVT was also a significant predictor for HCC development in our study, consistent with that in previous studies.[5,22] However, once patients undergo prolonged potent AVT, cirrhosis on ultrasonography during prolonged AVT no longer played a crucial role in HCC risk prediction. Although the proportion of patients with liver cirrhosis on ultrasonography significantly decreased by about 10% after prolonged potent AVT, the prognostic value of this gross finding was surpassed by those of microscopic characteristics incorporated in LS. Consistent with our results, Papatheodoridis et al[24] developed the SAGE-B score for patients receiving long-term AVT, which showed a similarly excellent prognostic performance even without including the variable of "cirrhosis." Therefore, for cases involving discrepancies between TE and ultrasonography data in real-life practice, it would be more reasonable to make clinical decisions based on TE-based information.

Our study has several strengths and clinical implications. First, the homogeneous study population, large sample size (n=880), and sufficient number of HCC events (9.2%) as well as the long-term follow-up enhanced the statistical reliability. Moreover, to support scientific validity, cutoff points for continuous variables were determined using an outcome-oriented statistical method rather than arbitrary determination or simple adoption of previously suggested cutoffs. Second, although LS may not perfectly reflect the degree of change in histological fibrosis, the gold standard for predicting prognosis in chronic liver diseases, among CHB patients receiving prolonged AVT, LS remains the most widely validated tool by which clinically relevant information can be obtained easily and non-invasively in real-life practice. Third, from a practical viewpoint, we selected the time point of ≥2 years of AVT to re-assess the risk of HCC based on the study by Chon et al[37] which indicated significant dynamic changes in HCC risk scores occur for up to 2 ~ 3 years after AVT initiation. In contrast, Papatheodoridis et al[24] focused on patients who had been receiving potent AVT for at least 5 years. However, considering that the annual risk of HCC development usually exceeds 1.5% in patients with HBV-related cirrhosis and that the proportion of such patients among our study population was approximately 50%, a minimum follow-up duration of 5 years was too long in terms of our practice milieu.

Furthermore, when our study population was stratified into four groups based on both pre-AVT and on-treatment LS, the prognosis was determined according to on-treatment LS (≥6.4 vs <6.4 kPa), regardless of the pre-AVT LS (≥12.0 vs <12 kPa). Thus, patients with relatively higher LS before AVT may have a significantly lower risk of HCC occurrence provided that they showed a good response in terms of fibrosis regression due to long-term potent AVT. Conversely, patients with a relatively favorable fibrotic status before AVT may have a significantly higher risk if they show a suboptimal response despite prolonged potent AVT. Our results indicate the need for the re-assessment of HCC risk during long-term NUC therapy to develop personalized HCC surveillance strategies.

This study also has several limitations. First, since it was conducted from a single tertiary referral hospital-based cohort in the Republic of Korea, our results were potentially subject to selection bias. Nevertheless, a homogeneous study population, a statistically reliable sample size, event number, and follow-up duration, and an outcome-oriented statistical method could help overcome this drawback. In the similar context, >98% of patients are infected with HBV genotype C through vertical transmission, both of which were associated with a higher risk of HCC development.[3] Thus, these results may not be generalizable to the full spectrum of the population with chronic HBV infection. However, because the overall virological response rates for potent AVT are similar among HBV genotypes, in contrast to those for pegylated interferon therapy, our results are likely to be reproduced in other countries.[3] Second, the incorporation of new biomarkers for CHB (eg, serum quantitative HBsAg, serum hepatitis B core-related antigen, serum HBV-RNA, or specific HBV mutants) into the model may have provided more precise predictions.[40–43] Last, along with an issue of how to identify so called, a high-risk group, the development of a diagnostic modality to detect early de-novo carcinogenesis with high sensitivity and specificity should be required in the future researches.[44–46]

In conclusion, the on-treatment LS cutoff for the appropriate stratification of HCC risk among patients receiving long-term potent AVT should be lowered to 6.4 kPa, approximately half of the conventional cutoff. Liver cirrhosis on ultrasonography after ≥2 years of AVT did not predict HCC development. Therefore, for cases with discrepancies between TE and ultrasonography data, decision-making based on TE-based information might be more reasonable. Further studies are required for external validation.

Data Sharing Statement

The data in this study will be available after approval by all authors, upon reasonable request.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560–1599. doi:10.1002/hep.29800
2. Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. *J Hepatol*. 2018;68(6):1129–1136. doi:10.1016/j.jhep.2018.01.031
3. Korean Association for the Study of the Liver (KASL) clinical practice guidelines for management of chronic hepatitis B. *Clin Mol Hepatol*. 2019;25(2):93–159. doi:10.3350/cmh.2019.1002
4. Yim HJ, Kim JH, Park JY, et al. Comparison of clinical practice guidelines for the management of chronic hepatitis B: when to start, when to change, and when to stop. *Clin Mol Hepatol*. 2020;26(4):411–429. doi:10.3350/cmh.2020.0049
5. Hsu YC, Yip TC, Ho HJ, et al. Development of a scoring system to predict hepatocellular carcinoma in Asians on antivirals for chronic hepatitis B. *J Hepatol*. 2018;69(2):278–285. doi:10.1016/j.jhep.2018.02.032

6. Chao X, Qian H, Wang S, Fulte S, Ding WX. Autophagy and liver cancer. *Clin Mol Hepatol*. 2020;26(4):606–617. doi:10.3350/cmh.2020.0169

7. Lee SB, Jeong J, Park JH, et al. Low-level viremia and cirrhotic complications in patients with chronic hepatitis B according to adherence to entecavir. *Clin Mol Hepatol*. 2020;26(3):364–375. doi:10.3350/cmh.2020.0012

8. Liu Y, Wang X, Yang Y. Hepatic Hippo signaling inhibits development of hepatocellular carcinoma. *Clin Mol Hepatol*. 2020;26 (4):742–750. doi:10.3350/cmh.2020.0178

9. Lee S, Choi EJ, Cho EJ, et al. Inhibition of PI3K/Akt signaling suppresses epithelial-to-mesenchymal transition in hepatocellular carcinoma through the Snail/GSK-3/beta-catenin pathway. *Clin Mol Hepatol*. 2020;26(4):529–539. doi:10.3350/cmh.2019.0056n

10. Lee YB, Ha Y, Chon YE, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. *Clin Mol Hepatol*. 2019;25(1):52–64. doi:10.3350/cmh.2018.0040

11. Park SH, Plank LD, Suk KT, et al. Trends in the prevalence of chronic liver disease in the Korean adult population, 1998–2017. *Clin Mol Hepatol*. 2020;26(2):209–215. doi:10.3350/cmh.2019.0065

12. EASL Clinical Practice. Guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019.

13. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67 (1):358–380. doi:10.1002/hep.29086

14. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;10(1):1–98. doi:10.1007/s12072-015-9675-4

15. European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370–398. doi:10.1016/j.jhep.2017.03.021

16. Hanouneh IA, Alkhouri N, Singal AG. Hepatocellular carcinoma surveillance in the 21st century: saving lives or causing harm? *Clin Mol Hepatol*. 2019;25(3):264–269. doi:10.3350/cmh.2019.1001

17. Yang JD. Detect or not to detect very early stage hepatocellular carcinoma? The western perspective. *Clin Mol Hepatol*. 2019;25 (4):335–343. doi:10.3350/cmh.2019.0010

18. Ahn KS, Kang KJ. Appropriate treatment modality for solitary small hepatocellular carcinoma: radiofrequency ablation vs. resection vs. transplantation? *Clin Mol Hepatol*. 2019;25(4):354–359. doi:10.3350/cmh.2018.0096

19. Yoon SM, Kim SY, Lim YS, et al. Stereotactic body radiation therapy for small (≤5 cm) hepatocellular carcinoma not amenable to curative treatment: results of a single-arm, Phase II clinical trial. *Clin Mol Hepatol*. 2020;26(4):506–515. doi:10.3350/cmh.2020.0038

20. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol*. 2011;12(6):568–574. doi:10.1016/s1470-2045(11)70077-8

21. Wong VW, Janssen HL. Can we use HCC risk scores to individualize surveillance in chronic hepatitis B infection? *J Hepatol*. 2015;63 (3):722–732. doi:10.1016/j.jhep.2015.05.019

22. Papatheodoridis GV, Voulgaris T, Papatheodoridi M, Kim WR. Risk scores for hepatocellular carcinoma in chronic Hepatitis B: a promise for precision medicine. *Hepatology*. 2020;72:2197–2205. doi:10.1002/hep.31440

23. Wu S, Kong Y, Piao H, et al. On-treatment changes of liver stiffness at week 26 could predict 2-year clinical outcomes in HBV-related compensated cirrhosis. *Liver Int*. 2018;38(6):1045–1054. doi:10.1111/liv.13623

24. Papatheodoridis GV, Sypsa V, Dalekos GN, et al. Hepatocellular carcinoma prediction beyond year 5 of oral therapy in a large cohort of Caucasian patients with chronic hepatitis B. *J Hepatol*. 2020;72 (6):1088–1096. doi:10.1016/j.jhep.2020.01.007

25. Facciorusso A, Garcia Perdomo HA, Muscatiello N, Buccino RV, Wong VW, Singh S. Systematic review with meta-analysis: change in liver stiffness during anti-viral therapy in patients with hepatitis B. *Dig Liver Dis*. 2018;50(8):787–794. doi:10.1016/j.dld.2018.05.005

26. Yang HI, Yeh ML, Wong GL, et al. Real-world effectiveness from the Asia Pacific Rim Liver Consortium for HBV risk score for the prediction of hepatocellular carcinoma in chronic hepatitis B patients treated with oral antiviral therapy. *J Infect Dis*. 2020;221 (3):389–399. doi:10.1093/infdis/jiz477

27. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003;29(12):1705–1713. doi:10.1016/j.ultrasmedbio.2003.07.001

28. Maruyama H, Kato N. Advances in ultrasound diagnosis in chronic liver diseases. *Clin Mol Hepatol*. 2019;25(2):160–167. doi:10.3350/cmh.2018.1013

29. Suk KT, Baik SK, Yoon JH, et al. Revision and update on clinical practice guideline for liver cirrhosis. *Korean J Hepatol*. 2012;18 (1):1–21. doi:10.3350/kjhep.2012.18.1.1

30. Aubé C, Oberti F, Korali N, et al. Ultrasonographic diagnosis of hepatic fibrosis or cirrhosis. *J Hepatol*. 1999;30(3):472–478. doi:10.1016/s0168-8278(99)80107-x

31. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: accuracy of US for detection–analysis of 300 cases. *Radiology*. 2003;227(1):89–94. doi:10.1148/radiol.2272020193

32. Gaiani S, Gramantieri L, Venturoli N, et al. What is the criterion for differentiating chronic hepatitis from compensated cirrhosis? A prospective study comparing ultrasonography and percutaneous liver biopsy. *J Hepatol*. 1997;27(6):979–985. doi:10.1016/s0168-8278(97)80140-7

33. Kim TH, Kim SY, Tang A, Lee JM. Comparison of international guidelines for noninvasive diagnosis of hepatocellular carcinoma: 2018 update. *Clin Mol Hepatol*. 2019;25(3):245–263. doi:10.3350/cmh.2018.0090

34. Lee S, Kim SS, Chang DR, Kim H, Kim MJ. Comparison of LI-RADS 2018 and KLCA-NCC 2018 for noninvasive diagnosis of hepatocellular carcinoma using magnetic resonance imaging. *Clin Mol Hepatol*. 2020;26(3):340–351. doi:10.3350/cmh.2020.0004

35. Kim YY, Park MS, Aljoqiman KS, Choi JY, Kim MJ. Gadoxetic acid-enhanced magnetic resonance imaging: hepatocellular carcinoma and mimickers. *Clin Mol Hepatol*. 2019;25(3):223–233. doi:10.3350/cmh.2018.0107

36. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Anal*. 1999;30(3):253–270. doi:10.1016/S0167-9473(98)00096-6

37. Chon HY, Seo YS, Lee JI, et al. Dynamics of liver stiffness-based risk prediction model during antiviral therapy in patients with chronic hepatitis B. *Eur J Gastroenterol Hepatol*. 2020. doi:10.1097/meg.0000000000001794

38. Jung KS, Kim SU, Ahn SH, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology*. 2011;53(3):885–894. doi:10.1002/hep.24121

39. Kim MN, Kim SU, Kim BK, et al. Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with transient elastography-defined subclinical cirrhosis. *Hepatology*. 2015;61 (6):1851–1859. doi:10.1002/hep.27735

40. Liang LY, Wong GL. Unmet need in chronic hepatitis B management. *Clin Mol Hepatol*. 2019;25(2):172–180. doi:10.3350/cmh.2018.0106

41. Inoue T, Tanaka Y. Novel biomarkers for the management of chronic hepatitis B. *Clin Mol Hepatol*. 2020;26(3):261–279. doi:10.3350/cmh.2020.0032

42. Liu S, Zhou B, Valdes JD, Sun J, Guo H. Serum HBV RNA: a New Potential Biomarker for Chronic Hepatitis B Virus Infection. *Hepatology*. 2018. doi:10.1002/hep.30325

43. Lall S, Agarwala P, Kumar G, Sharma MK, Gupta E. The dilemma of differentiating between acute hepatitis B and chronic hepatitis B with acute exacerbation: is quantitative serology the answer? *Clin Mol Hepatol*. 2020;26(2):187–195. doi:10.3350/cmh.2019.0060

44. Esfeh JM, Hajifathalian K, Ansari-Gilani K. Sensitivity of ultrasound in detecting hepatocellular carcinoma in obese patients compared to explant pathology as the gold standard. *Clin Mol Hepatol*. 2020;26 (1):54–59. doi:10.3350/cmh.2019.0039

45. Kim J, Kang W, Sinn DH, et al. Substantial risk of recurrence even after 5 recurrence-free years in early-stage hepatocellular carcinoma patients. *Clin Mol Hepatol*. 2020;26(4):516–528. doi:10.3350/cmh.2020.0016

46. Kim SY, An J, Lim YS, et al. MRI with liver-specific contrast for surveillance of patients with cirrhosis at high risk of hepatocellular carcinoma. *JAMA Oncol*. 2017;3(4):456–463. doi:10.1001/jamaoncol.2016.3147