Low-Level Viremia and the Increased Risk of Hepatocellular Carcinoma in Patients Receiving Entecavir Treatment

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The long-term clinical impact of low-level viremia (LLV; <2,000 IU/mL) is not well understood. As a result, it is unclear whether the development of LLV during entecavir monotherapy requires a change in therapy. A retrospective cohort of 875 treatment-naive chronic hepatitis B virus (HBV) monoinfected patients (mean age 47.7 years, male = 564 [65.5%], cirrhosis = 443 [50.6%]) who received entecavir monotherapy were analyzed for the development of hepatocellular carcinoma (HCC). The HCC risk was compared between patients who maintained virological response (MVR), defined by persistently undetectable HBV DNA (<12 IU/mL), and patients who experienced LLV, defined by either persistent or intermittent episodes of <2,000 IU/mL detectable HBV DNA. During a median 4.5 years of follow-up (range 1.0-8.7 years), HCC was diagnosed in 85 patients (9.7%). HCC developed more frequently in patients who experienced LLV than MVR (14.3% versus 7.5% at 5 years, $P = 0.015$). The hazard ratio comparing those with LLV to MVR was 1.98 (95% confidence interval = 1.28-3.06, $P = 0.002$, adjusted for age, sex, hepatitis B e antigen, baseline HBV DNA levels, and cirrhosis). Among patients with cirrhosis, those with LLV exhibited a significantly higher HCC risk than those with MVR (HCC incidence rate at 5 years 23.4% versus 10.3%, adjusted hazard ratio = 2.20, 95% confidence interval 1.34-3.60; $P = 0.002$). However, for patients without cirrhosis, there was no significant difference in the HCC risk between LLV and MVR. *Conclusion:* LLV observed during entecavir monotherapy was associated with a higher risk of HCC, especially for those with cirrhosis, indicating that LLV during potent antiviral therapy is consequential. (HEPATOLOGY 2017;66:335-343).

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Nucelos(t)ide analogues (NUCs) have changed the outcome of chronic hepatitis B virus (HBV) infection.[1] NUCs can cause a rapid decrease in HBV DNA levels, which is followed by alanine aminotransferase (ALT) normalization and improvement in hepatic inflammation.[1] Long-term treatment with NUCs can reverse cirrhosis,[2,3] decrease the incidence of hepatocellular carcinoma (HCC),[4] decrease hepatic decompensation,[5] and modify the natural history of decompensated cirrhosis.[6] In the past, the main drawback of NUCs (e.g., lamivudine) was the development of viral resistance, which lead to NUC treatment failure.[5] Currently, viral resistance is of less concern because there are drugs with high genetic barriers (entecavir and tenofovir) that are highly effective, are very well tolerated, and lead to very little or no resistance.[7]

When using low–genetic barrier drugs, the emergence of drug-resistant mutants was a great concern. Hence, an early switch or add-on strategy was recommended for patients who did not achieve HBV DNA suppression by week 24.[8,9] With prolonged use for

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVR, complete virological response; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LLV, low-level viremia; MVR, maintained virological response; NUC, nucelos(t)ide analogue.

Received July 14, 2016; accepted October 13, 2016.
Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28916/suppinfo.
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View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.28916

Potential conflict of interest: Nothing to report.

those without complete virological suppression at week 24, the development of resistance leading to clinical failure has been observed.[9,10] However, when using potent drugs with a high genetic barrier it is controversial whether a change in therapy is needed for patients who have a suboptimal virological response.[11] Some studies have shown that continued monotherapy for those with a suboptimal response to entecavir can lead to additional virologic response without developing resistance after prolonged use.[12,13] However, other studies have suggested that switching to tenofovir or adding on another NUC can further induce a virological response over continued entecavir monotherapy,[14,15] indicating that changing therapy can be a better approach.

The recently updated American Association for the Study of the Liver Disease guidelines recommend that people with low-level viremia (LLV; <2,000 IU/mL) who are on entecavir or tenofovir monotherapy continue monotherapy; however, there is little evidence to support this recommendation.[11] Considering that the ultimate goals of treatment are to decrease the morbidity and mortality related to chronic hepatitis B,[11] the decision to continue, switch, or add another drug for patients with a suboptimal virological response should be based on a hard endpoint of therapy (e.g., liver-related mortality or HCC) because the emergence of resistance is not a significant concern when using entecavir or tenofovir. However, there are not enough clinical data to address whether LLV observed during entecavir or tenofovir monotherapy is a benign condition. If LLV is not associated with a worse clinical outcome, it would be reasonable to monitor LLV without changing the therapy. If LLV is associated with a worse clinical outcome, it would be reasonable to instead consider a change in therapy. In this study, to determine whether LLV observed during entecavir therapy is a harmless situation, we assessed the long-term health outcomes (the development of HCC) according to the virological response.

Patients and Methods

STUDY DESIGN, SETTING, AND PATIENTS

This retrospective cohort study consisted of patients who received care at the Samsung Medical Center, Seoul, Korea. We screened patients who received a prescription for NUCs between January 2007 and June 2012 (n = 3,786). We included 996 who met all of the following inclusion criteria: (1) adults, aged 18 years or above; (2) chronic HBV infection, defined by the presence of hepatitis B surface antigen for ≥6 months or by clinical history; (3) HBV DNA ≥2,000 IU/mL at baseline; (4) no malignancy including HCC at baseline; (5) no coinfection with hepatitis C virus or human immunodeficiency virus; and (6) treatment-naive and started on 0.5 mg entecavir monotherapy. Among them, we excluded 121 patients who met the following exclusion criteria: (1) follow-up duration <1 year or development of HCC within 1 year (n = 60) and (2) HBV DNA levels ≥2,000 IU/mL during the follow-up period after once achieving HBV DNA levels <2,000 IU/mL with entecavir therapy (n = 61). The characteristics of 61 patients were as follows: 56 patients were not taking entecavir at the time of HBV DNA levels ≥2,000 IU/mL because of self-cessation (n = 47), pregnancy (n = 3), and planned cessation (n = 6). The remaining 5 patients experienced viral breakthrough while on entecavir therapy, and drug-resistant mutations were documented in 4 patients. Patients received rescue therapy, including tenofovir monotherapy in 3 patients, tenofovir add-on therapy in 1 patient, and adefovir add-on therapy in 1 patient. Finally, a total of 875 treatment-naive adult chronic hepatitis B patients treated with entecavir monotherapy for >1 year were analyzed (Fig. 1). This study protocol was reviewed and approved by the institutional review board at Samsung Medical Center. Because the study was a retrospective analysis of existing

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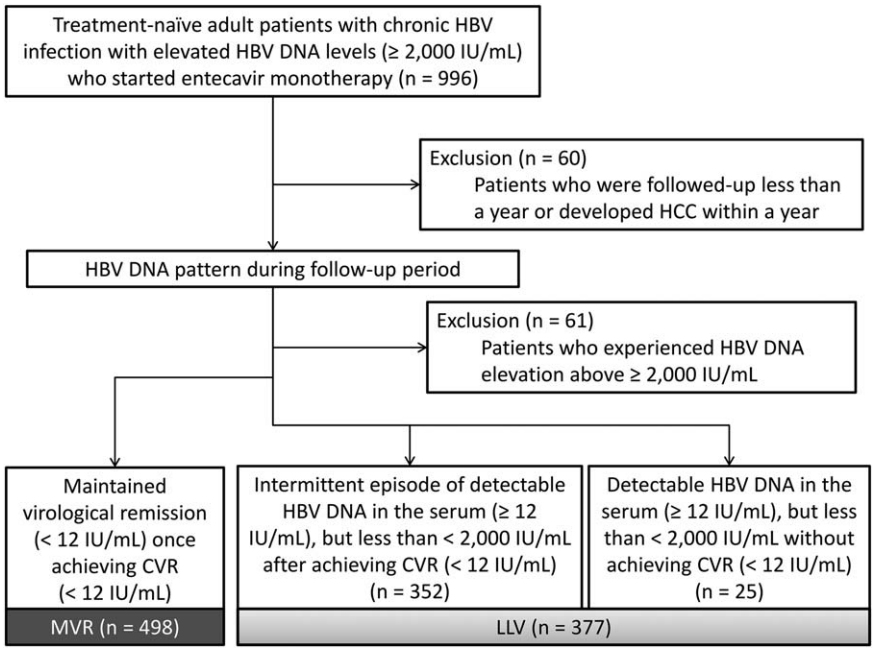

FIG. 1. Patient flowchart. A total of 875 treatment-naive adult chronic hepatitis B virus patients treated with entecavir monotherapy for more than 1 year were analyzed.

administrative and clinical data, the requirement to obtain informed patient consent was waived by the institutional review board.

PRIMARY OUTCOME AND FOLLOW-UP

The primary outcome was the diagnosis of HCC during follow-up. HCC was diagnosed either by histological evaluation or by clinical imaging according to the regional guidelines.[16] Follow-up assessments were usually performed every 3-6 months or more frequently as required for at least 1 year. Person-years were censored on the date of diagnosing the primary endpoint (HCC), the last date of entecavir therapy, or the last date of follow-up (reference December 15, 2015), whichever came first.

STUDY VARIABLES AND DEFINITION

Data collected for the following parameters were reviewed to determine study participant eligibility: age; sex; height; weight; medical history; ultrasonography and upper endoscopy results; serum platelet, hepatitis B e antigen (HBeAg), hepatitis B e antibody, and HBV DNA levels; and other blood chemistry parameters at baseline, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, albumin, and prothrombin time. We collected HBV DNA levels during the follow-up period for each patient. For the entire follow-up period, HBV DNA levels were usually monitored at 3-month to 6-month intervals. Serum HBV DNA was quantified using a real-time polymerase chain reaction method (COBAS Taq Man HBV assay; Roche Diagnostics, Branchburg, NJ) with a detection range of 12-170,000,000 IU/mL. The initial lower limit of 12 IU/mL for HBV DNA detection was lowered to 9 IU/mL during the study period. However, for this study, an HBV DNA level of 12 IU/mL was considered undetectable.

Based on the HBV DNA levels during the follow-up period, patients were classified as maintained virological response (MVR) or LLV. MVR was defined as having HBV DNA persistently undetectable throughout the follow-up period, after achieving a complete virological response (CVR, HBV DNA <12 IU/mL). MVR was observed for 498 patients. The remaining patients showed either persistent or intermittent episodes of detectable HBV DNA <2,000 IU/mL during follow-up, which was defined as LLV (Fig. 2). LLV was observed for 377 patients. Among 377 patients with LLV, 25 never achieved CVR (<12 IU/mL), which remained between 12 and 1,999 IU/mL throughout the follow-up period (persistent LLV). The remaining 352 patients achieved CVR, but they

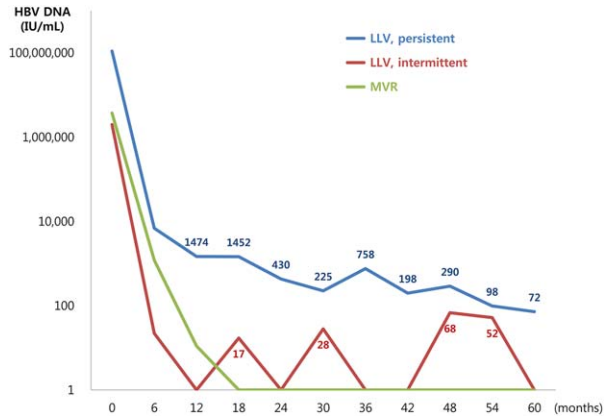

FIG. 2. Representative cases of each definition of virological response. MVR was defined as having HBV DNA persistently undetectable throughout the follow-up period, after achieving a complete virological response (green, case no. 540). LLV was defined for those who never achieved complete virological response (<12 IU/mL) and remained between 12 and 1,999 IU/mL throughout the follow-up period (persistent LLV, blue, case no. 207) and for those who achieved complete virological response but had intermittent episodes of detectable HBV DNA levels between 12 and 1,999 IU/mL (intermittent LLV, red, case no. 117).

had intermittent episodes of detectable HBV DNA levels in the serum (between 12 and 1,999 IU/mL, intermittent LLV). Liver cirrhosis was clinically defined when patients showed cirrhotic configuration of the liver on imaging studies (nodular liver surface or caudate lobe hypertrophy) with thrombocytopenia ($<150 \times 10^3$/L) or splenomegaly (by imaging) and/or by the presence of varices (by upper endoscopy or imaging studies).[17,18]

STATISTICAL ANALYSES

We compared the baseline characteristics between those with MVR and LLV using the chi-squared, *t* test, and Mann-Whitney U test, as appropriate. The difference in the cumulative incidence of HCC between MVR and LLV was plotted with a Kaplan-Meier curve and compared using the log-rank test. Multivariable Cox regression analysis was performed to evaluate an independent association between the virologic response and HCC risk using variables with $P < 0.10$ in the univariate analysis. When assessing the association between HCC and LLV, age, sex, and HBeAg were included in the multivariable model regardless of the results of univariate analysis because age and sex are well-known risk factors for HCC and HBeAg was an independent factor associated with LLV in this study. Statistical significance was defined as $P < 0.05$.

Results

PATIENT CHARACTERISTICS AND INCIDENCE OF THE PRIMARY ENDPOINT

The baseline characteristics of the patients are shown in Table 1. Those with LLV had a higher body mass index, higher proportion of HBeAg positivity, and higher baseline HBV DNA level, with a lower proportion of patients with cirrhosis (Table 1). During the median 4.5-year follow-up period (range 1.0-8.7 years), 85 patients were newly diagnosed with HCC. The cumulative HCC incidence rate was 4.5% and 10.6% at 3 and 5 years, respectively. Those who developed HCC showed more advanced liver disease, lower HBV DNA levels, and lower ALT levels at baseline (Table 1).

VIROLOGIC RESPONSE TO ENTECAVIR THERAPY

During follow-up, CVR, defined as undetectable HBV DNA by a sensitive polymerase chain reaction assay (<12 IU/mL), was observed in 850 patients (97.1%). The median time to first CVR was 8 months (range 1-82 months). The cumulative incidence rates of CVR were 69.8%, 86.6%, and 92.7% at 1, 2, and 3 years, respectively. However, among 850 patients who achieved CVR, MVR was seen for 498 patients (58.6%). The HBeAg status, HBV DNA levels, cirrhosis, and time to first CVR were associated with LLV. Sex and obesity had a marginal association with LLV in unadjusted analysis (Table 2). The MVR rate was higher in patients with cirrhosis than in those without cirrhosis (61.9% versus 51.9%, $P = 0.003$), in patients with intermediate viral load (2,000-20,000,000 IU/L) than high viral load (>20,000,000 IU/L; 62.0% versus 48.1%), and in patients who were HBeAg-negative than HBeAg-positive (65.6% versus 49.9%, $P < 0.001$). The MVR rate was 60.7% (360/593 patients) for those who achieved CVR within 1 year, 55.9% (80/143 patients) for those who achieved CVR between 1 and 2 years, and 50.9% (58/114 patients) for those who achieved CVR between 2 and 3 years ($P < 0.001$). In multivariable models, HBeAg

TABLE 1. Characteristics of Study Population at Baseline

	All (n = 875)	MVR (n = 498)	LLV (n = 377)	*P*	HCC$^-$ (n = 790)	HCC$^+$ (n = 85)	*P*
Age (years)	47.7 ± 10.7	48.1 ± 10.4	47.2 ± 11.0	0.18	47.8 ± 10.6	47.3 ± 11.4	0.67
Male (%)	564 (64.5)	308 (61.8)	256 (67.9)	0.064	506 (64.1)	58 (68.2)	0.44
Body mass index (kg/m^2)*	24.3 ± 3.0	24.1 ± 3.0	24.6 ± 2.9	0.035	24.3 ± 3.0	24.4 ± 3.0	0.93
HBeAg$^+$	483 (55.2)	241 (48.4)	242 (64.2)	<0.001	439 (55.6)	44 (51.8)	0.50
HBeAg seroconversion	117 (24.2)†	60 (24.9)†	57 (23.6)†	0.73	104 (23.7)†	13 (29.5)†	0.38
HBV DNA (log_{10}IU/L)	6.5 ± 1.3	6.4 ± 1.3	6.7 ± 1.3	<0.001	6.5 ± 1.3	6.2 ± 1.1	0.046
Platelet (×10^3/L)	149 (107-194)	143 (101-191)	158 (115-201)	0.002	155 (113-197)	106 (73-144)	<0.001
AST (U/L)	55 (46-104)	65 (46-108)	66 (46-99)	0.70	66 (46-104)	65 (45-93)	0.53
ALT (U/L)	89 (51-145)	85 (48-145)	91 (55-144)	0.27	92 (52-150)	60 (46-93)	<0.001
Bilirubin (mg/dL)	0.9 (0.7-1.3)	0.9 (0.7-1.3)	0.9 (0.7-1.2)	0.34	0.9 (0.7-1.2)	1.2 (0.8-1.7)	<0.001
Albumin (mg/dL)	4.1 (3.8-4.3)	4.1 (3.8-4.3)	4.0 (3.8-4.3)	0.21	4.1 (3.8-4.3)	3.8 (3.4-4.1)	<0.001
PT/INR	1.09 (1.03-1.16)	1.09 (1.03-1.18)	1.08 (1.03-1.15)	0.27	1.08 (1.02-1.15)	1.16 (1.08-1.29)	<0.001
Cirrhosis (%)	443 (50.6)	274 (55.0)	169 (44.8)	0.003	378 (47.8)	65 (76.5)	<0.001
Time to first CVR (%)				<0.001			0.056
<1 year	593 (67.8)	360 (72.3)	233 (61.8)		525 (66.5)	68 (80.0)	
1-2 years	143 (16.3)	80 (16.1)	63 (16.7)		135 (17.1)	8 (9.4)	
≥2 years	114 (13.0)	58 (11.6)	56 (14.9)		108 (13.7)	6 (7.1)	
None‡	25 (2.9)	—	25 (6.6)		22 (2.8)	3 (3.5)	

Values are expressed as number (percent), mean ± standard deviation, or median (quartile).
*Based on body weight at baseline. Missing in 115 patients (13.1%).
†Percent within patients with HBeAg$^+$.
‡Among 25 patients who showed persistent LLV, follow-up duration was ≥2 years for 18 patients (72.0%) and 1-2 years for 7 patients (28.0%).
Abbreviation: PT/INR, prothrombin time/international normalized ratio.

status was the only independent factor associated with LLV, and the time to the first CVR showed a marginal association (Table 2). Among patients who experienced LLV, 31 (8.2%) were analyzed for resistance-associated mutations and 3 were documented to have resistance-associated mutations (Supporting Table S1).

RISK OF HCC ACCORDING TO THE VIROLOGICAL RESPONSE

The cumulative incidence rates of HCC were 3.2% and 7.5% at 3 and 5 years for patients with MVR, respectively, which were lower than those for patients with LLV (6.2% and 14.3% at 3 and 5 years,

TABLE 2. Factors Associated With LLV

	Univariate		Multivariable model*	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (/year)	0.99 (0.97-1.01)	0.18	0.99 (0.97-1.00)	0.18
Female (versus male)	0.76 (0.57-1.02)	0.064	0.80 (0.60-1.07)	0.13
Obesity (yes versus no)†	1.34 (0.99-1.80)	0.051	1.26 (0.92-1.71)	0.13
HBeAg$^+$ versus $^-$	1.91 (1.45-2.51)	<0.001	1.55 (1.11-2.16)	<0.009
HBV DNA (/log_{10}IU/L)	1.22 (1.10-1.36)	<0.001	1.06 (0.93-1.21)	0.34
Cirrhosis (yes versus no)	0.66 (0.50-0.86)	0.003	0.78 (0.59-1.04)	0.10
ALT (/IU/L)	1.00 (0.99-1.00)	0.81		
Time to first CVR				
<1 year	Reference		Reference	
1-2 years	1.21 (0.84-1.76)	0.29	0.97 (0.65-1.45)	0.90
≥2 years	2.15 (1.48-3.14)	<0.001	1.49 (0.97-2.28)	0.066

*As data on obesity were missing in 13.1% of patients, the reported OR for obesity in the multivariable model involved 760 patients (multivariable model included age, sex, obesity, HBeAg, HBV DNA, cirrhosis, time to first CVR), while the reported OR for other variables involved 875 patients (multivariable model included age, sex, HBeAg, HBV DNA, cirrhosis, time to first CVR).
†Obesity was defined as body mass index >25 kg/m^2, according to the Asian cutoff for obesity.
Abbreviations: OR, odd ratio; CI, confidence interval.

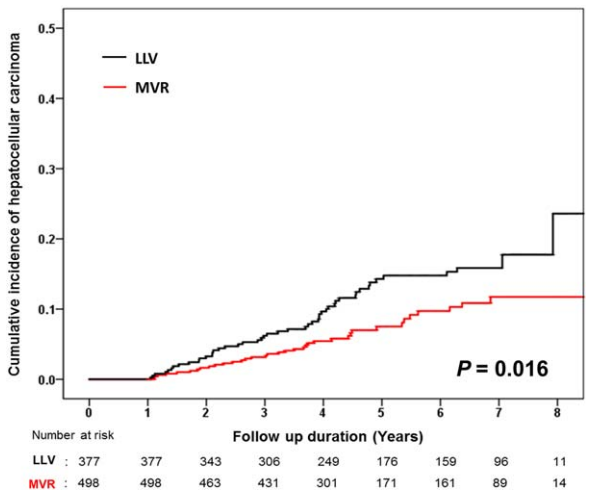

FIG. 3. Cumulative incidence of HCC according to virological response. The cumulative incidence rate of HCC was higher in patients with LLV than those with MVR.

respectively; $P = 0.016$; Fig. 3). LLV was associated with a higher risk for developing HCC than MVR. LLV and cirrhosis were independent risk factors for HCC (Table 3). When stratified according to cirrhosis, the cumulative incidence rate of HCC was higher (10.3% versus 23.4% at 5 years for MVR versus LLV; $P = 0.001$), and LLV was an independent risk factor for HCC in patients with cirrhosis (hazard ratio = 2.20, 95% confidence interval 1.34-3.60, adjusted for age, sex, HBeAg, and baseline HBV DNA levels; $P = 0.002$). However, for those without cirrhosis, there was no significant difference in HCC incidence rate (4.0% versus 6.9% at 5 years for MVR versus LLV, $P = 0.44$). LLV was not an independent factor for HCC in the multivariable model (hazard ratio = 1.65, 95% confidence interval 0.65-4.17, adjusted for age, sex, HBeAg, and baseline HBV DNA levels; $P = 0.29$) (Fig. 4).

Discussion

In this study, we observed an association between LLV and HCC development during entecavir monotherapy, indicating that LLV is not harmless. The association between LLV and the development of HCC was more evident in patients with cirrhosis. This finding can be explained when considering that LLV can be associated with persistent low-grade inflammation and liver fibrosis.[19,20] In our previous study, we also observed that LLV in compensated cirrhosis patients who were not receiving antiviral treatment was associated with an increased HCC risk compared to those with undetectable HBV DNA levels.[21] As LLV is associated with worse clinical outcome, these findings indicate that active management that can further induce MVR should be pursued for those with LLV during potent NUC therapy, especially for cirrhosis patients.

In this study, the MVR rate was low (57%), considering that patients were treatment-naive and receiving entecavir. Wong et al. assessed MVR in their 1,466 entecavir-treated patients[22] and reported an MVR rate of 78% for patient with cirrhosis and 77% for patients without cirrhosis. The lower MVR rate of this study can be partially explained by the different HBV DNA cutoff point and characteristics of the study cohort. In Wong et al.'s study, the HBV DNA cutoff level was 20 IU/mL, mean HBV DNA level was 5.0 ± 2.1 IU/mL, and HBeAg-positive patients comprised 30% of the cohort. In this study, the HBV DNA

TABLE 3. Risk of HCC According to Virological Response

	Univariate		Multivariable model*	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (/year)	1.00 (0.98-1.02)	0.94	1.00 (0.98-1.02)	0.73
Male (versus female)	1.16 (0.73-1.83)	0.51	1.21 (0.76-1.91)	0.41
Obesity (yes versus no)	0.86 (0.54-1.34)	0.49		
$HBeAg^+$ (yes versus no)	0.91 (0.59-1.40)	0.68	1.16 (0.72-1.86)	0.52
HBeAg seroconversion (yes versus no)†	1.05 (0.55-2.02)	0.86		
HBV DNA (/$\log_{10}$IU/L)	0.86 (0.73-1.01)	0.060	0.89 (0.74-1.08)	0.24
Cirrhosis (yes versus no)	3.32 (2.02-5.50)	<0.001	3.53 (2.11-5.94)	<0.001
Virological response				
MVR	Reference		Reference	
LLV	1.69 (1.10-2.60)	0.017	1.98 (1.28-3.06)	0.002

*Multivariable model included age, sex, HBeAg, HBV DNA, cirrhosis, and virological response.
†Among HBeAg positive patients (n = 483).
Abbreviations: CI, confidence interval; HR, hazard ratio.

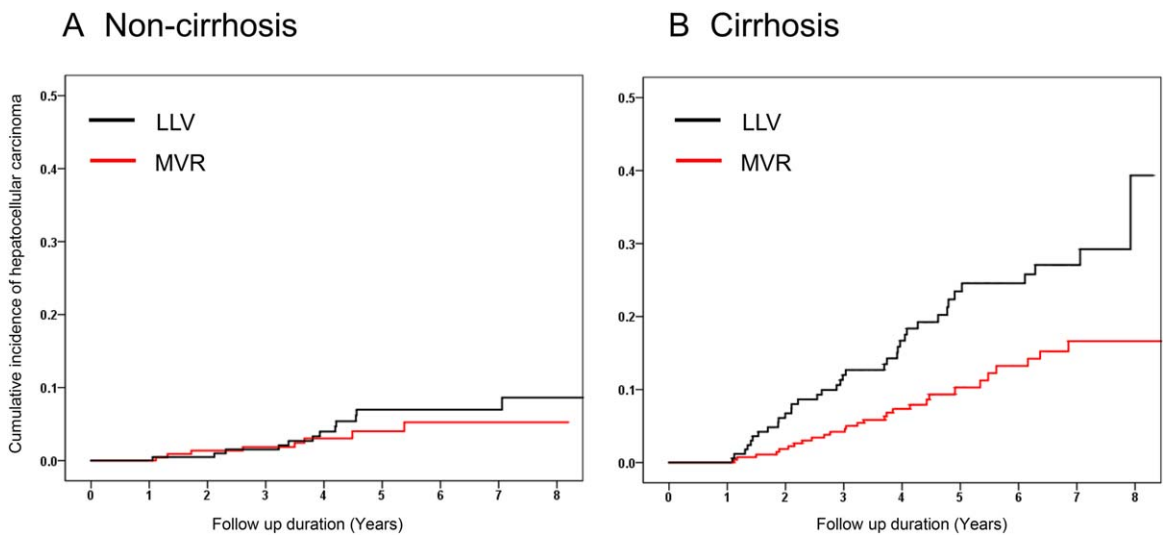

FIG. 4. Cumulative incidence of HCC according to the virological response stratified by cirrhosis status. The cumulative incidence of HCC in cirrhosis patients was higher in patients with LLV than those with MVR (B, n = 443; 10.3% versus 23.4% at 5 years, P = 0.001), while the difference was not statistically significant in patients without cirrhosis (A, n = 432; 4.0% versus 6.9% at 5 years, P = 0.44).

cutoff was 12 IU/mL, the mean HBV DNA level was 6.5 ± 1.3 IU/mL, and HBeAg-positive patients comprised 55% of the cohort. The virologic response to NUC therapy was poorer in patients with HBeAg-positive status and high baseline HBV DNA levels.[23-25] However, more importantly, MVR (persistently undetectable HBV DNA levels) is a time-dependent variable that depends on the follow-up period and interval of HBV DNA measurements. The virological response can be assessed at specific time points (e.g., at week 48 or week 96). However, as the purpose of this study was to investigate the impact of LLV on long-term outcomes, we used a time-dependent variable (MVR) rather than the virological response at a single time point. Notably, CVR, defined by a decrease in HBV DNA to an undetectable level (<12 IU/mL), was observed in almost all patients (97%) in our cohort. However, during long-term follow-up, only 498 of 875 patients (57%) showed persistently undetectable HBV DNA levels (MVR), while the remaining patients experienced intermittent or transient episodes of detectable HBV DNA with levels <2,000 IU/mL (LLV). This suggests that patients receiving potent NUC therapy need regular HBV DNA monitoring to verify that they are not experiencing LLV because a single CVR does not guarantee MVR.

We then evaluated factors associated with LLV. HBeAg status, HBV DNA levels, presence of cirrhosis, and time to first CVR were associated with LLV. Sex and obesity showed a marginal association in the unadjusted analysis. In a multivariable model, HBeAg status was the only significant factor associated with LLV and the time to first CVR showed a marginal association. It takes time to achieve a virological response. In this study, patients who achieved first CVR late (after 2 years) were more likely to experience LLV than those who achieved an early first CVR (within 1 year). Thus, patients who were HBeAg-positive and did not achieve CVR early warrant closer attention during follow-up to see whether they maintain CVR.

It is possible that adherence to drug or the development of drug-associated mutations is associated with LLV. Adherence to the drug regimen is an important factor in maintaining the virological response. Among 377 patients with LLV, there was no documented history of stopping the drug. However, because of the retrospective design of this study, detailed information on adherence was lacking. Among patients with LLV, drug-resistance mutations were documented in only a minor proportion. However, drug-resistance testing was not systematically performed in patients showing LLV. Therefore, there remains a possibility that the development of resistance-associated mutations is associated with LLV. In this study, body mass index was higher in those with LLV than MVR (24.6 ± 2.9

versus 24.1 ± 3.0, $P = 0.035$). Although high body mass index (>25 kg/m^2) was not an independent factor for LLV in multivariable models, the reliability is low because of a high missing rate of baseline body mass index (13.1%). More studies are needed to assess the factors associated with LLV and better understand how we can decrease the LLV rate in clinical practice.

As patients with LLV showed poorer clinical outcomes than patients with MVR, it would be helpful to consider a change of therapy that can further induce MVR for patients with LLV. Studies have shown conflicting results; continued monotherapy is supported in some studies, and an alternative strategy is supported in other studies.[12-15] The clinical efficacy of adding high-potency NUCs to an existing monotherapy versus switching to another high-potency NUC versus continuing monotherapy is unknown.[11] The present data are limited in addressing which strategy is the better approach and the optimal time point for considering a change in therapy. To the best of our knowledge, no data are available demonstrating a clinical benefit (e.g., reduced risk of HCC) of changing therapy in patients with LLV who are taking potent NUC monotherapy. This study provides a rationale for searching for strategies that can further induce MVR in those with LLV because LLV was associated with a worse clinical outcome.

The degree of fibrosis is a strong risk factor for HCC. During antiviral therapy, the fibrosis burden is known to be a dynamic process, and regression of fibrosis has been reported when patients take NUCs for a long period of time.[3] In one study for which fibrosis burden was estimated by transient elastography, patients with decreased liver stiffness values during follow-up showed a lower risk for developing HCC than those with a persistently high liver stiffness value.[26] Because LLV can be associated with persistent low-grade inflammation and liver fibrosis,[19] it may impact dynamic changes in the degree of fibrosis during NUC therapy, which may in turn translate into clinical outcomes. Yet, as this study was a retrospective cohort without a predefined protocol to assess dynamic changes in liver fibrosis status by liver biopsy or transient elastography, we could not assess whether LLV is associated with a change in liver fibrosis during NUC therapy. The noninvasive serum markers, such as the aspartate aminotransferase to platelet ratio index and Fibrosis-4 score, could be alternative measures for estimating dynamic changes in liver fibrosis; however, these serum markers were recently reported to unsuitable for gauging improvements in liver fibrosis following therapy.[27] Therefore, the dynamic interaction between LLV, fibrosis regression, and HCC development warrants further evaluation. This study has other limitations that affect generalizability and applicability. Our cohort entirely consisted of Koreans. Almost all Korean chronic hepatitis B patients are infected with HBV genotype C,[28] which has characteristics of later HBeAg seroconversion and more rapid progression to HCC than other genotypes.[9,29] The generalizability of the findings to other HBV genotypes and other ethnicities needs to be demonstrated.

In summary, this large-scale, homogenous, and real-world cohort demonstrated the importance of MVR during entecavir monotherapy. LLV was associated with an increased risk of HCC, especially in patients with cirrhosis, indicating that LLV is not benign. Because MVR was clearly associated with a better outcome (HCC) of antiviral therapy, it should be a surrogate endpoint of potent NUC monotherapy,[30] and LLV should not be left unmanaged. However, it is unclear how we can reduce the LLV rate in clinical practice and how we can further induce MVR for those with LLV already on treatment with potent NUC monotherapy. More data that can guide clinical practice are needed. Until such data are available, clinicians must evaluate adherence for patients with LLV. If adherence is not a concern, providers should discuss the risks and benefits of each treatment strategy (add-on, switching, and continuing monotherapy) in everyday practice, and the treatment decisions should be individualized.

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