Prognosis of Untreated Minimally Active Chronic Hepatitis B Patients in Comparison With Virological Responders by Antivirals

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OBJECTIVES: **Serum hepatitis B virus (HBV)-DNA > 2,000 IU/mL is associated with higher risk of disease progression. However, without hepatocellular carcinoma (HCC) or cirrhosis, nucleos(t)ide analogs (NUCs) are recommended only for patients with elevated serum HBV-DNA and alanine aminotransferase ≥2 × upper normal limit.**

METHODS: **We evaluated prognosis of untreated minimally active (MA) hepatitis patients (defined as HBV-DNA > 2,000 IU/mL, but never fulfilling current criteria for NUCs during follow-up) (untreated MA group), compared to virological responders by NUCs (NUC-VR group). Eligible patients undergoing transient elastography were consecutively enrolled. Patients with an immune-tolerant or inactive phase and with cirrhosis or HCC at enrollment were excluded. Cumulative risks of disease progression were assessed using the Kaplan-Meier method.**

RESULTS: **The untreated MA group (n = 152) had higher HBV-DNA, alanine aminotransferase, and total bilirubin levels, and lower proportions of male and positive hepatitis B e antigen, compared to the NUC-VR group (n = 641). The untreated MA group had higher risks of HCC (adjusted hazard ratio [HR] 3.485, 95% confidence interval [CI] 1.234–9.846; *P* = 0.018), but similar risks of cirrhotic complications (adjusted HR 0.649, 95% CI 0.227–1.854; *P* = 0.420), compared to the NUC-VR group. Inverse probability of treatment weighting analysis using propensity score showed that the untreated MA group had higher risks of HCC (HR 4.464, 95% CI 2.008–9.901; *P* < 0.001), but similar risks of cirrhotic complications (HR 1.171, 95% CI 0.594–2.309; *P* = 0.649), compared to the NUC-VR group.**

DISCUSSION: **Through appropriate adjustment of potential prognostic factors, the untreated MA group consistently showed higher risks of HCC, but similar risks of cirrhotic complications, compared to the NUC-VR group. HCC risk might be reduced through earlier NUCs for the untreated MA group.**

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a dynamic process with the interaction between viral replication and the host immune system and has complicated clinical courses covering the immune-tolerant phase, immune-active phase, inactive carrier to reactivation phase (1). Since an elevated level of HBV replication is associated with an increased risk of disease, replication-suppressing antiviral therapy is the mainstay of management by lowering the incidence of disease progression (2–4). By current guidelines, in case of absence of hepatocellular carcinoma (HCC) or cirrhosis, nucleos(t)ide analogs (NUCs) therapy is recommended only for patients who fulfilled both criteria of elevated serum HBV-DNA level (≥20,000 IU/mL for hepatitis B e antigen [HBeAg]-positive chronic hepatitis B (CHB) and ≥2,000 IU/mL for HBeAg-negative CHB) and serum alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN) (4–7). In the real practice, except those with definite "immune-tolerant" or "inactive carrier" phase, a significant proportion of patients with chronic HBV infection belongs to so called "minimally active (MA) CHB" status, where serum HBV-DNA level is persistently >2,000 IU/mL, a well-known threshold closely associated with an increased risk of HCC or progression to cirrhosis (2,3), and above criteria for NUCs therapy have been never fulfilled during the follow-up.

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However, there have been little data concerning the natural history of such untreated patients with MA-CHB status (referred to as the "untreated MA group") across the long-term follow-up. As a matter of fact, there exist discrepancies among studies in terms of optimal ULN of serum ALT level, age, and timing to guide NUCs therapy for prevention of disease progression (4,5). Theoretically speaking, liver biopsy to assess the hepatic necroinflammation and fibrosis more accurately for patients who belong to "gray zone" in order to determine the commencement of NUCs therapy seemed to be in general desirable; however, its wide use might be limited primarily owing to its invasiveness, discomfort, and cost in the real clinical setting (8).

Here, in this study, we aimed to evaluate long-term risk of development of HCC and cirrhotic complication among the untreated MA group compared to those who achieved virological response (VR) by NUCs according to practice guidelines (NUC-VR group).

METHODS

Study subjects

Among patients with chronic HBV infection visiting Severance Hospital between April 2006 and August 2015, consecutive patients who belonged to the untreated MA or NUC-VR group were considered eligible for enrollment. Inclusion criteria were as follows: (i) age ≥ 19 year-old, (ii) reliable liver stiffness (LS) value by transient elastography (TE), (iii) well-preserved liver function, and (iv) follow-up duration of at least 6 months. The untreated MA group had serum HBV-DNA level of >2,000 IU/mL but had never fulfilled the below criteria for NUCs described in Supplementary Table 1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A36) during the whole follow-up period. NUCs were commenced according to the treatment guideline (Supplementary Table 1, see Supplementary Digital Content 1, http://links.lww.com/CTG/A36), which were developed in accordance with the practice guideline by the Korean Association for the Study of the Liver (6) and the reimbursement criteria of the national health insurance service in the Republic of Korea. VR was defined as achievement of serum HBV-DNA level < 2,000 IU/mL by NUCs. Exclusion criteria were as follows: (i) immune-tolerant or inactive phase, (ii) a history of cirrhosis and/or HCC at enrollment, (iii) co-infection with other viral hepatitis or presence of other overt liver diseases, (iv) current use of immunosuppressive agents, and (v) other significant medical illness. Immune-tolerant phase was defined as persistently serum HBV-DNA level of ≥20,000 IU/mL, positive HBeAg, and normal serum ALT level during the whole follow-up period (5). Inactive phase was defined as persistently serum HBV-DNA level < 2,000 IU/mL, negative HBeAg, and normal serum ALT level during the whole follow-up period. If histologic information was not available, cirrhosis was clinically defined as follows: (i) platelet count <150,000/μL and ultrasonographic findings suggestive of cirrhosis, including a blunted, nodular liver edge accompanied by splenomegaly (>12 cm); or (ii) esophageal or gastric varices (9). Serum ALT level was measured using standard laboratory procedures with an ULN of 40 IU/mL (4).

The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board.

Clinical evaluation and follow-up

During follow-up, all patients received laboratory tests every 6 months and underwent periodic surveillance with ultrasonography and serum alpha-fetoprotein levels to screen for HCC and cirrhotic complications every 6 months. HCC was diagnosed based on histological evidence or radiological findings determined by dynamic computed tomography and/or magnetic resonance imaging (nodule >1 cm with arterial hyper-vascularity and portal/delayed-phase washout) (10,11). In the NUC-VR group, in case of virological breakthrough (defined as >1 $\log_{10}$ IU/mL increase in serum HBV-DNA level from nadir on 2 consecutive tests) or genotypic mutation during NUCs therapy, rescue therapy was applied, if appropriate (6).

LS values were determined using TE (FibroScan; EchoSens, Paris, France) at the time of enrollment for the untreated MA group and at the time of VR for the NUC-VR group. The principles of LS measurement have been described previously (12,13). Only LS values with at least 10 valid measurements, a success rate of at least 60%, and an interquartile range-to-median ratio <30% were considered reliable.

Evaluation of disease progression

The primary outcome was the cumulative risk of development of HCC. Furthermore, we also investigated the cumulative risk of development of cirrhotic complications, which included hepatic decompensation (hepatic encephalopathy, ascites, variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome), liver transplantation, or cirrhosis-related mortality. To avoid statistical repetition in a patient experiencing different types of cirrhotic complications at different times, we selected the first event of cirrhotic complications for statistical analysis.

Statistical analysis

Data are expressed as the mean ± SD, median (interquartile range), or number (%) as appropriate. Differences among continuous and categorical variables were examined for statistical significance with Student's t test (or Mann-Whitney test, if appropriate) and χ^2 test (or Fisher's exact test, if appropriate). Cumulative risks of development of HCC and cirrhotic complication were calculated using Kaplan-Meier method with a comparison by log-rank test between the 2 groups. Hazard ratio (HR) and 95% confidence interval (CI) were calculated with Cox-proportional hazard model.

Furthermore, to reduce the effect of selection bias and potential confounders between the untreated MA and NUC-VR groups, propensity score was calculated using logistic regression and inverse probability of treatment weighting analysis was performed to compare the cumulative risks of HCC or cirrhotic complication between the 2 groups.

All statistical analyses were conducted using the SAS software, version 9.2 (SAS Institute) and R (V.3.0, http://cran.r-project.org/). Two-sided P-values < 0.05 were considered to indicate statistical significance.

RESULTS

Patients characteristics

Patients' baseline characteristics are summarized in Table 1. The untreated MA group (n = 152) had lower proportions of male gender (53.3% vs 63.8%, $P = 0.020$), HBeAg positivity (25.7% vs 66.8%, $P < 0.001$), higher mean serum ALT (55.8 vs 24.9 U/mL, $P < 0.001$), and total bilirubin (1.2 vs 0.8 mg/dL, $P = 0.001$) than the NUC-VR group (n = 641). The mean serum HBV-DNA level in the untreated MA group was 4.7 ± 1.1 $\log_{10}$ IU/mL, whereas all patients in the NUC-VR group had serum HBV-DNA level < 3.3 $\log_{10}$ IU/mL (2,000 IU/mL).

Table 1. Baseline characteristics of study population (before matching)

Variables	Untreated MA group (n = 152)	NUC-VR group (n = 641)	*P* value
Age, yr	54.3 ± 10.5	53.5 ± 10.7	0.371
Male gender, no. (%)	81 (53.3)	409 (63.8)	0.020
Diabetes, no. (%)	16 (10.5)	54 (8.4)	0.427
Positive HBeAg, no. (%)	39 (25.7)	428 (66.8)	<0.001
Platelet count, $\times 10^3/\mu L$	203.5 ± 61.2	197.4 ± 59.6	0.333
ALT, U/mL	55.8 ± 8.1	24.9 ± 10.2	<0.001
ALT, U/mL	27.0 (19.3–43.0)	23.0 (16.0–33.0)	<0.001
Total bilirubin, mg/dL	1.2 ± 2.5	0.8 ± 0.3	0.001
Liver stiffness values, kPa	6.9 ± 4.6	7.7 ± 6.5	0.190
Liver stiffness values, kPa	4.5 (5.7–7.3)	5.9 (4.8–8.1)	0.202

Data are expressed as mean ± s.d, median (IQR), or no. (%).
ALT, alanine aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; MA, minimally active; NUC, nucleos(t)ide analogue; VR, virological response.

Supplementary Figure 1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A36) shows the serial serum ALT (A) and HBV-DNA (B) levels at different time points in the untreated MA group.

Clinical outcomes in the untreated MA vs NUC-VR groups

Among entire population, a total of 16 (2.0%) cases of HCC and 33 (4.2%) cases of cirrhotic complication occurred during the follow-up period. Six (3.9%) patients in the untreated MA group and 10 (1.6%) in the NUC-VR group developed HCC, whereas 4 (2.6%) patients in the untreated MA group and 29 (4.5%) in the NUC-VR group developed cirrhotic complication, respectively. Baseline characteristics between patients with HCC and without and between patients with cirrhotic complication and without were described in Supplementary Tables 2 and 3 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A36), respectively. Patients with HCC were significantly older (mean age 61.4 vs 53.5 years, $P = 0.003$) and had higher proportion of male gender (87.5% vs 61.3%, $P = 0.037$), diabetes (25.0% vs 8.5%, $P = 0.045$), and lower proportion of HBeAg (31.3% vs 59.5%, $P = 0.037$) compared to those without HCC. Patients with cirrhotic complication were significantly older (mean age 61.8 vs 53.5 years, $P < 0.001$) and had higher proportion of diabetes (30.3% vs 7.9%, $P < 0.001$), and lower proportion of HBeAg (39.4% vs 59.3%, $P = 0.029$) compared to those without cirrhotic complication.

The cumulative risks of HCC development at 3, 5, 7, and 9 years were 1.1%, 1.4%, 2.1%, and 2.7% in the untreated MA group, which were higher compared to 0.2%, 0.4%, 0.4%, and 0.7% in the NUC-VR group (Figure 1; $P = 0.018$ by log-rank test), respectively, with an adjusted HR of 3.485 (95% CI 1.234–9.846; $P = 0.018$) by Cox proportional hazard model.

In terms of cirrhotic complication development, the cumulative risks at 3, 5, 7, and 9 years were 1.0%, 1.0%, 1.5%, and 1.9%, in the untreated MA group, which were similar to 0.4%, 0.6%, 0.7%, and 1.1%, in the NUC-VR group (Figure 2; $P = 0.483$ by log-rank test), respectively, with an adjusted HR of 0.649 (95% CI 0.227–1.854; $P = 0.420$) by Cox proportional hazard model.

Inverse probability of treatment weighting analysis

The well-known prognostic variables used to calculate propensity scores were as follows: age, gender, HBeAg status, diabetes, and LS values. After inverse probability of treatment weighting analysis, similar baseline characteristics between the 2 groups regarding these 5 variables were observed (Table 2). Absolute standardized differences were described in Supplementary Figure 2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A36).

In terms of HCC development, the cumulative risks at 3, 5, 7, and 9 years were 0.5%, 2.7%, 4.0%, and 9.8% in the untreated MA group, which were higher compared to 0.8%, 1.1%, 1.1%, and 2.2% in the NUC-VR group (Figure 3; $P = 0.001$ by log-rank test), respectively, with an HR of 4.464 (95% CI 2.008–9.901; $P < 0.001$) by Cox proportional hazard model.

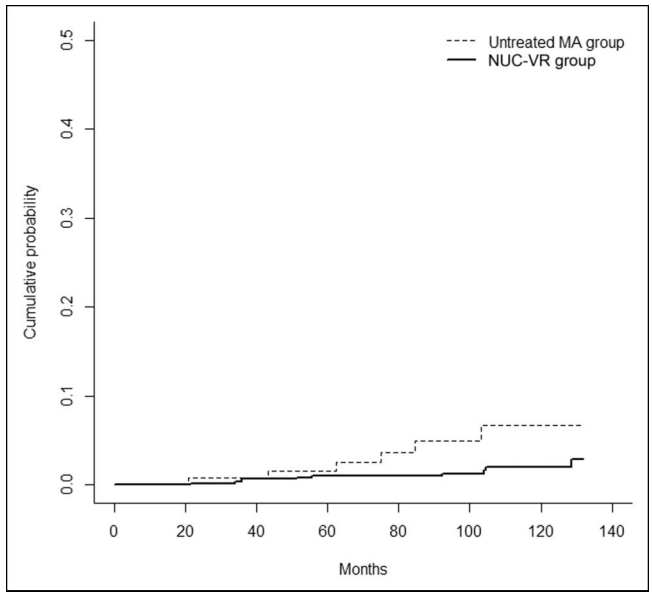

Figure 1. Cumulative risks of HCC development among the entire study population. HCC, hepatocellular carcinoma; MA, minimally active; NUC, nucleos(t)ide analogue; VR, virological response.

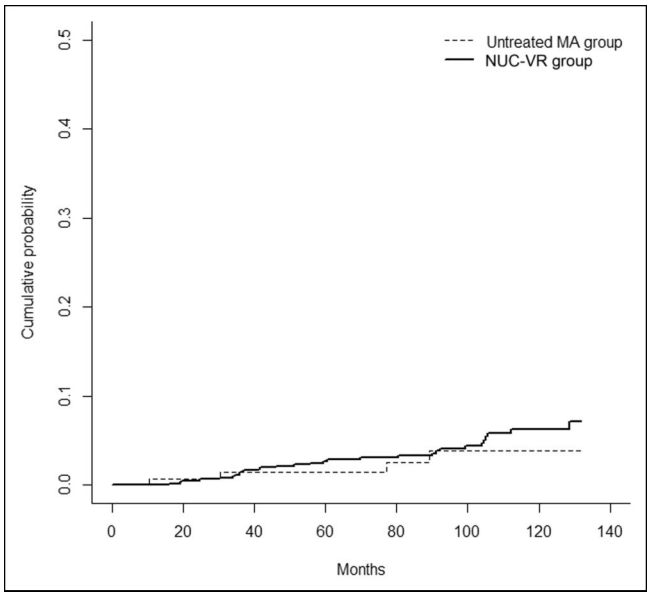

Figure 2. Cumulative risks of cirrhotic complication development among the entire study population. MA, minimally active; NUC, nucleos(t)ide analogue; VR, virological response.

In terms of cirrhotic complication development, the cumulative risks at 3, 5, 7, and 9 years were 2.0%, 2.0%, 2.8%, and 7.5% in the untreated MA group, which were similar to 1.6%, 3.0%, 3.7%, and 6.1% in the NUC-VR group (Figure 4; $P = 0.767$ by log-rank test), respectively, with an HR of 1.171 (95% CI 0.594–2.309; $P = 0.649$) by Cox proportional hazard model.

DISCUSSION

REVEAL-HBV cohort studies (2,3) concerning the natural history of untreated patients with chronic HBV infection indicated a strong relationship between the level of serum HBV-DNA and the risk of HCC development or progression to cirrhosis. Nevertheless, current practice guidelines generally recommend against initiating NUCs for patients with elevated serum HBV-DNA level, but "borderline" serum ALT level (<2 × ULN), unless either HCC or cirrhosis occurs (4–6). Such a discrepancy between the theoretical backgrounds and the practice in the real-life might raise an issue of whether earlier intervention by NUCs for MA-CHB patients who have been untreated by this time in accordance with treatment guidelines would be indeed beneficial in terms of reducing the risk of disease progression. To date, since there has been lack of reimbursement by the insurer organizations as well as recommendation of starting NUCs by the current practice guidelines for the untreated MA group in real-world practice settings, we tried to evaluate the potential therapeutic benefit from NUCs through assessing their long-term risk of HCC or cirrhotic complication development, in comparison with immune-active patients who achieved VR by NUCs.

Our study has several strengths. First, we tried to adjust for imbalances including fibrotic burden between the 2 groups as much as possible, using quantitative scales by the validated method, i.e., TE. On the basis of ultrasonographic findings and/or clinical symptoms which are vulnerable to subjective and variable interpretation, refined evaluation of a fibrotic burden and the corresponding long-term prognosis would not be feasible. To the best knowledge of ours, this is the first study incorporating quantitative scale of LS value into major analyses for patents before the transition to overt cirrhosis. Second, our results were consistently reproduced through diverse statistical approaches such as unadjusted analysis, adjusted analysis, and inverse probability of treatment weighting using propensity score, which can provide robust evidences.

In this study, we consistently demonstrate that the untreated MA group is more likely to have a higher cumulative risk of HCC development than the NUC-VR group. Theoretically, in the untreated MA group, long-lasting HBV-DNA integration into hepatocytes can lead to persistent genomic alterations and chromosomal instability, both of which would accelerate hepatic carcinogenesis even before the progression to highly active necro-inflammation status or advanced stage of fibrosis (14). Furthermore, in the setting of high serum HBV-DNA level, even though serum ALT level is persistently normal, a considerable portion of patients has significant necro-inflammation and/or fibrosis on

Table 2. Results of the balancing by inverse probability of treatment weighting analysis based upon propensity score

Variables	Untreated MA group	NUC-VR group	*P* value
Age, yr	53.5 ± 1.3	53.6 ± 0.4	0.963
Male gender, no. (%)	81 (61.5%)	409 (61.7%)	0.961
Diabetes, no. (%)	16 (12.2)	54 (9.0)	0.367
Positive HBeAg, no. (%)	39 (58.6)	428 (58.8)	0.963
Platelet count, $\times 10^3/\mu L$	209.8 ± 8.5	196.5 ± 2.4	0.131
ALT, U/mL	56.7 ± 1.3	24.8 ± 0.4	0.019
Total bilirubin, mg/dL	1.8 ± 0.7	0.8 ± 0.0	0.125
LS values, kPa	8.2 ± 0.9	7.6 ± 0.2	0.476

Data are expressed as mean ± s.d or no. (%).
HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LS, liver stiffness; MA, minimally active; NUC, nucleos(t)ide analogue; VR, virological response.

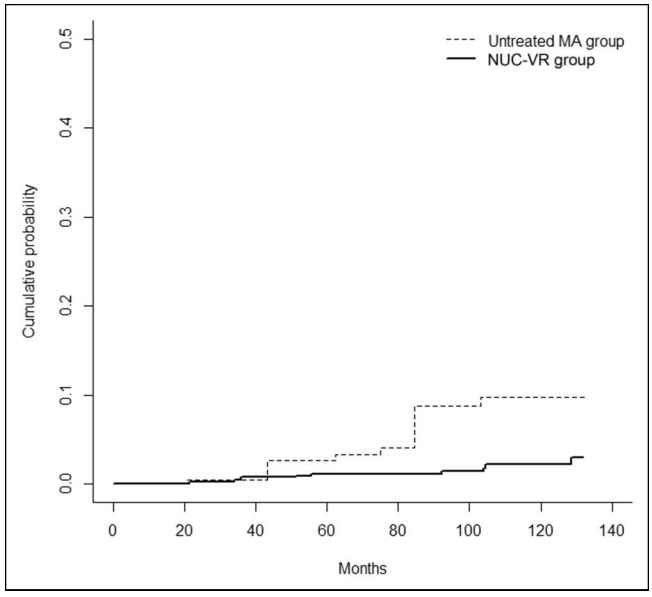

Figure 3. Cumulative risks of HCC development after inverse probability of treatment weighting analysis. HCC, hepatocellular carcinoma; MA, minimally active; NUC, nucleos(t)ide analogue; VR, virological response.

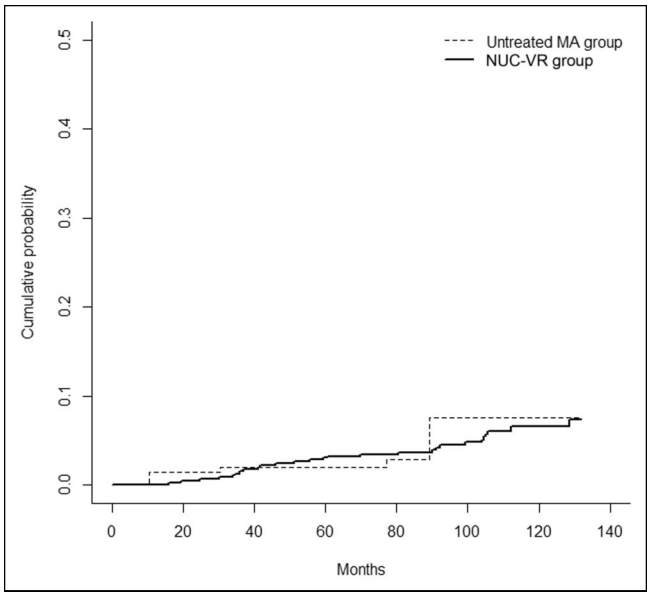

Figure 4. Cumulative risks of cirrhotic complication development after inverse probability of treatment weighting analysis. MA, minimally active; NUC, nucleos(t)ide analogue; VR, virological response.

liver histology (15,16), where NUCs may be recommended (4,5). To confirm this hypothesis, further studies based upon histological and/or immunological data are required. Taken together, since NUCs can suppress viral replication and prevent resultant carcinogenesis as well as necro-inflammation and subsequent fibrogenesis, our data at least provided a corner stone which can justify future prospective trials to evaluate the role of expanding criteria for NUCs. Simultaneously, considering not only the relative high incidence of HBV-related HCC in the Republic of Korea but also the high recurrence and mortality rates and the high socio-economical burden among patients with HCC (11,17,18), the reimbursement guidelines currently available in the real-life practice should be re-appraised in terms of the cost-effectiveness in order to reduce a burden of HCC.

In contrast, in our study, there was no significant difference in terms of development of cirrhotic complication between the untreated MA and NUC-VR group. Such a discrepancy according to the study end points may be explained, at least partly, by the fact that the primary pathways causing HBV-induced HCC or cirrhotic complication are somewhat different from each other. While cirrhotic complication occurs most likely due to portal hypertension caused by fibrosis progression accumulated through persistent necro-inflammation lasting for several decades, HCC occurs due to not only such an indirect pathway but also the direct oncogenic pathway. From the previous studies, 3 major mechanisms for direct carcinogenesis had been suggested; insertional mutagenesis by viral integration into hepatocytes' DNA; genomic instability caused by such a viral integration and the activity of viral proteins; and mutated/truncated viral proteins (HBx, HBc, and pre-S) affecting the microenvironment of liver (19). Further molecular studies explaining these phenomena are required.

There are several unresolved issues in the present study. First, since this is the observational study from a single tertiary referral hospital, the findings were potentially subject to selection bias. However, we conducted multiple statistical strategies to adjust for imbalances between the 2 groups, confirming the reproduction of similar results. Second, in the Republic of Korea, most patients (>98%) are infected with HBV genotype C through vertical transmission, both of which were associated with a higher risk of HCC development (20–22). Thus, these results may not be generalizable for the full spectrum of the population with chronic HBV infection, especially in other countries. Further prospective studies including larger different cohorts are required for external validation. Finally, the incorporation of novel laboratory biomarkers to assess the prognosis in patients with CHB in this study would have been better (23–25). In particular, hepatitis B core-related antigen level might be useful for a stratification of HCC risk among those who achieved sustained viral suppression *via* long-term NUCs (26) and quantitative HBsAg level might be useful to identify inactive carriers more reliably (27,28). Thus, further studies to evaluate the prognosis more delicately using such novel biomarkers are required.

In conclusion, our study consistently showed a higher risk of HCC but a similar risk of cirrhotic complication in the untreated MA group, compared to the NUC-VR group. Many HCC cases among the previously untreated MA group might be prevented by earlier intervention using NUCs before the transition into clinically immune-active status. Randomized controlled trials to confirm the therapeutic benefit for untreated patients with MA-chronic HBV infection would be worthwhile.

Study Highlights

WHAT IS KNOWN

- ✓ A significant proportion of patients with chronic HBV infection belong to so called "minimally active CHB" status, where serum HBV-DNA level is persistently >2,000 IU/mL.
- ✓ There is little data concerning the natural history of untreated patients with minimally active chronic hepatitis B who had persistently serum HBV-DNA level>2,000 IU/mL and had never fulfilled other criteria for initiating nucleos(t)ide analogues (NUCs) during the follow-up.

WHAT IS NEW HERE

- ✓ Such untreated minimally active chronic hepatitis B patients had significantly higher risks of hepatocellular carcinoma (HCC), but similar risks of cirrhotic complications, compared to virological responders by NUCs.
- ✓ Inverse probability of treatment weighting analysis using propensity score to overcome imbalances between two groups also showed the consistent results.

TRANSLATIONAL IMPACT

- ✓ HCC cases might be reduced through earlier intervention by NUCs for such untreated minimally active chronic hepatitis B patients.

CONFLICTS OF INTEREST

Article Guarantor: Beom Kyung Kim, MD, PhD.
Specific author contributions: H.W.L. and B.K.K.: acquisition of data, analysis and interpretation of data, drafting of manuscript, and statistical analysis. B.K.K.: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision, and

study supervision. S.U.K., O.B., J.Y.P., D.Y.K., S.H.A., K.-H.H.: critical revision of manuscript.

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REFERENCES

1. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49:S45–55.
2. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678–86.
3. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006; 295:65–73.
4. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–98.
5. 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;67:1560–99.
6. The Korean Association for the Study of the Liver. KASL clinical practice guidelines: Management of chronic hepatitis B. Clin Mol Hepatol 2016;22:18–75.
7. 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;10:1–98.
8. Su TH, Kao JH. Unmet needs in clinical and basic hepatitis B virus research. J Infect Dis 2017;216:S750–s756.
9. 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;53:885–94.
10. Bruix J, Sherman M; American Association for the Study of Liver D. Management of hepatocellular carcinoma: An update. Hepatology 2011; 53:1020–2.
11. European Association For the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56: 908–43.
12. Park SH, Kim SY, Suh CH, et al. What we need to know when performing and interpreting US elastography. Clin Mol Hepatol 2016;22:406–14.
13. Kim BK, Fung J, Yuen MF, et al. Clinical application of liver stiffness measurement using transient elastography in chronic liver disease from longitudinal perspectives. World J Gastroenterol 2013;19:1890–900.
14. 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;61:1851–9.
15. Seto WK, Lai CL, Ip PP, et al. A large population histology study showing the lack of association between ALT elevation and significant fibrosis in chronic hepatitis B. PLoS One 2012;7:e32622.
16. Park JY, Park YN, Kim DY, et al. High prevalence of significant histology in asymptomatic chronic hepatitis B patients with genotype C and high serum HBV DNA levels. J Viral Hepat 2008;15:615–21.
17. Kim BH, Park JW. Epidemiology of liver cancer in South Korea. Clin Mol Hepatol 2018;24:1–9.
18. Choi J, Han S, Kim N, et al. Increasing burden of liver cancer despite extensive use of antiviral agents in a hepatitis B virus-endemic population. Hepatology 2017;66:1454–63.
19. Kim G, Kim MY, Baik SK. Transient elastography versus hepatic venous pressure gradient for diagnosing portal hypertension: A systematic review and meta-analysis. Clin Mol Hepatol 2017;23:34–41.
20. Kim BK, Revill PA, Ahn SH. HBV genotypes: Relevance to natural history, pathogenesis and treatment of chronic hepatitis B. Antivir Ther (Lond) 2011;16:1169–86.
21. Kim H, Jee YM, Song BC, et al. Molecular epidemiology of hepatitis B virus (HBV) genotypes and serotypes in patients with chronic HBV infection in Korea. Intervirology 2007;50:52–7.
22. Cho EJ, Kim SE, Suk KT, et al. Current status and strategies for hepatitis B control in Korea. Clin Mol Hepatol 2017;23:205–11.
23. Lin CL, Kao JH. New perspectives of biomarkers for the management of chronic hepatitis B. Clin Mol Hepatol 2016;22:423–31.
24. Mak LY, Wong DK, Cheung KS, et al. Review article: hepatitis B core-related antigen (HBcrAg): An emerging marker for chronic hepatitis B virus infection. Aliment Pharmacol Ther 2018;47:43–54.
25. Zhang ZQ, Wang YB, Lu W, et al. Performance of hepatitis B core-related antigen versus hepatitis B surface antigen and hepatitis B virus DNA in predicting HBeAg-positive and HBeAg-negative chronic hepatitis. Ann Lab Med 2019;39:67–75.
26. Hosaka T, Suzuki F, Kobayashi M, et al. Impact of hepatitis B core-related antigen on the incidence of hepatocellular carcinoma in patients treated with nucleos(t)ide analogues. Aliment Pharmacol Ther 2019;49:457–71.
27. Yim SY, Um SH, Jung JY, et al. Role of hepatitis B surface antigen (HBsAg) in identifying true inactive HBsAg carriers infected with genotype C hepatitis B virus. J Clin Gastroenterol 2014;48:166–71.
28. Liu J, Yang HI, Lee MH, et al. Serum levels of hepatitis B surface antigen and DNA can predict inactive carriers with low risk of disease progression. Hepatology 2016;64:381–9.