# Natural History of Untreated HBeAg-Positive Chronic HBV Infection With Persistently Elevated HBV DNA but Normal Alanine Aminotransferase

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OBJECTIVES: **Nucleos(t)ide analogues (NUCs) are not routinely recommended for patients with hepatitis B e antigen–positive chronic hepatitis B virus (HBV) infection who have persistently elevated serum HBV DNA level (>20,000 IU/mL) but normal alanine aminotransferase (<40 IU/L) level. Here, we evaluated the cumulative risks of hepatocellular carcinoma (HCC) in such patients (the untreated persistently elevated serum HBV DNA [pEDNA] group) compared with inactive carriers (the IC group).**

METHODS: **Patients with untreated pEDNA (n = 126) and IC (n = 621) were enrolled between 2006 and 2012. Patients with cirrhosis or HCC at enrollment or a history of NUC treatment were excluded.**

RESULTS: **The cumulative HCC risks at 5 and 9 years in the untreated pEDNA group were 1.1% and 1.9%, which were comparable with those of the IC group ($P = 0.549$). Inverse probability of treatment weighting and propensity score matching also showed similar HCC risks. In the untreated pEDNA group, there were no cases of HCC in the subgroup with serum HBV DNA level >1,000,000 IU/mL (immune-tolerant phase), which was significantly ($P = 0.002$) different compared with those with an intermediate serum HBV DNA level (20,000–1,000,000 IU/mL).**

DISCUSSION: **The cumulative HCC risk in the untreated pEDNA group was minimal and comparable with that of the IC group. Further studies are required to determine whether early NUC treatment, indeed, reduces the HCC risk in patients with an intermediate serum HBV DNA level.**

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/CTG/A190, http://links.lww.com/CTG/A193, http://links.lww.com/CTG/A191, http://links.lww.com/CTG/A192

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## INTRODUCTION

Chronic hepatitis B virus (HBV) infection shows diverse clinical manifestations with dynamic mutual interactions among HBV, the host, and the environment (1–3). In general, indications for antiviral therapy with nucleos(t)ide analogues (NUCs) are based on the serum hepatitis B e antigen (HBeAg) status, serum HBV DNA level, serum alanine aminotransferase (ALT) level, and hepatocellular carcinoma (HCC) or cirrhosis status. Most current clinical practice guidelines (2,4,5) recommend against routine NUC use for patients with HBeAg-positive chronic HBV infection who have persistently elevated serum HBV DNA level but normal serum ALT level (referred to as the "persistently elevated serum HBV DNA [pEDNA] group") in the absence of underlying HCC or cirrhosis.

On the other hand, higher serum HBV DNA levels are also associated with greater risks of developing HCC and liver cirrhosis, regardless of the HBeAg status and serum ALT level (6,7). Furthermore, some investigators reported chromosomal HBV DNA integration and clonal hepatocyte expansion leading to histological inflammation, HBV-specific immune responses, and subsequent hepatocarcinogenesis even in the immune-tolerant (IT) phase, when there is minimal or no hepatic necroinflammation or fibrosis by definition, and the overall risk of disease progression is therefore regarded as negligible (2,8–11).

Therefore, the question of whether patients with elevated serum HBV DNA level during the IT phase would also benefit from NUCs, similar to immune-active patients, has been raised (12). The European Association for the Study of the Liver

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(EASL) guidelines challenged the classical concept of the "IT phase" and suggested a new nomenclature, "HBeAg-positive chronic infection" as an alternative to "chronic hepatitis." In this category, NUCs "may be" considered for HBeAg-positive patients older than 30 years with an elevated serum HBV DNA level and normal serum ALT level (1). However, the evidence level was still only "III," and the recommendation was classified as "weaker," indicating that this may be subject to change depending on future investigations.

There is little consensus regarding early NUC treatment for previously untreated chronic HBV infection with persistently elevated serum HBV DNA but normal ALT level to prevent disease progression. Accordingly, in real-world settings, there is limited reimbursement of NUCs for such patients from a socioeconomic viewpoint, and there are concerns regarding the development of genotypic resistance because of selection pressure.

The present study was performed to assess the long-term risk of HCC development in cases of untreated HBeAg-positive chronic HBV infection with persistently elevated serum HBV DNA but normal serum ALT level, in comparison with inactive carriers (ICs), and to conduct a subgroup analysis of patients in the untreated IT phase.

## METHODS

### Subjects

Among patients with chronic HBV infection visiting the Severance Hospital between 2006 and 2012, untreated HBeAg-positive patients with chronic HBV infection who have persistently elevated serum HBV DNA but normal serum ALT level during the whole follow-up (referred as the "untreated pEDNA group"), and the IC group were screened for eligibility. The inclusion criteria were as follows: (i) age 19 years and older, (ii) reliable liver stiffness (LS) measurements by transient elastography (TE), and (iii) follow-up duration of at least 1 year. The IC status was designated when all 3 of the following criteria were persistently maintained during the follow-up: serum HBV DNA level <2,000 IU/mL, negative HBeAg status, and normal serum ALT level.

The exclusion criteria were as follows: (i) a history of NUC or undergoing NUC treatment in accordance with the clinical practice guidelines during the follow-up, (ii) a history of cirrhosis and/or HCC at enrollment, (iii) decompensated liver function, (iv) coinfection with another viral hepatitis, (v) heavy alcohol consumption, (vi) current use of immunosuppressive agents, and (vii) other significant medical illnesses. The criteria for initiating NUCs are described in Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A193, which were determined by the National Health Insurance Service of the Republic of Korea based on the clinical practice guidelines set by the Korean Association for the Study of the Liver (13). Serum ALT levels were measured using standard laboratory procedures, with an upper limit of normal of 40 U/mL. If histological information was not available, cirrhosis was defined clinically 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. 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, follow-up, and primary outcome

During the follow-up, all patients underwent laboratory tests, including routine blood chemistry, serum HBV DNA, and other serological viral marker measurements every 3–6 months, as well as periodic surveillance with ultrasonography and measurement of the serum alpha-fetoprotein level to screen for HCC and portal hypertension–related complications every 6 months. LS was determined by TE (FibroScan; EchoSens, Paris, France) at enrollment. The LS measurement procedure has been described previously (14–16). Only LS values with at least 10 valid measurements, a success rate of at least 60%, and an interquartile range-to-median ratio <10% were considered acceptable for the analysis (17). The primary outcome in this study was the development of HCC, which was diagnosed based on histological evidence or radiological findings determined by a dynamic computed tomography and/or magnetic resonance imaging (18,19).

### Statistical analysis

Data are expressed as mean ± SD or number (%), as appropriate. Differences in continuous and categorical variables were examined for statistical significance using the Student *t* test (or the Mann-Whitney test when appropriate) and the $\chi^2$ test (or the Fisher exact test when appropriate). The cumulative HCC risks were calculated using the Kaplan-Meier method. The hazard ratio (HR) and 95% confidence interval (CI) were calculated using the Cox proportional hazards models. Furthermore, to reduce the effects of selection bias and potential confounders between the 2 groups, the propensity score (PS) was calculated using logistic regression analysis based on age, gender, presence of diabetes, and LS value. Differences between the 2 groups were minimized by inverse probability of treatment weighting and PS matching.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC) and R (V.3.0, http://cran.r-project.org/). Two-sided *P*-values <0.05 were considered statistically significant.

## RESULTS

### Patient characteristics

The primary study population consisted of the untreated pEDNA (n = 126) (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A190) and IC (n = 621) groups. The baseline characteristics of the patients are summarized in Table 1. The study population had a mean age of 56.4 years and showed a male predominance (54.5%). All patients had well-preserved liver function of Child–Pugh class A. The untreated pEDNA group, compared with the IC group, had a younger age (mean, 47.7 ± 11.1 vs 58.2 ± 11.2 years; $P < 0.001$) and higher platelet count (mean, 219.0 ± 61.5 vs 206.5 ± 54.9 × $10^3$/μL; $P = 0.029$). The mean serum HBV DNA level in the untreated pEDNA group was 6.9 ± 2.0 $\log_{10}$ IU/mL.

### Risk of HCC in the untreated pEDNA and IC groups

Among the entire study population, 8 (1.1%) HCC cases occurred during the follow-up period (median, 73.1 months), consisting of 2 (1.6%) and 6 (1.0%) patients in the untreated pEDNA and IC groups, respectively. Patients with HCC had higher LS values than did those without HCC (mean, 7.7 ± 3.0 vs 5.6 ± 2.0 kPa; $P = 0.004$).

**Table 1.** Baseline characteristics among the entire study population

| Variables | Entire population | Untreated pEDNA group | IC group | *P* value |
|---|---|---|---|---|
| Age, yr | 56.4 ± 11.8 | 47.7 ± 11.1 | 58.2 ± 11.2 | <0.001 |
| Male, n (%) | 407 (54.5) | 62 (49.2) | 345 (55.6) | 0.192 |
| Diabetes, n (%) | 68 (9.1) | 6 (4.8) | 62 (10.0) | 0.063 |
| HBeAg positive, n (%) | 126 (16.9) | 126 (100) | 0 (0) | <0.001 |
| Platelet count, $\times 10^3$/uL | 208.5 ± 56.1 | 219.0 ± 61.5 | 206.5 ± 54.9 | 0.029 |
| LS values, kPa | 5.6 ± 2.1 | 5.7 ± 2.4 | 5.6 ± 2.0 | 0.738 |

Data are expressed as mean ± SD or n (%).
HBeAg, hepatitis B e antigen; IC, inactive carrier; LS, liver stiffness; pEDNA, persistently elevated serum HBV DNA.

The cumulative HCC risks at 3, 5, 7, and 9 years in the untreated pEDNA group were 0.0%, 1.1%, 1.9%, and 1.9%, respectively, which were similar to the values in the IC group (0.0%, 0.0%, 0.4%, and 1.2%, respectively; $P = 0.549$; Figure 1), with an HR of 1.624 (95% CI 0.328–8.050; $P = 0.552$). Adjusted HR of 2.314 (95% CI 0.356–15.029; $P = 0.380$) suggested that there was no significant difference in the risk of HCC development between the untreated pEDNA and IC groups. In terms of cirrhotic complication other than HCC development among the untreated pEDNA group, only 2 patients developed variceal bleeding during the follow-up.

### Inverse probability of treatment weighting

After balancing by inverse probability of treatment weighting, the untreated pEDNA and IC groups also showed similar baseline characteristics (Table 2). The cumulative HCC risks at 3, 5, 7, and 9 years in the untreated pEDNA group were 0.0%, 1.0%, 3.4%, and 3.4%, respectively, which were similar to the values in the IC group (0.0%, 0.2%, 0.5%, and 2.3%, respectively), with an HR of 2.020 (95% CI 0.561–7.299; $P = 0.282$) (Figure 2).

### PS matching

PS matching at a 1:1 ratio generated 114 pairs in each group. After matching, the untreated pEDNA and IC groups showed similar baseline characteristics (Table 3). Similar results were achieved when PS matching was applied. The cumulative HCC risks at 3, 5, 7, and 9 years in the untreated pEDNA group were 0%, 2.0%, 2.0%, and 2.0%, respectively, which were similar to the values of 0%, 1.1%, 1.1%, and 1.1% in the IC group, respectively, with an HR of 2.018 (95% CI 0.180–22.571; $P = 0.569$) (Figure 3).

### Subgroup analysis according to the lower serum ALT levels among the untreated pEDNA group

In the untreated pEDNA group, we analyzed the cumulative HCC risk in a subgroup redefined using much lower serum ALT cutoff values (<30 U/L for men and <19 U/L for women) according to the previous criteria by the American Association for the Study of Liver Diseases (AASLD) (2). The cumulative HCC risks at 3, 5, and 7, and 9 years in this subgroup (n = 67) were 0%, 0%, 2.9%, and 2.9%, respectively, and were not significantly different from those with relatively higher serum ALT levels (30–40 U/L for men and 19–40 U/L for women) ($P = 0.936$).

### Clinical definition of the IT phase using the 2 practice guidelines among the untreated pEDNA group

Given that the proper identification of the IT phase without liver biopsy among the untreated pEDNA group is of paramount importance in the real-life practice, we clinically defined the IT phase considering age, serum HBV DNA level, and serum ALT level based on the 2 recent guidelines by the AASLD (2) and the EASL (1). Detailed criteria are described in Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A193. No HCC case developed in a subgroup (n = 17) defined based on the recent AASLD guideline (2). Similarly, no HCC case also developed in a subgroup (n = 5) defined based on the recent EASL guideline (1).

### Subgroup analysis according to the higher HBV DNA level among the untreated pEDNA group

Because only a small portion of patients could be identified by such rigid criteria by the 2 practice guidelines, we applied the relatively less rigid criteria where the IT phase was defined when all 3 of the following criteria were maintained through the follow-up: serum HBV DNA level >1,000,000 IU/mL, HBeAg positivity, and normal serum ALT level (up to 40 U/mL). No HCC occurred in such a subgroup (n = 96) during the follow-up, compared with 2 HCC cases in those with an intermediate serum HBV DNA level (n = 30), with a statistical significance in the cumulative HCC risk ($P = 0.002$) (see Figure 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A191). The mean age of those with a high serum

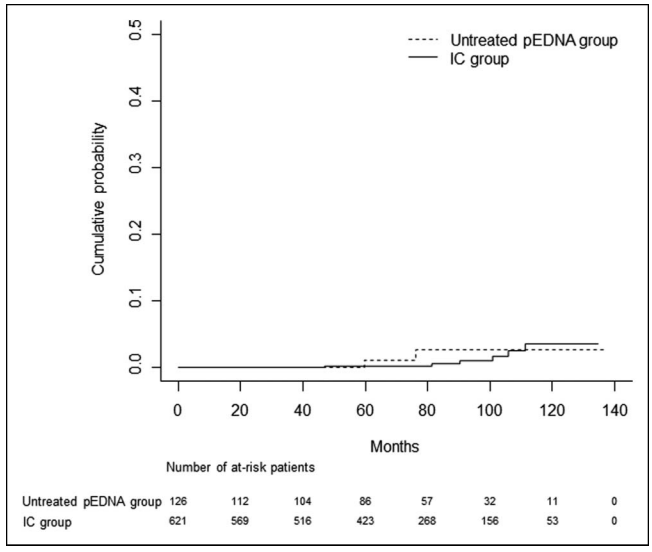


**Figure 1.** The cumulative risks of hepatocellular carcinoma development between the untreated pEDNA and inactive carrier groups among the entire study population. pEDNA, persistently elevated serum HBV DNA.

**Table 2. Results of the balancing by inverse probability of treatment weights analysis**

| Variables | Untreated pEDNA group | IC group | *P* value |
|---|---|---|---|
| Age, yr | 55.2 ± 1.3 | 56.4 ± 0.5 | 0.391 |
| Male, n (%) | 62 (51.4) | 345 (54.5) | 0.607 |
| Diabetes, n (%) | 6 (10.4) | 62 (9.1) | 0.764 |
| Platelet count, $\times 10^3$/μL | 212.4 ± 6.5 | 209.2 ± 2.4 | 0.645 |
| LS values, kPa | 5.8 ± 0.2 | 5.7 ± 0.1 | 0.713 |

Data are expressed as mean ± SD or n (%).
HBeAg, hepatitis B e antigen; IC, inactive carrier; LS, liver stiffness; pEDNA, persistently elevated serum HBV DNA.

**Table 3. Results of the balancing by propensity score matching with 1:1 ratio**

| Variables | Untreated pEDNA group | IC group | *P* value |
|---|---|---|---|
| Age, yr | 49.6 ± 10.0 | 49.4 ± 9.7 | 0.693 |
| Male, n (%) | 55 (48.3) | 58 (50.9) | 0.668 |
| Diabetes, n (%) | 6 (5.3) | 6 (5.3) | >0.999 |
| Platelet count, $\times 10^3$/μL | 215.9 ± 62.1 | 213.9 ± 58.1 | 0.746 |
| LS values, kPa | 5.7 ± 2.5 | 5.7 ± 2.0 | 0.937 |

Data are expressed as mean ± SD or n (%).
HBeAg, hepatitis B e antigen; IC, inactive carrier; LS, liver stiffness; pEDNA, persistently elevated serum HBV DNA.

HBV DNA level >1,000,000 IU/mL only tended to be younger than that of those with an intermediate serum HBV DNA level (47.1 vs 49.8 years; $P = 0.247$).

## DISCUSSION

With the exception of cases with underlying HCC or cirrhosis, the current guidelines recommend NUCs for HBeAg-positive CHB when both serum HBV DNA and serum ALT levels are significantly elevated. Thus, routine NUCs are not generally recommended for patients in the IT phase (2,4,12). However, an opposing perspective has recently been suggested based on 2 lines of evidence. Kim et al. (20) demonstrated significantly higher risks of developing HCC and death/transplantation in untreated patients in the IT phase than in immune-active patients treated with NUCs according to the clinical practice guidelines. In a similar context, another report indicated that NUCs be started during the IT phase because a reduced risk of HCC was observed in the treatment group compared with the controls (21). In both studies, serum HBV DNA level >20,000 IU/mL was used to define the IT phase; however, some critical questions have been raised regarding the appropriateness (22,23). To provide a more definitive answer to this controversial issue, we conducted a longitudinal follow-up study tracking the patients with a natural history of untreated HBeAg-positive CHB, including those in the IT phase, with persistently elevated HBV DNA level but normal ALT level (the untreated pEDNA group).

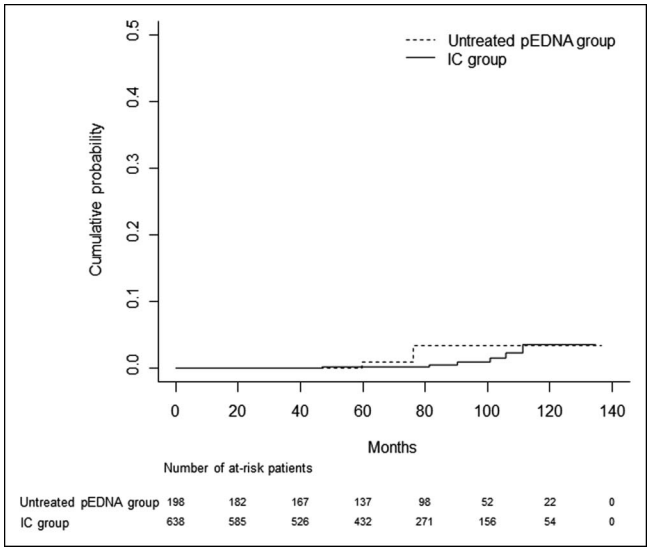


**Figure 2.** The Cumulative risks of hepatocellular carcinoma development between the untreated pEDNA and inactive carrier groups through inverse probability of treatment weighting analysis. pEDNA, persistently elevated serum HBV DNA.

In the present study, the HCC risk was low in the untreated pEDNA group and comparable with that in the IC group. We confirmed the reproducibility of these phenomena by unadjusted and adjusted analyses, inverse probability of treatment weighting, and PS matching. This is the first study to incorporate the quantitative fibrotic burden assessed by TE into statistical analyses. Primarily because of recent advances in the control of CHB by potent NUCs, the background fibrotic burden has increased in the pathogenesis of HCC development. Because fibrotic burden even before progression in compensated cirrhosis substantially influences the overall prognosis, adjustment of the fibrotic burden between groups is essential to reach accurate conclusions (22,24,25). Hence, a more detailed assessment of the degree of fibrosis at subcirrhotic levels and a more precise comparison of the overall prognosis between 2 groups were possible. Furthermore, in contrast to 2 previous reports (20,21), we found that the HCC risk during the untreated IT phase, defined by a high serum HBV DNA cutoff of >1,000,000 IU/mL (26), may be negligible because no HCC cases were observed in this patient group. This result was supported immunologically because HBeAg may act as an IT protein that renders HBV undetectable by the host immune system (27). Under such conditions, HBV is regarded as noncytopathic in hepatocytes and is the main reason for the absence of liver disease despite high levels of HBV replication (28).

There are several possible explanations for the discrepancies between our study and the report by Kim et al. (20). First, from the practical viewpoint, we defined the IT phase by a high serum HBV DNA cutoff of >1,000,000 IU/mL according to the serum HBV DNA criteria of the AASLD (26), whereas Kim et al. (20) adopted a much lower serum HBV DNA cutoff of >20,000 IU/mL. Therefore, as noted by Chu et al. (23), the untreated IT group in the study by Kim et al. (20) may have included immune-active patients who were in remission after experiencing previous unrecognized necroinflammatory events. Second, whereas we defined patients in the IT phase as those exhibiting a persistent IT phase over the entire follow-up period, Kim et al. (20) used a more limited IT phase duration of at least 1 year since enrollment. As virological phases may change because of interactions between the host and virus over

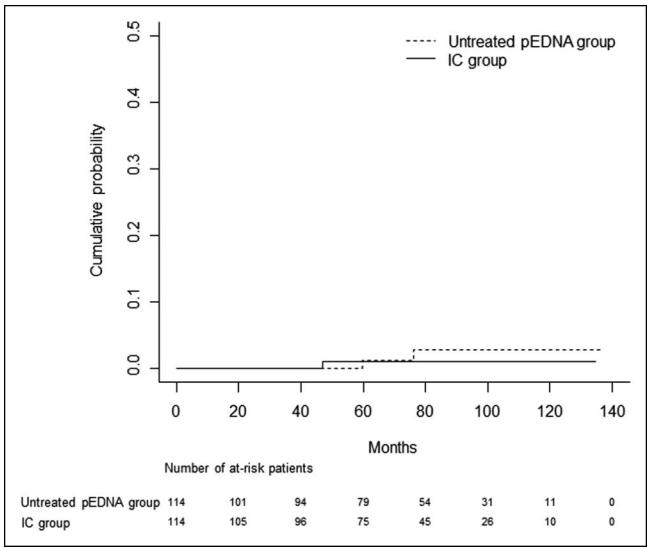


**Figure 3.** The Cumulative risks of hepatocellular carcinoma development between the untreated pEDNA and inactive carrier groups through propensity score matching. pEDNA, persistently elevated serum HBV DNA.

time, some patients initially classified as belonging to the untreated IT group in the study by Kim et al. (20) may subsequently experience significant necroinflammation and fibrosis, both of which have the potential to develop into HCC. Because hepatic carcinogenesis occurs gradually over a long period by both direct and indirect pathways, limiting the definition of the IT phase to 1 year of observation may be inappropriate.

It is noteworthy that untreated patients with an intermediate serum HBV DNA level (20,000–1,000,000 IU/mL) among the untreated pEDNA group, despite the normal ALT level, are paradoxically more likely to develop HCC than are untreated patients with a high serum HBV DNA level (>1,000,000 IU/mL). In the similar context, in the study by Kim et al. (20), the HCC risk was also negatively correlated with the serum HBV DNA level. Because the proper identification of the IT phase without liver biopsy among the untreated pEDNA group is of paramount importance in the real-life practice in terms of physicians' viewpoint, the definition of the "genuine" IT phase should be reviewed more carefully and a high serum HBV DNA cutoff level should become a mandatory criterion for defining the IT phase in accordance with its original definition. Furthermore, when applying the lower age limit (e.g., up to 30 or 40 years) for the definition of the IT phase, there was no HCC case. However, by such strict criteria, only a small portion of patients could be identified. So, what is the optimal age criteria in the practical definition of the IT phase remains to be determined yet.

Although we attempted to overcome the shortcomings of previous studies, this study had several limitations. First, because this was an observational study, the results were potentially subject to selection bias. However, we used multiple statistical strategies to adjust for differences in the baseline susceptibility between the 2 groups and confirmed the consistency of the results. Second, in the Republic of Korea, most (>98%) patients with CHB are infected with genotype C *via* vertical transmission, both of which are associated with a higher HCC risk (29–31). Therefore, these results may not be generalizable to the full spectrum of HBV infections, especially in other countries, and further studies including larger and diverse cohorts are required for external validation. Another limitation is that the follow-up LS values were available only in approximately 60% of the untreated pEDNA group, given that hepatic fibrogenesis is fundamental for HCC development among such a population. Whereas 44 and 3 patients showed the regression of LS and no change, respectively, 29 had the progression of LS (see Figure 3, Supplementary Digital Content 1, http://links.lww.com/CTG/A192). However, because only 2 HCC cases occurred among the untreated pEDNA group, the clinical significance of changes in LS value should be further evaluated. Finally, neither histological data nor novel prognostic biomarkers, by which subclinical hepatic necroinflammation, fibrogenesis, and hepatocarcinogenesis as well as immunological interaction between the host and HBV could be analyzed more accurately, were available in our study (32).

In conclusion, we showed that the cumulative HCC risk in the untreated pEDNA group was minimal and comparable with that in the IC group. In particular, the HCC risk of untreated patients in the IT phase is negligible. Further studies are required to determine whether early NUC treatment can reduce the HCC risk in patients with an intermediate serum HBV DNA level (20,000–1,000,000 IU/mL).

### CONFLICTS OF INTEREST

**Guarantor of the article:** Beom Kyung Kim, MD, PhD.

**Specific author contributions:** B.K.K.: conception and design of the study; H.W.L., B. K.K., E.H.K., J.L., S.U.K., J.Y.P., D.Y.K., S.H.A., and K.-H.H.: generation, collection, assembly, analysis, and/or interpretation of data; H.W.L. and B.K.K.: drafting or revision of the manuscript; all authors: approval of the final version of the manuscript.

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## Study Highlights

### WHAT IS KNOWN

- ✓ Antiviral therapy is not recommended for patients with hepatitis B e antigen–positive chronic hepatitis B virus infection in the immune-tolerant (IT) phase.
- ✓ The question of whether patients during the IT phase would benefit from antivirals, similar to immune-active patients, has been raised.

### WHAT IS NEW HERE

- ✓ The cumulative hepatocellular carcinoma risk in the untreated IT phase was minimal comparable with that of the inactive carrier group.

### TRANSLATIONAL IMPACT

- ✓ The definition of the genuine IT phase in the real-life setting should be established more carefully, and a high serum hepatitis B virus DNA cutoff level should be a mandatory criterion for defining the IT phase in accordance with its original concept.

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