

# Antiviral Therapy Reduces Hepatocellular Carcinoma and Cirrhosis Risk in Chinese Chronic Hepatitis B Patients With Mildly Elevated Alanine Aminotransferase



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## BACKGROUND & AIMS:

The long-term benefit of antiviral treatment with nucleos(t)ide analogues (NAs) for non-cirrhotic patients with chronic hepatitis B (CHB) without significant alanine aminotransferase (ALT) elevation remains debatable. We investigated the impact of NA treatment on the long-term risk of hepatocellular carcinoma (HCC) and cirrhosis in these patients.

## METHODS:

This retrospective multicenter study included 3734 non-cirrhotic patients with CHB with ALT  $< 2 \times$  the upper limit of normal (ULN). To balance baseline characteristics between treated and untreated patients, inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) were applied. The risk of HCC and cirrhosis development was compared between the treated and untreated patients.

## RESULTS:

Of all patients, 37.8% received NA treatment. After IPTW, treated patients had a significantly lower 5-year cumulative incidence of HCC (0.9% vs 4.4%;  $P < .001$ ) and cirrhosis (4.0% vs 8.9%;  $P < .001$ ) than untreated patients. In multivariate Cox analyses, NA therapy was associated with a significantly lower risk of developing HCC (adjusted hazard ratio [aHR], 0.14; 95% confidence interval [CI], 0.05–0.37;  $P < .001$ ) and cirrhosis (aHR, 0.30; 95% CI, 0.18–0.50;  $P < .001$ ) in the IPTW cohort. The findings were consistent in the subgroup of patients with ALT 1 to  $2 \times$  ULN but not in those with ALT  $\leq 1 \times$  ULN. Similar results were obtained in the PSM cohort.

## CONCLUSIONS:

NA therapy reduced the risk of HCC and cirrhosis in non-cirrhotic CHB patients with mildly elevated ALT levels ( $1\text{--}2 \times$  ULN). These findings support the expansion of antiviral treatment criteria for the early treatment of these patients.

**Keywords:** Alanine Aminotransferase; Chronic Hepatitis B; Hepatocellular Carcinoma; Liver Cirrhosis; Nucleos(T)Ide Analogue.

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**Abbreviations used in this paper:** AASLD, American Association for the Study of Liver Diseases; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; CHB, chronic hepatitis B; CI, confidence interval; CT, computed tomography; DM, diabetes mellitus; EASL, European Association for the Study of the Liver; ETV, entecavir; FIB-4, Fibrosis-4 Index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting; IQR, interquartile range; LSM, liver stiffness

measurement; MRI, magnetic resonance imaging; NA, nucleos(t)ide analogue; PSM, propensity score matching; SMD, standardized mean difference; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; WHO, World Health Organization.

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Chronic hepatitis B virus (HBV) infection remains a major global health burden and is the primary cause of end-stage liver diseases such as cirrhosis and hepatocellular carcinoma (HCC).<sup>1,2</sup> Nucleos(t)ide analogues (NAs) effectively suppress HBV replication and improve long-term prognosis in patients with chronic hepatitis B (CHB).<sup>3–5</sup> The indications of antiviral treatment for patients with CHB are largely based on the severity of liver disease and HCC risk as reflected by serum alanine aminotransferase (ALT), HBV DNA levels, and other indicators.<sup>3–5</sup>

Generally, patients with normal or mildly elevated ALT levels have a low risk of disease progression and HCC, and regular follow-up instead of immediate antiviral therapy is recommended in most international CHB guidelines.<sup>3–6</sup> However, emerging evidence suggests that a considerable proportion of patients with CHB and normal or mildly elevated ALT levels have significant histological changes and relatively high risk of HCC and cirrhosis, especially in individuals with high HBV DNA levels.<sup>7–13</sup> The interim results from a recent randomized controlled trial (ATTENTION) add important evidence that early antiviral treatment with tenofovir alafenamide (TAF) reduces the risk of liver-related adverse events in patients with non-cirrhotic livers and normal or mildly elevated ALT levels compared with untreated patients.<sup>14</sup> However, this study was limited by a relatively short follow-up period of only 17.7 months, the inclusion of only patients with moderate-to-high HBV DNA levels, the lack of adjustment for the impact of metabolic comorbidities (eg, hepatic steatosis and diabetes), and the use of a composite endpoint owing to the limited number of events. Other prior studies are also limited by their single-center design, inclusion of only hepatitis B e antigen (HBeAg)-negative patients, relatively small sample sizes, short follow-up periods, and unbalanced baseline characteristics.<sup>11,12,15</sup>

In this multicenter study, we compared the long-term impact of NA on the risk of HCC and cirrhosis between treated and untreated non-cirrhotic patients with CHB and normal or mildly elevated ALT levels, using inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) methods to balance baseline background characteristics.

## Methods

### Study Population

This was a retrospective, multicenter, real-world cohort study that included patients with CHB and serum ALT levels  $<2 \times$  the upper limit of normal (ULN) and without evidence of cirrhosis at baseline across 3 medical institutions in China between January 2014 and February 2025. Chronic HBV infection was defined as persistent hepatitis B surface antigen (HBsAg) positivity for at least 6 months. Patients who met any of the following criteria for cirrhosis were excluded at

## What You Need to Know

### Background

There has been ongoing debate on whether non-cirrhotic patients with chronic hepatitis B (CHB) without significant alanine aminotransferase elevation should receive antiviral therapy.

### Findings

Nucleos(t)ide analogues reduce the risks of hepatocellular carcinoma and cirrhosis development in non-cirrhotic patients with CHB with mildly elevated alanine aminotransferase levels.

### Implications for patient care

The results support expanding treatment criteria to include this large subgroup of patients with CHB. Clinicians should prioritize early initiation of nucleos(t)ide analogues, and this can inform future guidelines.

baseline: histologic evidence of cirrhosis, noninvasive fibrosis tests of aspartate aminotransferase to platelet ratio index (APRI)  $>2.0$ , Fibrosis-4 Index (FIB-4)  $>6.5$ , or liver stiffness measurement (LSM)  $>11$  kPa<sup>16</sup>; thrombocytopenia (platelet count  $<100 \times 10^9/L$ ); and clinical evidence of cirrhosis or evidence of cirrhosis by abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). Patients were also excluded if they had hepatitis C, hepatitis D, or human immunodeficiency virus coinfection, concurrent autoimmune liver disease, significant alcohol consumption, incomplete baseline data, or developed HCC or cirrhosis within 6 months after enrollment.

The study received ethical approval from the Institutional Review Board of Nanjing Drum Tower Hospital and each study site, and informed consent was waived owing to the retrospective design. The study adhered to the principles of the Declaration of Helsinki.

### Definitions and Outcomes

Demographic characteristics, laboratory parameters, imaging findings, comorbidities, and treatment information were collected from electronic medical records using a unified structured data frame. The ULN of ALT was defined as 40 U/L.<sup>4</sup> Patients were divided into untreated and treated groups. Patients in the treatment group were treatment-naïve and received first-line NA therapy at enrollment, including entecavir (ETV), tenofovir disoproxil fumarate (TDF), or TAF.

Patients generally underwent surveillance every 6 months, or more frequently when clinically indicated, for cirrhosis and HCC surveillance with abdominal ultrasound, CT, MRI, and laboratory testing, including alpha-fetoprotein. The primary outcome was HCC

development, which was defined as typical imaging findings or histological examinations based on the recommendations of the guidelines.<sup>4,17</sup> The secondary outcome was the occurrence of cirrhosis, which was defined as evidence of cirrhosis by abdominal ultrasound, CT, MRI, histologic and/or radiologic tests, or complications of cirrhosis, such as splenomegaly with thrombocytopenia, ascites, and gastroesophageal varices.<sup>3–5</sup> Time to clinical outcome was defined as the time from baseline until date of event occurrence. Censoring criteria included the end of the study observation period (February 2025), occurrence of clinical outcomes, initiation of antiviral treatment (for untreated patients), and loss to follow-up, whichever came first.

### Statistical Analysis

Continuous variables were expressed as medians with interquartile ranges (IQRs) and categorical variables as frequencies (percentages). Comparisons of continuous variables between groups were performed using independent *t*-tests or Mann-Whitney *U* tests according to the normality of the data.  $\chi^2$  tests were used to compare categorical variables. IPTW was used to balance the baseline characteristics between the treated and untreated groups, including age, sex, liver steatosis, ALT, HBeAg status, and HBV DNA levels. In addition, PSM was performed using a 1:1 nearest-neighbor algorithm between treated and untreated patients for the above-mentioned factors, applying a caliper width equivalent to 0.2 standard deviations of the logit of the propensity score. The balance between the treated and untreated groups was evaluated using the standardized mean difference (SMD), with an SMD below 0.1, indicative of a good balance. The cumulative incidence of outcomes was derived from Kaplan-Meier estimates and compared using log-rank tests. Cox proportional hazards regression was used to identify the factors associated with HCC and cirrhosis development. Subgroup analyses were conducted according to sex, age, HBeAg status, and ALT and HBV DNA level. *P* value for interaction was calculated to assess the differences in the associations between subgroups. Given the importance of diabetes mellitus (DM) and family history of HCC on the outcomes of CHB,<sup>4,18–20</sup> we adjusted for the presence of DM and family history of HCC in sensitivity analyses. Further sensitivity analysis was performed with additional censoring applied to untreated patients at the time of development of ALT levels  $>2 \times$  ULN. We also conducted sensitivity analyses in patients with persistently normal ALT levels and in those with persistent ALT 1 to  $2 \times$  ULN levels, defined by at least 2 measurements over a minimum of 6 months. In addition, we compared the clinical outcomes between treated and untreated patients according to the more stringent ULNs of ALT based on the 2025 hepatitis B American Association for the Study of Liver Diseases (AASLD) guideline (35 U/L

for male and 25 U/L for female) as another sensitivity analysis.<sup>21</sup> All statistical analyses were conducted using the R software (version 4.3.1, R Foundation). Statistical significance was defined as a 2-sided *P* value of  $<.05$ .

## Results

### Baseline Characteristics of Patients

Of the 4859 patients with CHB and ALT levels  $<2 \times$  ULN and without evidence of cirrhosis, 3734 were included in the analyses ([Supplementary Figure 1](#)). A total of 1411 patients (37.8%) received antiviral treatment with first-line NAs (ETV, TDF, or TAF) for a median of 2.9 years, and 292 (20.7%) underwent drug switching among first-line NAs during follow-up. However, none of the patients in the treated group discontinued NA therapy.

In the overall cohort, the treated patients were older (39.0 vs 35.0 years;  $P < .001$ ) with higher median levels of ALT (38.0 vs 25.8 U/L;  $P < .001$ ) and HBV DNA (4.5  $\log_{10}$  vs 3.2  $\log_{10}$  IU/mL;  $P < .001$ ) and a higher proportion of HBeAg positivity (42.6% vs 23.4%;  $P < .001$ ) than the untreated patients at baseline ([Supplementary Table 1](#)).

### HCC Risk

In the overall cohort, 6 treated patients (0.4%) and 22 untreated patients (0.9%) developed HCC during follow-up. Treated patients had a lower 5-year cumulative HCC incidence (0.9%; 95% confidence interval [CI], 0.0%–1.8%) than untreated patients (2.1%; 95% CI, 1.0%–3.1%;  $P = .091$ ) ([Supplementary Table 2](#)). In multivariable Cox regression analysis, antiviral therapy was associated with a significantly low risk of HCC (adjusted hazard ratio [aHR], 0.19; 95% CI, 0.07–0.49;  $P < .001$ ) ([Supplementary Table 3](#)).

The baseline characteristics were well balanced between the treated and untreated groups after IPTW was applied (all SMD  $<0.1$ ) ([Table 1](#)). In the IPTW cohort, treated patients had a significantly lower 5-year cumulative incidence rate of HCC than untreated patients (0.9% vs 4.4%;  $P < .001$ ) ([Figure 1A](#), [Table 2](#)). In the PSM cohort, which yielded 1131 pairs of patients, a consistently lower 5-year cumulative incidence rate of HCC (1.2% vs 3.1%;  $P = .029$ ) was also found in treated patients than in untreated ones ([Figure 1C](#), [Table 2](#)). In the multivariable Cox regression analysis, antiviral therapy was associated with a significantly lower risk of HCC in the IPTW cohort (aHR, 0.14; 95% CI, 0.05–0.37;  $P < .001$ ) and PSM cohort (aHR, 0.24; 95% CI, 0.09–0.68;  $P = .007$ ) ([Table 3](#)). The results were consistent after adjusting for DM ([Supplementary Table 4](#)) and family history of HCC ([Supplementary Table 5](#)) in both the IPTW and PSM cohorts. We also found similar directions in most subgroup analyses in both the IPTW and PSM

cohorts, especially for subgroups with male sex, age older than 40 years, ALT 1 to 2  $\times$  ULN, HBeAg positivity, HBV DNA  $>20,000$  IU/mL, and those without liver steatosis (Figure 2, Supplementary Figures 2 and 3).

To further investigate the association between antiviral therapy and clinical outcomes, we conducted a subgroup analysis of patients with a lower HBV DNA threshold. In patients with baseline HBV DNA  $\geq 2000$  IU/mL, treated patients had lower 5-year cumulative incidence rates of HCC than untreated patients in both the IPTW and PSM cohorts, whereas no significant differences were observed in patients with HBV DNA  $<2000$  IU/mL (Supplementary Figure 4). We also conducted a subgroup analysis stratified by ALT and HBV DNA levels. Treated patients had a lower 5-year cumulative incidence of HCC than untreated patients among those with ALT 1 to 2  $\times$  ULN and HBV DNA  $\geq 2000$  IU/mL; however, no significant differences were observed in patients with ALT 1 to 2  $\times$  ULN and HBV DNA  $<2000$  IU/mL or in those with ALT  $\leq 1 \times$  ULN, regardless of the

HBV DNA level (Supplementary Figure 5). Only 1 patient with inactive phase developed HCC, and none of the patients with the immune-tolerant phase developed HCC. Therefore, we did not compare the incidence of HCC between treated and untreated groups due to the limited number of events.

### Liver Cirrhosis Risk

In the overall cohort, 30 treated (2.1%) and 82 untreated (3.5%) patients developed cirrhosis during the follow-up period. The 5-year cumulative cirrhosis incidence rate was significantly lower in the treated patients than in the untreated patients (4.1% vs 5.8%;  $P = .023$ ) (Supplementary Table 2). In the multivariable Cox regression analysis, antiviral therapy was associated with a significantly lower risk of cirrhosis (aHR, 0.34; 95% CI, 0.21–0.55;  $P < .001$ ) in the overall cohort (Supplementary Table 3).

**Table 1.** Baseline Characteristics of Patients in the IPTW Cohort and PSM Cohort

| Variables                  | IPTW cohort                   |                             |       | PSM cohort                    |                             |          |
|----------------------------|-------------------------------|-----------------------------|-------|-------------------------------|-----------------------------|----------|
|                            | Untreated group<br>(n = 2337) | Treated group<br>(n = 1409) | SMD   | Untreated group<br>(n = 1131) | Treated group<br>(n = 1131) | SMD      |
| Sex                        |                               |                             | 0.001 |                               |                             | 0.022    |
| Female                     | 941 (40.3)                    | 566 (40.2)                  |       | 472 (41.7)                    | 460 (40.7)                  |          |
| Male                       | 1396 (59.7)                   | 843 (59.8)                  |       | 659 (58.3)                    | 671 (59.3)                  |          |
| Age, y                     | 35.9 (29.5–47.3)              | 37.1 (30.4–47.5)            | 0.015 | 37.0 (30.0–49.0)              | 38.0 (31.0–49.0)            | 0.019    |
| Age range, y               |                               |                             | 0.010 |                               |                             | 0.036    |
| $\leq 40$                  | 1399 (59.9)                   | 837 (59.4)                  |       | 640 (56.6)                    | 620 (54.8)                  |          |
| $> 40$                     | 938 (40.1)                    | 572 (40.6)                  |       | 491 (43.4)                    | 511 (45.2)                  |          |
| DM                         |                               |                             | 0.023 |                               |                             | $<0.001$ |
| No                         | 2187 (93.6)                   | 1327 (94.2)                 |       | 1064 (94.1)                   | 1064 (94.1)                 |          |
| Yes                        | 150 (6.4)                     | 82 (5.8)                    |       | 67 (5.9)                      | 67 (5.9)                    |          |
| Liver steatosis            |                               |                             | 0.007 |                               |                             | 0.025    |
| No                         | 1466 (62.7)                   | 879 (62.4)                  |       | 679 (60.0)                    | 693 (61.3)                  |          |
| Yes                        | 871 (37.3)                    | 530 (37.6)                  |       | 452 (40.0)                    | 438 (38.7)                  |          |
| HBeAg                      |                               |                             | 0.006 |                               |                             | 0.004    |
| Negative                   | 1622 (69.4)                   | 974 (69.1)                  |       | 734 (64.9)                    | 732 (64.7)                  |          |
| Positive                   | 715 (30.6)                    | 435 (30.9)                  |       | 397 (35.1)                    | 399 (35.3)                  |          |
| ALT, U/L                   | 28.6 (19.9–44.0)              | 28.0 (18.9–45.0)            | 0.027 | 30.4 (21.8–45.9)              | 31.8 (21.3–47.2)            | 0.035    |
| ALT range                  |                               |                             | 0.039 |                               |                             | 0.063    |
| $\leq 1 \times$ ULN        | 1652 (70.7)                   | 971 (68.9)                  |       | 758 (67.0)                    | 724 (64.0)                  |          |
| 1–2 $\times$ ULN           | 685 (29.3)                    | 438 (31.1)                  |       | 373 (33.0)                    | 407 (36.0)                  |          |
| HBV DNA, $\log_{10}$ IU/mL | 3.5 (2.7–6.5)                 | 3.8 (2.9–5.8)               | 0.011 | 3.6 (2.7–7.3)                 | 4.0 (3.0–6.4)               | 0.018    |
| HBV DNA range, IU/mL       |                               |                             | 0.053 |                               |                             | 0.082    |
| $\leq 20,000$              | 1486 (63.6)                   | 860 (61.0)                  |       | 672 (59.4)                    | 626 (55.3)                  |          |
| $> 20,000$                 | 851 (36.4)                    | 549 (39.0)                  |       | 459 (40.6)                    | 505 (44.7)                  |          |
| Follow-up time, y          | 2.8 (1.6–4.6)                 | 2.7 (1.4–4.2)               | 0.093 | 2.6 (1.4–4.5)                 | 2.8 (1.5–4.3)               | 0.013    |

NOTE. Data are presented as number (%) or median (interquartile range).

ALT, alanine aminotransferase; DM, diabetes mellitus; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; SMD, standardized mean difference; ULN, upper limit of normal.

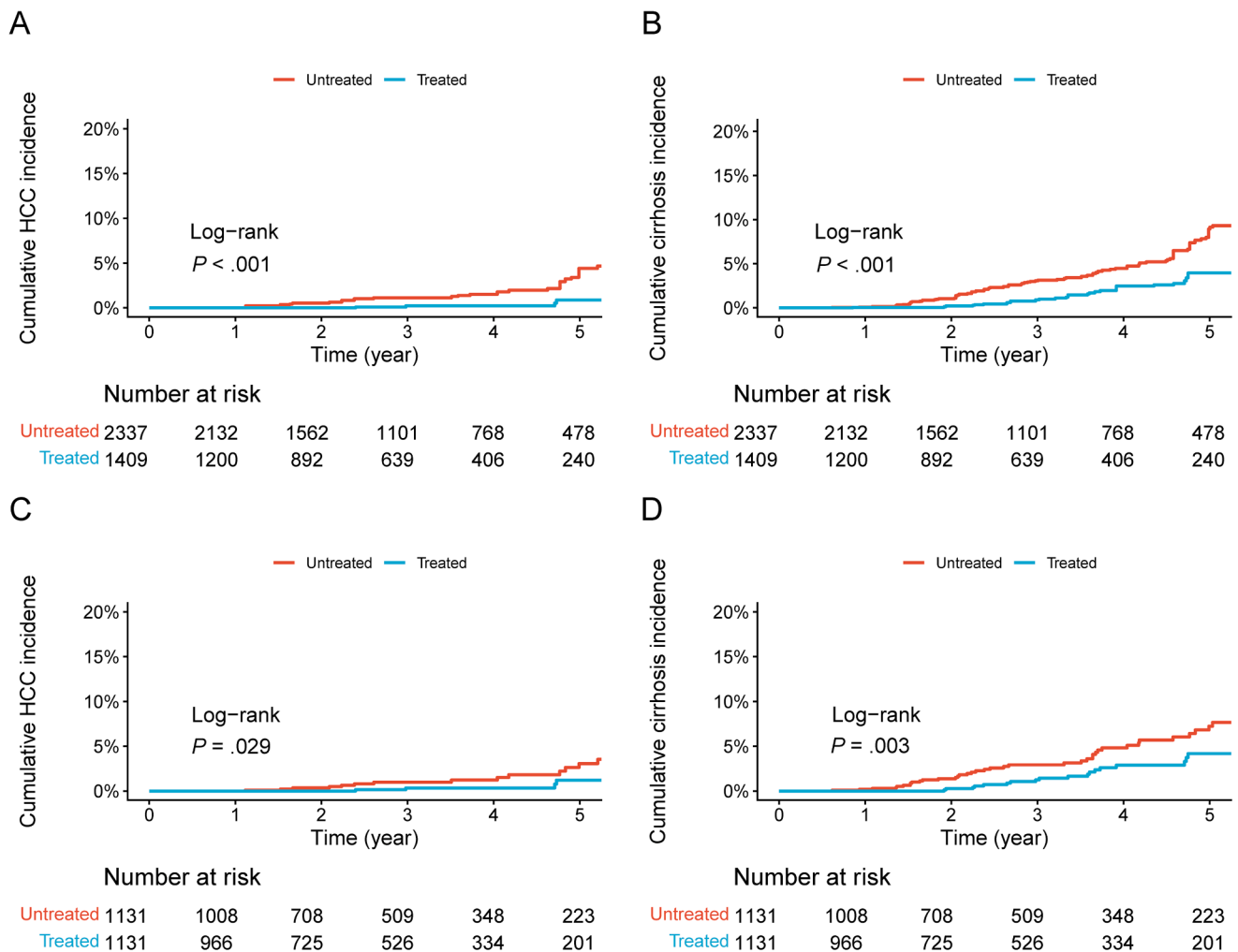


**Figure 1.** Comparison of cumulative incidence of HCC and cirrhosis between treated group and untreated group in the IPTW cohort (A and B) and PSM cohort (C and D).

**Table 2.** Cumulative Incidence Rates of HCC and Cirrhosis in the Treated Group and Untreated Group After IPTW and PSM

| Follow-up time, y | Cumulative incidence, % (95% CI) |                 |               |                 |
|-------------------|----------------------------------|-----------------|---------------|-----------------|
|                   | IPTW cohort                      |                 | PSM cohort    |                 |
|                   | Treated group                    | Untreated group | Treated group | Untreated group |
| <b>HCC</b>        |                                  |                 |               |                 |
| 1                 | 0                                | 0               | 0             | 0               |
| 2                 | 0                                | 0.5 (0.0–1.1)   | 0             | 0.4 (0.0–0.8)   |
| 3                 | 0.2 (0.0–0.5)                    | 1.1 (0.3–1.9)   | 0.3 (0.0–0.8) | 1.0 (0.2–1.7)   |
| 4                 | 0.2 (0.0–0.5)                    | 1.5 (0.6–2.4)   | 0.3 (0.0–0.8) | 1.2 (0.4–2.1)   |
| 5                 | 0.9 (0.0–1.8)                    | 4.4 (1.6–7.1)   | 1.2 (0.0–2.5) | 3.1 (1.2–4.9)   |
| <b>Cirrhosis</b>  |                                  |                 |               |                 |
| 1                 | 0.1 (0.0–0.2)                    | 0.1 (0.0–0.2)   | 0.0 (0.0–0.0) | 0.2 (0.0–0.4)   |
| 2                 | 0.2 (0.0–0.5)                    | 1.0 (0.5–1.6)   | 0.3 (0.0–0.6) | 1.4 (0.6–2.2)   |
| 3                 | 0.9 (0.3–1.5)                    | 3.1 (1.9–4.2)   | 1.2 (0.4–2.1) | 2.9 (1.7–4.1)   |
| 4                 | 2.5 (1.1–3.9)                    | 4.5 (3.1–5.9)   | 2.9 (1.4–4.4) | 4.8 (3.0–6.6)   |
| 5                 | 4.0 (1.9–5.9)                    | 8.9 (5.6–12.2)  | 4.2 (2.1–6.2) | 7.2 (4.7–9.7)   |

CI, confidence interval; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting; PSM, propensity score matching.

The 5-year cumulative cirrhosis incidence rates were also significantly lower in treated patients than in untreated patients in both the IPTW (4.0% vs 8.9%;  $P < .001$ ) and PSM cohorts (4.2% vs 7.2%;  $P = .003$ ) (Figure 1B and D, Table 2). In the multivariable Cox regression analyses, antiviral therapy was associated with a significantly lower risk of cirrhosis in both the IPTW (aHR, 0.30; 95% CI, 0.18–0.50;  $P < .001$ ) and PSM cohorts (aHR, 0.37; 95% CI, 0.22–0.63;  $P < .001$ ) (Table 4). The results were consistent after adjusting for the presence of DM in both the IPTW and PSM cohorts (Supplementary Table 6). We also found similar directions in most subgroup analyses, in both of the IPTW and PSM cohorts, especially for those with male sex, age older than 40 years, ALT 1 to 2  $\times$  ULN, HBV DNA  $>20,000$  IU/mL, irrespective of HBeAg status, and the presence of hepatic steatosis (Supplementary Figures 6–8). In both IPTW and PSM cohorts, treated patients had a significantly lower 5-year cumulative incidence of cirrhosis than untreated patients, regardless of baseline HBV DNA  $\geq 2000$  IU/mL or  $<2000$  IU/mL (Supplementary Figure 4). However, a lower 5-year cumulative incidence of cirrhosis in treated patients

**Table 3.** Associated Factors of HCC Development in the IPTW Cohort and PSM Cohort

| Variables        | N    | Events | Annual incidence<br>rate, % (95% CI) | Univariate         |                | Multivariate        |                |
|------------------|------|--------|--------------------------------------|--------------------|----------------|---------------------|----------------|
|                  |      |        |                                      | HR (95% CI)        | <i>P</i> value | aHR (95% CI)        | <i>P</i> value |
| IPTW cohort      |      |        |                                      |                    |                |                     |                |
| Treatment status |      |        |                                      |                    |                |                     |                |
| Untreated        | 2337 | 42     | 0.55 (0.39–0.74)                     | Reference          |                | Reference           |                |
| Treated          | 1409 | 4      | 0.10 (0.04–0.23)                     | 0.19 (0.07–0.50)   | <.001          | 0.14 (0.05–0.37)    | <.001          |
| Age, <i>y</i>    |      |        |                                      |                    |                |                     |                |
| ≤40              | 2236 | 8      | 0.11 (0.05–0.20)                     | Reference          |                | Reference           |                |
| >40              | 1510 | 38     | 0.82 (0.59–1.11)                     | 7.88 (2.92–21.31)  | <.001          | 10.91 (4.36–27.32)  | <.001          |
| Sex              |      |        |                                      |                    |                |                     |                |
| Female           | 1507 | 6      | 0.13 (0.05–0.25)                     | Reference          |                | Reference           |                |
| Male             | 2239 | 40     | 0.55 (0.40–0.74)                     | 4.30 (0.74–24.88)  | .103           | 4.59 (0.68–30.79)   | .117           |
| Liver steatosis  |      |        |                                      |                    |                |                     |                |
| No               | 2345 | 39     | 0.53 (0.38–0.71)                     | Reference          |                | Reference           |                |
| Yes              | 1401 | 7      | 0.16 (0.07–0.30)                     | 0.29 (0.09–0.91)   | .035           | 0.36 (0.11–1.18)    | .092           |
| ALT              |      |        |                                      |                    |                |                     |                |
| ≤1 × ULN         | 2623 | 17     | 0.21 (0.13–0.33)                     | Reference          |                | Reference           |                |
| 1–2 × ULN        | 1123 | 29     | 0.78 (0.54–1.12)                     | 3.69 (1.62–8.42)   | .002           | 2.00 (0.57–6.99)    | .277           |
| HBeAg status     |      |        |                                      |                    |                |                     |                |
| Negative         | 2596 | 22     | 0.27 (0.17–0.40)                     | Reference          |                | Reference           |                |
| Positive         | 1150 | 24     | 0.65 (0.42–0.96)                     | 2.48 (1.01–6.08)   | .048           | 3.48 (1.05–11.57)   | .042           |
| HBV DNA, IU/mL   |      |        |                                      |                    |                |                     |                |
| ≤20,000          | 2346 | 17     | 0.22 (0.14–0.36)                     | Reference          |                | Reference           |                |
| >20,000          | 1400 | 29     | 0.65 (0.45–0.93)                     | 3.00 (1.20–7.47)   | .018           | 1.63 (0.36–7.43)    | .525           |
| PSM cohort       |      |        |                                      |                    |                |                     |                |
| Treatment status |      |        |                                      |                    |                |                     |                |
| Untreated        | 1131 | 15     | 0.42 (0.23–0.69)                     | Reference          |                | Reference           |                |
| Treated          | 1131 | 5      | 0.14 (0.05–0.33)                     | 0.34 (0.12–0.94)   | .037           | 0.24 (0.09–0.68)    | .007           |
| Age, <i>y</i>    |      |        |                                      |                    |                |                     |                |
| ≤40              | 1260 | 5      | 0.12 (0.04–0.28)                     | Reference          |                | Reference           |                |
| >40              | 1102 | 15     | 0.50 (0.28–0.82)                     | 4.27 (1.55–11.77)  | .005           | 7.76 (2.57–23.43)   | <.001          |
| Sex              |      |        |                                      |                    |                |                     |                |
| Female           | 932  | 1      | 0.04 (0.00–0.20)                     | Reference          |                | Reference           |                |
| Male             | 1330 | 19     | 0.44 (0.26–0.68)                     | 11.66 (1.56–87.13) | .017           | 15.11 (1.97–115.80) | .009           |
| Liver steatosis  |      |        |                                      |                    |                |                     |                |
| No               | 1372 | 16     | 0.38 (0.22–0.62)                     | Reference          |                | Reference           |                |
| Yes              | 890  | 4      | 0.14 (0.04–0.35)                     | 0.34 (0.11–1.02)   | .054           | 0.39 (0.13–1.23)    | .107           |
| ALT              |      |        |                                      |                    |                |                     |                |
| ≤1 × ULN         | 1482 | 10     | 0.22 (0.11–0.40)                     | Reference          |                | Reference           |                |
| 1–2 × ULN        | 780  | 10     | 0.38 (0.18–0.70)                     | 1.62 (0.67–3.90)   | .280           | 0.88 (0.34–2.28)    | .794           |
| HBeAg status     |      |        |                                      |                    |                |                     |                |
| Negative         | 1466 | 9      | 0.20 (0.09–0.38)                     | Reference          |                | Reference           |                |
| Positive         | 796  | 11     | 0.41 (0.21–0.74)                     | 2.02 (0.84–4.86)   | .119           | 2.59 (0.80–8.33)    | .111           |
| HBV DNA, IU/mL   |      |        |                                      |                    |                |                     |                |
| ≤20,000          | 1298 | 6      | 0.15 (0.06–0.32)                     | Reference          |                | Reference           |                |
| >20,000          | 964  | 14     | 0.44 (0.24–0.74)                     | 2.91 (1.12–7.56)   | .029           | 3.09 (0.85–11.17)   | .086           |

aHR, adjusted hazard ratio; ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; ULN, upper limit of normal.

compared with untreated patients was observed only among those with ALT 1 to 2 × ULN and HBV DNA ≥2000 IU/mL (Supplementary Figure 5). However, no significant difference in the development of cirrhosis was observed between treated and untreated patients in either the immune-tolerant phase or inactive phase (Supplementary Figure 9).

### Sensitivity Analyses

A total of 278 untreated patients developed ALT >2 × ULN during follow-up period. A similar lower risk

of HCC and cirrhosis was also observed in the treated group, with additional censoring applied to untreated patients at the time of development of ALT levels >2 × ULN (Supplementary Figure 10). Additionally, treated patients had a lower risk of HCC and cirrhosis than untreated patients in patients with persistently ALT 1 to 2 × ULN levels, but not in patients with persistently normal ALT levels (Supplementary Figure 11).

In the sensitivity analyses using more stringent ULNs of ALT according to the 2025 AASLD guideline (Supplementary Tables 7 and 8), the 5-year cumulative HCC and cirrhosis incidence rates were significantly

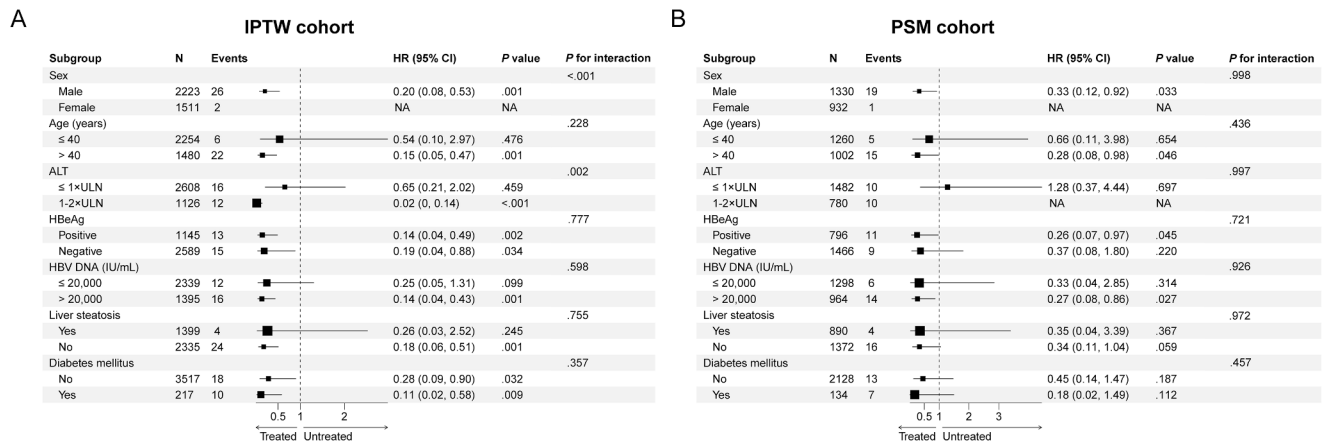


**Figure 2.** Association of antiviral therapy and HCC risk in different subgroups in the IPTW cohort (A) and PSM cohort (B).

**Table 4.** Associated Factors of Cirrhosis Development in the IPTW Cohort and PSM Cohort

| Variables        | N    | Events | Annual incidence rate<br>(%, 95% CI) | Univariate       |                | Multivariate     |                |
|------------------|------|--------|--------------------------------------|------------------|----------------|------------------|----------------|
|                  |      |        |                                      | HR (95% CI)      | <i>P</i> value | aHR (95% CI)     | <i>P</i> value |
| IPTW cohort      |      |        |                                      |                  |                |                  |                |
| Treatment status |      |        |                                      |                  |                |                  |                |
| Untreated        | 2337 | 109    | 1.41 (1.16–1.69)                     | Reference        |                | Reference        |                |
| Treated          | 1409 | 24     | 0.55 (0.35–0.79)                     | 0.40 (0.25–0.64) | <.001          | 0.30 (0.18–0.50) | <.001          |
| Age, <i>y</i>    |      |        |                                      |                  |                |                  |                |
| ≤40              | 2236 | 60     | 0.81 (0.62–1.03)                     | Reference        |                | Reference        |                |
| >40              | 1510 | 73     | 1.55 (1.23–1.95)                     | 1.98 (1.28–3.06) | .002           | 2.63 (1.68–4.14) | <.001          |
| Sex              |      |        |                                      |                  |                |                  |                |
| Female           | 1507 | 44     | 0.93 (0.69–1.25)                     | Reference        |                | Reference        |                |
| Male             | 2239 | 89     | 1.21 (0.97–1.48)                     | 1.24 (0.75–2.04) | .396           | 1.23 (0.70–2.15) | .473           |
| Liver steatosis  |      |        |                                      |                  |                |                  |                |
| No               | 2345 | 80     | 1.10 (0.88–1.36)                     | Reference        |                | Reference        |                |
| Yes              | 1401 | 53     | 1.10 (0.83–1.43)                     | 0.94 (0.60–1.47) | .790           | 1.01 (0.66–1.56) | .957           |
| ALT              |      |        |                                      |                  |                |                  |                |
| ≤1 × ULN         | 2623 | 69     | 0.83 (0.65–1.05)                     | Reference        |                | Reference        |                |
| 1–2 × ULN        | 1123 | 64     | 1.71 (1.32–2.16)                     | 2.00 (1.27–3.14) | .003           | 1.71 (0.95–3.11) | .076           |
| HBeAg status     |      |        |                                      |                  |                |                  |                |
| Negative         | 2596 | 75     | 0.89 (0.70–1.11)                     | Reference        |                | Reference        |                |
| Positive         | 1150 | 58     | 1.57 (1.21–2.02)                     | 1.80 (1.15–2.82) | .011           | 1.97 (0.98–3.96) | .057           |
| HBV DNA, IU/mL   |      |        |                                      |                  |                |                  |                |
| ≤20,000          | 2346 | 61     | 0.80 (0.61–1.03)                     | Reference        |                | Reference        |                |
| >20,000          | 1400 | 72     | 1.61 (1.26–2.01)                     | 2.07 (1.32–3.24) | .002           | 1.64 (0.80–3.35) | .174           |
| PSM cohort       |      |        |                                      |                  |                |                  |                |
| Treatment status |      |        |                                      |                  |                |                  |                |
| Untreated        | 1131 | 47     | 1.30 (0.96–1.73)                     | Reference        |                | Reference        |                |
| Treated          | 1131 | 22     | 0.62 (0.39–0.93)                     | 0.47 (0.28–0.78) | .003           | 0.37 (0.22–0.63) | <.001          |
| Age, <i>y</i>    |      |        |                                      |                  |                |                  |                |
| ≤40              | 1260 | 36     | 0.87 (0.61–1.20)                     | Reference        |                | Reference        |                |
| >40              | 1102 | 33     | 1.09 (0.75–1.53)                     | 1.35 (0.84–2.17) | .218           | 2.24 (1.30–3.88) | .004           |
| Sex              |      |        |                                      |                  |                |                  |                |
| Female           | 932  | 21     | 0.74 (0.46–1.14)                     | Reference        |                | Reference        |                |
| Male             | 1330 | 48     | 1.10 (0.81–1.46)                     | 1.39 (0.84–2.33) | .204           | 1.38 (0.80–2.40) | .251           |
| Liver steatosis  |      |        |                                      |                  |                |                  |                |
| No               | 1372 | 36     | 0.85 (0.60–1.18)                     | Reference        |                | Reference        |                |
| Yes              | 890  | 33     | 1.11 (0.77–1.56)                     | 1.23 (0.77–1.97) | .396           | 1.29 (0.79–2.10) | .308           |
| ALT              |      |        |                                      |                  |                |                  |                |
| ≤1 × ULN         | 1482 | 37     | 0.81 (0.57–1.12)                     | Reference        |                | Reference        |                |
| 1–2 × ULN        | 780  | 32     | 1.22 (0.84–1.73)                     | 1.41 (0.88–2.26) | .158           | 1.27 (0.76–2.14) | .368           |

Table 4. Continued

| Variables            | N    | Events | Annual incidence rate<br>(%, 95% CI) | Univariate       |         | Multivariate     |         |
|----------------------|------|--------|--------------------------------------|------------------|---------|------------------|---------|
|                      |      |        |                                      | HR (95% CI)      | P value | aHR (95% CI)     | P value |
| HBeAg status         |      |        |                                      |                  |         |                  |         |
| Negative             | 1466 | 33     | 0.73 (0.50–1.02)                     | Reference        |         | Reference        |         |
| Positive             | 796  | 36     | 1.35 (0.95–1.87)                     | 1.78 (1.11–2.86) | .017    | 1.87 (0.93–3.76) | .080    |
| HBV DNA range, IU/mL |      |        |                                      |                  |         |                  |         |
| ≤20,000              | 855  | 26     | 0.65 (0.42–0.95)                     | Reference        |         | Reference        |         |
| >20,000              | 1407 | 43     | 1.36 (0.99–1.84)                     | 2.05 (1.27–3.36) | .004    | 1.97 (1.00–3.92) | .052    |

aHR, adjusted hazard ratio; ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; ULN, upper limit of normal.

lower in treated patients than in untreated patients in both the IPTW and PSM cohorts (Supplementary Figure 12). In the multivariable Cox regression analyses, antiviral therapy was associated with a significantly low risk of HCC and cirrhosis in the overall cohort (Supplementary Table 9), as well as in both the IPTW and PSM cohorts (Supplementary Tables 10 and 11). Similar trends were observed in most subgroup analyses (Supplementary Figures 13 and 14).

## Discussion

In this large, multicenter, real-world cohort study that included 3734 non-cirrhotic patients with CHB and ALT <2 × ULN, we found that patients who received NA treatment had a significantly lower incidence of HCC and cirrhosis than those who did not receive antiviral treatment during a median follow-up period of 2.9 years. Consistent results were observed after adjusting for family history of HCC, the presence of DM, and using a more stringent definition of normal or mildly elevated ALT or ULN for ALT, as recommended by the 2025 AASLD guideline. Several subgroups of patients receiving NA showed particularly significant reductions in HCC and cirrhosis incidence among patients with ALT 1 to 2 × ULN.

Although untreated non-cirrhotic patients with CHB without significant ALT elevation are generally not indicated for antiviral treatment, the 5-year incidence rates of HCC and cirrhosis in our study were 2.1% and 5.8%, respectively. Our results were consistent with those of a previous study that reported that untreated HBeAg-negative patients with CHB, high viral load, and non-significant ALT elevation had a high 10-year cumulative HCC incidence.<sup>11</sup> A recent study also reported that 2% of patients with non-cirrhotic CHB and moderate or high viremia (median, 5.0 log<sub>10</sub> IU/mL), but normal or mildly elevated ALT, developed HCC during approximately 1.5 years of follow-up.<sup>14</sup> Taken together, our findings and those of previous studies indicate that untreated non-cirrhotic patients with CHB without significant ALT elevation beyond the treatment indications

may still carry a substantial risk of disease progression. Using both IPTW and PSM to balance the baseline clinical characteristics of our comparative patient groups, our study provides robust evidence that antiviral treatment is associated with a significantly lower incidence of HCC and cirrhosis. In addition, the results are consistent with those of several sensitivity analyses. The current study expands on prior data by showing that NA treatment was significantly and independently associated with reduced cirrhosis and HCC risk in non-cirrhotic patients with CHB without significant ALT elevation, especially in patients with mildly elevated ALT levels (1–2 × ULN).

Our findings have several significant clinical implications. Given that a large number of patients with CHB have ALT <2 × ULN, this represents a major proportion of patients with CHB at an increased risk of HCC and cirrhosis that can be mitigated by well-tolerated NA therapy, as shown in the present study. Our results support the expansion of antiviral indications for CHB to include patients without significant ALT elevation at higher risk of HCC and cirrhosis, such as male patients, those >40 years, positive HBeAg, those with HBV DNA >2000 IU/mL, and those with ALT 1 to 2 × ULN. These factors have also been reported to be associated with a higher risk of HCC and cirrhosis in patients with CHB.<sup>22,23</sup> Our real-world evidence supports the ongoing shift toward a more proactive treatment approach for expanding eligibility to include patients with lower threshold ALT levels (>ULN) and HBV DNA (>2000 IU/mL), as recently recommended by the 2025 European Association for the Study of the Liver (EASL) guidelines and the 2024 World Health Organization (WHO) guidelines.<sup>4,6</sup> The updated recommendations also allow antiviral treatment in patients with normal ALT levels and any level of viremia, who are at risk of disease progression and HCC.<sup>4,6</sup> However, the evidence for this recommendation is weak.<sup>4,6</sup> Moreover, the updated 2025 AASLD guidelines continue to endorse the use of higher ALT (>2 × ULN) and HBV DNA thresholds (>20,000 IU/mL for HBeAg-positive CHB and >2000 IU/mL for HBeAg-negative CHB) to guide treatment decisions.<sup>21</sup> Our real-world evidence may fill this gap and help inform

future hepatitis B clinical management guidelines to expand the pool of patients with CHB at higher risk who should be considered for antiviral treatment.

The major strengths of this study include the use of both IPTW and PSM methods to balance the baseline confounding factors and to conduct comprehensive subgroup and sensitivity analyses to confirm the robustness of the findings. In addition, accumulating evidence has shown that family history and metabolic comorbidities, particularly the presence of DM and liver steatosis, significantly affect the risk of HCC and cirrhosis in patients with CHB.<sup>4,18,24</sup> In our study, we also found that a family history of HCC and the presence of DM were associated with a higher risk of HCC and cirrhosis, whereas the presence of liver steatosis was associated with a lower risk, which is consistent with previous reports.<sup>4,18</sup> After balancing and/or adjusting for the family of HCC, presence of DM, and liver steatosis, antiviral therapy was consistently associated with significantly lower HCC and cirrhosis risk in patients with mildly elevated ALT levels.

However, this study has several limitations. First, the retrospective study design may have introduced biases. Second, although patients with cirrhosis were excluded, most were identified using noninvasive assessments, which may have introduced additional bias. Third, the identification of normal or mildly elevated ALT levels was based on the data from a single test at enrollment. However, we conducted sensitivity analyses in patients with persistently normal ALT levels and persistent ALT 1 to  $2 \times$  ULN levels, which yielded similar results. Fourth, the data on HBV genotype were not available, whereas HBV genotypes B and C are predominant in China.<sup>25</sup> Thus, our findings require validation in populations with different HBV genotypes and ethnic backgrounds.

## Conclusion

In conclusion, this large, real-world, multicenter cohort study demonstrated that NA therapy reduced the risk of HCC and cirrhosis development in non-cirrhotic patients with CHB without significant ALT elevation, especially in patients with mildly elevated ALT levels ( $1-2 \times$  ULN). These findings provide evidence to support the expansion of treatment criteria to allow early antiviral therapy in non-cirrhotic patients with mildly elevated ALT levels, thereby reducing the risk of HCC and cirrhosis. However, the clinical benefit of antiviral therapy in patients with normal ALT levels requires further investigation.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at <https://doi.org/10.1016/j.cgh.2026.02.008>.

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#### Conflicts of interest

The authors disclose no conflicts.

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#### Data Availability

The data supporting the study findings are available upon reasonable request from the corresponding authors.