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Antiviral Therapy for Chronic Hepatitis B Virus Infection and Development of Hepatocellular Carcinoma in a US Population

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Abstract

BACKGROUND & AIMS—Antiviral therapy could reduce the risk of hepatocellular carcinoma (HCC) among persons with chronic hepatitis B virus (HBV) infection. We evaluated the relationship between therapy for chronic HBV infection and HCC incidence using data from a longitudinal study of patients at 4 US healthcare centers.

METHODS—We analyzed electronic health records of 2671 adult participants in the Chronic Hepatitis Cohort Study who were diagnosed with chronic HBV infection from 1992 through 2011 (49% Asian). Data analyzed were collected for a median of 5.2 years. Propensity-score adjustment was used to reduce bias, and Cox regression was used to estimate the relationship between antiviral treatment and HCC. The primary outcome was time to event of HCC incidence.

RESULTS—Of study subjects, 3% developed HCC during follow-up period: 20 cases among the 820 patients with a history of antiviral HBV therapy and 47 cases among the 1851 untreated patients. In propensity-adjusted Cox regression, patients who received antiviral therapy had a lower risk of HCC than those who did not receive antiviral therapy (adjusted hazard ratio, 0.39; 95% confidence interval, 0.27–0.56; $P < .001$), after adjusting for abnormal level of alanine aminotransferase. In a subgroup analysis, antiviral treatment was associated with a lower risk of HCC after adjusting for serum markers of cirrhosis (adjusted hazard ratio, 0.24; 95% confidence interval, 0.15–0.39; $P < .001$). In a separate subgroup analysis of patients with available data on

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Conflicts of interest

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HBV DNA viral load, treated patients with viral loads >20,000 IU/mL had a significantly lower risk of HCC than untreated patients with viral loads >20,000 IU/mL.

CONCLUSIONS—In a large geographically, clinically, and racially diverse US cohort, antiviral therapy for chronic HBV infection was associated with a reduced risk for HCC.

Keywords

Liver Cancer; Fibrosis; Alanine Aminotransferase; Tumor

Recent comprehensive critical reviews,[1] meta-analyses,[2] and other studies[3–5] have suggested that the use of various antiviral therapies for chronic hepatitis B virus (HBV) can reduce the risk of hepatocellular carcinoma (HCC) and HCC recurrence after liver resection.[6] However, the definitive effect of antivirals on the development of HCC remains in doubt, because there is insufficient evidence from randomized controlled clinical trials to assess a treatment effect on clinical outcomes.[7,8]

Outstanding questions still remain. For example, it is unclear whether treatment of patients with noncirrhotic HBV eliminates the risk of HCC[9]; additionally, what benefits antiviral therapy has across a broad spectrum of viral load levels is uncertain. Observational studies and clinical trials examining the relationship between antiviral therapy and the development of HCC have generally been conducted in small cohorts that have been homogeneous in terms of geography, race, treatment, clinical profile, and/or viral characteristics. The Chronic Hepatitis Cohort Study (CHeCS) is a comprehensive, longitudinal cohort study assessing the clinical impact of chronic HBV and hepatitis C virus (HCV) infection in the United States.[10] Retrospective and real-time data are being collected at 4 large, integrated health systems serving approximately 4 million people in 5 geographically and racially disparate states, resulting in a diverse cohort. We examined whether antiviral HBV therapy was associated with a risk of HCC among CHeCS participants with chronic HBV infection.

Methods

CHeCS Cohort

The CHeCS investigation follows the guidelines of the US Department of Health and Human Services regarding the protection of human subjects. The protocol was approved and is renewed annually by the institutional review board at each participating site.

The CHeCS project's methods have been summarized previously.[10] Briefly, electronic administrative data and electronic health records of patients 18 years or older who had received any health services between January 1, 2006 and December 31, 2010 at a study site were used to identify candidates for the study cohort. For inclusion, patients had to fulfill at least 2 criteria (i.e., 2 positive laboratory tests consistent with current HBV infection [positive for HBV surface antigen, e-antigen, or DNA test], or a positive laboratory test and an International Classification of Diseases-9 diagnosis code, or 2 International Classification of Diseases-9 diagnosis codes obtained at least 6 months apart). Chronic HBV infection was then confirmed during chart abstraction. Eligibility for inclusion was not restricted to any particular chronic HBV disease phase.

Time of HBV diagnosis was defined as the date of the earliest finding of an HBV-associated diagnosis code and/or a positive test for HBV infection within each health system's records. Follow-up began with initiation of antiviral therapy in the treated group or time of HBV diagnosis in the untreated group, and ended with HCC, death, or last patient encounter.

Outcome

The primary outcome was time to event of HCC incidence. We searched for primary liver tumors in tumor registry records, which were implemented according to Surveillance, Epidemiology and End Results program standards at each site. Potential cancer cases for inclusion in the registry were based on a review of pathology and cytology reports, and credentialed cancer registrars completed data abstraction. Cancer diagnosis codes in administrative databases (International Classification of Diseases-9-CM codes in the range of 140–208.9) were also a source for registry case finding. Primary liver tumors diagnosed during the follow-up period were included as HCC cases. All confirmed HCC cases were incident cases, and 91% were established by anatomic pathology, cytology, and as reported on imaging reports in tumor registry records. The remaining were diagnosed clinically and by tumor marker.

To study the effect of antiviral HBV therapy on HCC incidence, antiviral treatment data were collected by chart abstraction, including any available documentation of treatment received at outside facilities. Patients were classified as having received antiviral HBV therapy if the patient had been treated with interferon α-2b, pegylated interferon α-2a or α-2b, lamivudine, entecavir, tenofovir, telbivudine, or adefovir and treatment had begun at least 1 year before HCC diagnosis (for patients who developed HCC) or the last encounter date (for patients not developing HCC). The 1-year interval was chosen to minimize both inclusion of preexisting malignancies in analyses of antiviral treatment effect and misattribution of treatment effect.

Control Variables

The methods for collecting demographic information were reported previously.[10] Clinical data were collected from the electronic health records and included assessment of comorbid conditions, coinfection with human immunodeficiency virus (HIV), liver transplantation, and laboratory testing. We calculated the Charlson/Deyo comorbidity index score from diagnosis codes in inpatient, outpatient, and claims data during the year before chronic HBV infection was diagnosed.

Coinfection with HIV was determined by the presence of HIV antibodies or a detectable HIV RNA level on quantitative or qualitative testing and was included as time-dependent covariate in prediction of HCC development.

We collected data for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count during the 12 months before the diagnosis of chronic HBV infection. We then calculated 2 surrogate markers of liver fibrosis: the AST/platelet ratio index (APRI score); and a composite of 4 markers of fibrosis (FIB4), which is a composite of age, ALT, AST, and platelet count. If multiple values were available, the one closest to the time of HBV diagnosis was used. For analytical purposes, log transformation was used for APRI

and FIB4 because they were not normally distributed. ALT was categorized as normal or abnormal according to each site's reference range, or as unknown.

We collected HBV DNA viral load data throughout the follow-up period. Viral loads were grouped into three categories (<2000, 2000–20,000, and >20,000 IU/mL) and were included as a time-dependent covariate in prediction of HCC development. Result values reported in copies per milliliter were divided by 5 to convert to IU/mL.

Statistical Analysis

We used a propensity-score weighting method to adjust for differences between patients who had and had not received antiviral therapy. Logistic regression was used to compute the probability of receiving treatment (propensity score) based on all previously mentioned baseline covariates (study site, patient demographics, ALT elevation, and comorbidity index) except baseline serum-based fibrosis markers and HBV DNA viral loads because of incompleteness of data, and HIV status because it was time dependent. We then weighted each patient's data based on the inverse of the propensity score.

We examined the risk for HCC using simple Cox regression, followed by multiple Cox regression, including the variable of "received antiviral HBV therapy" adjusted by inverse of the propensity score. Any variable that showed a significant ($P < .05$) simple relationship with HCC was considered a candidate for the multiple Cox regression model. The final model retained variables that showed a significant relationship with HCC ($P < .05$). All analyses were adjusted for study site.

We also conducted several sensitivity analyses. We used a sample matched one-to-one on propensity score using a greedy matching algorithm.[11] This analysis resulted in 748 treated patients (of 820 possible; 91.2%) matched to 748 untreated patients. Two additional subgroup analyses were performed: a serum fibrosis marker subgroup analysis that included patients for whom baseline laboratory data were available for imputing serum-based fibrosis markers (APRI and FIB4, n = 1404), and an HBV DNA viral load subgroup analysis that included patients for whom viral load data were available (n = 1986).

In the serum fibrosis marker subgroup analysis, both APRI and FIB4 were included when calculating the propensity score and for assessing possible predictors of HCC. Because of a high correlation between the two markers ($r > .80$), each was included one at a time in multiple regression modeling if there was a simple relationship with HCC ($P < .05$).

In the HBV DNA viral load subgroup analysis, baseline ALT was included in the propensity score adjustment to balance the treated and untreated groups and also for assessing possible predictors of HCC. Viral load was included as a time-dependent covariate for prediction of HCC development. Analysis was first tested for treatment by viral load interaction followed by assessment of treatment effect at each viral load level, and other subgroup comparisons if an interaction was detected at a $P = .10$ level. A significant interaction indicates that the antiviral HBV treatment effect might be influenced by viral load levels, or that viral load effects were dependent on the presence or absence of antiviral HBV therapy. The adjusted hazard ratio (aHR), 95% confidence interval (CI), and P value were reported.

Results

We found 4158 chronic HBV infection candidates based on electronic criteria, of which 2775 were confirmed to have chronic HBV infection based on chart abstraction to date. Of the 2775 patients, 99 were coinfected with HCV, and 4 had received a diagnosis of HCC more than 60 days before the diagnosis of HBV; these patients were excluded. This left 2671 patients in the study cohort. The earliest HBV diagnosis was in 1992, and median diagnosis year was 2005 (interquartile range, 2002–2007). Median follow-up time was 5.2 years (interquartile range, 3–9 years).

Enrollment and demographic information are shown in Table 1. In all, 9% of the patients had major comorbidity at baseline (index score of 2 or 3) and 6% tested positive for HIV coinfection during follow-up. Over the follow-up period, 67 patients (3%) developed HCC. The crude HCC incidence rate was 4.2 cases per 1000 person-years.

Antiviral Hepatitis B Virus Therapy and Risk of Hepatocelluar Carcinoma Development

Of 2671 patients in the study cohort, 820 (31%) received antiviral HBV therapy. Ninety-four percent (n = 770) of those treated received nucleos(t)ide analog therapy, alone or before or after interferon-based therapy, whereas the remaining 6% received only interferon or pegylated interferon-based therapy. Median treatment duration during follow-up was 45 months (interquartile range, 22–81 months). Twenty patients in the antiviral HBV treatment group developed HCC (crude incidence rate, 4.2 per 1000 person-years) versus 47 in the group that did not receive antiviral therapy (crude incidence rate, 4.2 per 1000 person-years).

Patients' characteristics were unbalanced between treated and untreated groups. Patients who received antiviral HBV therapy were older, more often male, and less likely to be Asian or Pacific Islander than were untreated patients (Table 2). Treated patients also had higher comorbidity scores. Among the patients with available laboratory data, a larger proportion of the treated patients had abnormal ALT at baseline. After propensity-score adjustment, demographic and clinical characteristics were balanced between the comparison groups (Table 2).

In simple Cox regression based on the overall cohort, age >40 years, male gender, greater comorbidity, and abnormal ALT were significantly associated with an increased risk of HCC (Table 3). In contrast, a history of antiviral HBV therapy was significantly associated with a reduced incidence of HCC. In multiple Cox regression, older age, male gender, abnormal ALT, and comorbidity remained significantly associated with development of HCC (Table 4). Antiviral therapy was associated with a reduction of HCC (aHR, 0.50; 95% CI, 0.35–0.72; $P < .001$), and this reduction persisted in analyses of the matched-pairs cohort (aHR, 0.48; 95% CI, 0.27–0.86; $P = .01$).

A total of 1404 patients were included in the serum fibrosis marker subgroup analysis. Patients' demographic characteristics were similar to those among the overall cohort (Table 1). Patients who received antiviral therapy had higher APRI and FIB4 scores compared with those who were not treated ($P < .001$). After propensity-score adjustment, the demographic and clinical characteristics, including APRI and FIB4, were balanced between the treatment

groups (adjusted *P* values of 0.21–0.91). The multiple Cox regression results showed that the relationship between the use of antiviral HBV therapy and reduced risk of HCC persisted (aHR, 0.24; 95% CI, 0.15–0.39; $P < .001$; Table 4). Higher $_{\log}$FIB4 was also independently associated with HCC development (aHR, 1.97; 95% CI, 1.65–2.34; $P < .001$). In a separate multiple model analysis, higher $_{\log}$APRI was likewise associated with HCC development (aHR, 1.43; 95% CI, 1.28–1.61; $P < .001$).

A total of 1986 patients were included in the HBV DNA viral load subgroup analysis. Patients' demographic characteristics were similar to those among the overall cohort (Table 1). Patients who received antiviral therapy had higher baseline ALT levels than those in the untreated group ($P < .001$). Among patients with viral levels available at baseline, 70% and 22% of the treated and untreated groups, respectively, had levels >20,000 IU/mL. After propensity-score adjustment, the demographic and clinical characteristics, including baseline ALT, were balanced between the treatment groups (adjusted *P* values of .69–.99). In the multiple Cox regression model, a significant interaction between antiviral HBV therapy and viral load level was observed ($P = .07$). Antiviral therapy was consistently associated with a lower risk of HCC in all 3 viral load categories, with the largest and statistically significant risk reduction observed in the >20,000 IU/mL category (aHR, 0.17; 95% CI, 0.06–0.52; $P = .002$; Table 4). In addition, HCC risk was significantly higher in the > 20,000 IU/mL viral load category compared with the <2000 IU/mL category in the untreated group (aHR, 1.92; 95% CI, 1.16–3.17; $P = .011$; Table 4) but not in the treated group.

Discussion

In this large American community-based cohort, a history of antiviral therapy for chronic HBV infection was associated with a reduction in the risk of HCC over a median of 5 years. To our knowledge, this analysis is the only US-based study to show such a benefit, and the large size and diversity of the cohort (geographic, clinical, and racial) and long duration of follow-up extend the generalizability of similar findings observed in smaller, more homogenous populations.

Given that persistent elevations in HBV DNA levels are associated with HCC,[12] viral suppression of HBV through antiviral therapy intuitively should ameliorate some of the risk of carcinogenesis. In the case of HCV infection, successful antiviral therapy that eradicates the virus has been associated with a reduced risk of HCC,[13] whereas unsuccessful antiviral therapy fails to reduce the risk of HCC.[14] In a recent comprehensive review, viral suppression with antivirals was found to be the most effective way to reduce the incidence of HBV-related HCC.[1] In our large hepatitis B cohort, multiple Cox regression analysis showed that antiviral therapy reduced the risk for HCC (aHR, 0.50; 95% CI, 0.35–0.72; $P < .001$), and the antiviral effect was persistent in sensitivity analyses. Our findings are therefore consistent with the predominantly Asian and European analyses included in the review, and extend them into a broader, US community-based population.

Age, male gender, degree of comorbidity, and ALT abnormality also were independent predictors of HCC in our study, in concordance with previous analyses in persons with

chronic HBV infection[15] and those with cirrhosis of any etiology.[16] In addition, lack of reduction in ALT levels[12] was also associated with an increased risk for HCC.

The association between antiviral therapy and reduced risk of HCC persisted in the serum fibrosis subgroup analysis (aHR, 0.24; 95% CI, 0.15–0.39; $P < .001$), after adjusting for other covariates including $_{log}$FIB4. Higher $_{log}$FIB4 was also an independent predictor of increased risk of HCC. Notably, however, we found no interaction between $_{log}$FIB4 and antiviral therapy, indicating that antiviral therapy benefits are consistent across the spectrum of fibrosis levels. Because previous studies showing antiviral therapy benefit have been predominantly in the cirrhotic population,[9] we also substituted a dichotomous FIB4 variable for $_{log}$FIB4 in the multiple regression model, using a FIB4 cutoff value of 5.17 for cirrhosis that has been validated in the CHeCS HBV population (unpublished data, 2013). The results of the model with dichotomous FIB4 were consistent with the results of the model that included $_{log}$FIB4. Antiviral therapy remained associated with a reduced risk of developing HCC, and patients with FIB4 levels over 5.17 had significantly higher risk of HCC compared with patients with lower FIB4 levels (aHR, 3.95; 95% CI, 2.61–5.97; $P < .001$). We also found no interaction between antiviral therapy and dichotomous FIB4, suggesting that patients with and without cirrhosis both benefit from antiviral therapy in reducing the risk of HCC. Our study therefore extends previous studies[9] by suggesting that antiviral therapy effectively reduces the risk of developing HCC across a spectrum of fibrosis levels, including in patients without cirrhosis.

The beneficial effect of antiviral therapy persisted in each of the three DNA viral load levels in our viral load subgroup analysis, although the largest and statistically significant effect was among patients with viral levels >20,000 IU/mL (Table 4). Higher viral loads were associated with a higher risk of HCC in the untreated group, whereas in the treated group, we did not see a significant difference in risk of HCC among the three viral load categories. We also compared risk of HCC in the treated group, after viral load was suppressed to <2000 IU/mL, versus the untreated group whose viral loads remained >20,000 IU/mL. We found a significantly lower risk in the treated, virally suppressed group (aHR, 0.37; 95% CI, 0.22–0.65; $P < .001$).

The major strengths of our study are its size, setting, and diversity. The study represents outcomes in real-world scenarios rather than in restrictive clinical trial environments, and is not limited to any particular subgroup by e-antigen status, presence of cirrhosis, or other viral or disease characteristics. Furthermore, given its setting in 4 large catchment areas, our analysis reflects a broad American racial diversity. Finally, the large sample size and adjustment for covariates and propensity score enhance the robustness of the findings, as does the fact that all available antiviral treatment data were obtained from both internal and external records. The observed reduction of HCC risk associated with antiviral therapy persisted across the spectrum of liver disease (represented by ALT and FIB4) and HBV viral loads.

Our study has several important limitations. First, our ability to assess the significance of various clinical and behavioral covariates was limited because study data were collected only during the routine process of care. Specifically, we had insufficient data to characterize

baseline behavioral characteristics, such as alcohol, tobacco and drug use, e-antigen status, genotypes, extent of liver fibrosis determined through histologic assessment, and duration of antiviral and other therapies to include as covariates. Thus, we could not assess the possible antifibrotic effect of antiviral therapy on HCC risk.[17,18] Nevertheless, our inclusion of FIB4 and APRI as covariates in our serum fibrosis marker subgroup analysis showed that more advanced fibrosis in patients with HBV infection was associated with an increased risk for HCC, whereas antiviral therapy remained an independent predictor of reduced risk for HCC development. Second, because CHeCS participants necessarily represent patients known to health systems, they cannot fully represent persons with chronic HBV infection in the United States, up to 30% of whom might be unaware of their infection.[19] Third, we were not able to include body mass index, diabetes, or lipid profiles in our analysis because of the high proportion of missing data for these elements. However, we did include the Charlson/Deyo comorbidity index, which was included in both the propensity score adjustment and as a covariate in the Cox regression modeling.

Finally, we used propensity score methods to adjust for differences between the treated and untreated groups based on known factors, but this uncontrolled observational study could not take into account unknown factors. Although we were not able to incorporate baseline HBV DNA levels or e-antigen status in our propensity adjustment, we note that FIB4 scores in the serum markers subgroup analysis were balanced between the treated and untreated groups after propensity score adjustment.

In conclusion, in this large US-based observational cohort study we found that HBV antiviral therapy was associated with a significantly decreased risk of HCC in patients with chronic HBV infection. These findings corroborate existing and emerging evidence of the beneficial effect of antiviral therapy in reducing risk of HBV-related HCC. Most of these studies suggest that the reduced risk of carcinogenesis is the result of suppression of HBV through antiviral therapy[1]; we found that antiviral treatment had a beneficial effect across a spectrum of viral load levels. Inclusion of all patients infected with HBV in our community-based cohort, without restriction to any particular stage of fibrosis or baseline viral level, allowed assessment of the effects of antiviral therapy across a range of disease severity. There was a wide distribution of FIB4 scores within our serum fibrosis subgroup, and we found no interaction between FIB4 levels and antiviral treatment in predicting HCC development, indicating that the beneficial effect of treatment is not changed by presumed fibrosis level. This is a fairly novel finding, because most studies to date have focused primarily on patients with cirrhosis.[9] Prospective studies with comprehensive baseline fibrosis data collection are needed in additional cohorts to corroborate these findings.

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The CHeCS Investigators are listed in the Appendix.

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Abbreviations used in this paper

aHR	adjusted hazard ratio
ALT	alanine aminotransferase
APRI	aspartate aminotransferase/platelet ratio index
AST	aspartate aminotransferase
CHeCS	Chronic Hepatitis Cohort Study
CI	confidence interval
FIB4	composite of 4 markers of fibrosis
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus

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Table 1

Baseline Demographic and Clinical Characteristics of the Overall HBV Cohort, the Serum Fibrosis Marker Subgroup, and the DNA Viral Load Subgroup

	Overall (N = 2671)	Serum fibrosis marker subgroup (n = 1404)	DNA viral load subgroup (n = 1986)
Study site			
Kaiser Permanente–Northwest, n (%)	839 (31)	378 (27)	584 (29)
Kaiser Permanente–Hawaii, n (%)	857 (32)	397 (28)	623 (31)
Henry Ford Health System, n (%)	823 (31)	535 (38)	673 (34)
Geisinger Health System, n (%)	152 (6)	94 (7)	106 (5)
Age category, *y*			
≤40, n (%)	743 (28)	335 (24)	524 (26)
>40–50, n (%)	646 (24)	319 (23)	495 (25)
>50–60, n (%)	669 (25)	371 (26)	508 (26)
≥60, n (%)	613 (23)	379 (27)	459 (23)
Male gender, n (%)	1491 (56)	844 (60)	1154 (58)
Race			
Asian, n (%)	1298 (49)	619 (44)	1021 (51)
White, n (%)	567 (21)	322 (23)	399 (20)
Black, n (%)	340 (13)	235 (17)	257 (13)
Pacific Islander/Hawaiian, n (%)	160 (6)	71 (5)	107 (5)
Native American, n (%)	12 (<1)	7 (<1)	9 (<1)
Unknown, n (%)	294 (11)	150 (11)	193 (10)
Median annual household income			
<$15,000, n (%)	33 (1)	21 (1)	24 (1)
≥$15,000 to <$30,000, n (%)	318 (12)	209 (15)	230 (12)
≥$30,000 to <$50,000, n (%)	1061 (40)	566 (40)	775 (39)
≥$50,000 to <$75,000, n (%)	857 (32)	402 (29)	635 (32)
≥$75,000, n (%)	325 (12)	167 (12)	265 (13)
Missing, n (%)	77 (3)	39 (3)	57 (3)
Insurance status			
Not insured, n (%)	40 (1)	24 (2)	24 (1)
Insured, n (%)	2538 (95)	1332 (95)	1901 (96)
Unknown, n (%)	93 (3)	48 (3)	61 (3)
Charlson/Deyo comorbidity index score			
0, n (%)	1995 (75)	940 (67)	1482 (75)
1, n (%)	442 (17)	292 (21)	333 (17)
2 or 3, n (%)	234 (9)	172 (12)	171 (9)
APRI score	(n = 1463)	(n = 1403)	(n = 1108)
Median (IQR)	0.42 (0.25–0.99)	0.43 (0.26–1.04)	0.46 (0.27–1.04)
FIB4 score	(n = 1404)	(n = 1404)	(n = 1068)
Median (IQR)	1.25 (0.75–2.24)	1.25 (0.75–2.24)	1.30 (0.78–2.24)
ALT, *U/mL*			

	Overall (N = 2671)	Serum fibrosis marker subgroup (n = 1404)	DNA viral load subgroup (n = 1986)
Abnormal, n (%)[a]	746 (28)	573 (41)	595 (30)
Normal, n (%)[a]	1470 (55)	831 (59)	1062 (53)
Unknown, n (%)	455 (17)	0 (0)	329 (17)

[a]According to each site's reference range.

Table 2

Characteristics Included in Multiple Cox Regression Modeling in the Overall Cohort, by Receipt of Antiviral HBV Therapy, Before and After Propensity Adjustment

	Overall cohort (N = 2671)			
	Received antiviral HBV therapy			
	No (n = 1851)	Yes (n = 820)	Unadjusted *P* value	IPTW-Adjusted *P* value
Age category, *y*				
<40, n (%)	594 (32)	149 (18)	<.001	.423
>40–50, n (%)	431 (23)	215 (26)		
>50–60, n (%)	425 (23)	244 (30)		
≥60, n (%)	401 (22)	212 (26)		
Gender				
Female, n (%)	931 (50)	249 (30)	<.001	.772
Male, n (%)	920 (50)	571 (70)		
Race/ethnicity				
Asian/Pacific Islander, n (%)	1062 (57)	396 (48)	<.001	.201
Other, n (%)[a]	547 (30)	372 (45)		
Unknown, n (%)	242 (13)	52 (6)		
Median annual household income				
Missing, n (%)	47 (3)	30 (4)	.066	.819
<$15,000, n (%)	23 (1)	10 (1)		
≥$15,000 to <$30,000, n (%)	218 (12)	100 (12)		
≥$30,000 to <$50,000, n (%)	727 (39)	334 (41)		
≥$50,000 to <$75,000, n (%)	624 (34)	233 (28)		
≥$75,000, n (%)	212 (11)	113 (14)		
Insurance status				
Not insured, n (%)	29 (2)	11 (1)	.014	.543
Insured, n (%)	1745 (94)	793 (97)		
Unknown, n (%)	77 (4)	16 (2)		
ALT status				
Normal, n (%)[b]	1187 (64)	283 (35)	<.001	.768
Abnormal, n (%)[b]	394 (21)	352 (43)		
Unknown, n (%)[b]	270 (15)	185 (23)		
Charlson/Deyo comorbidity index score				
0	1468 (79)	527 (64)	<.001	.494
1	251 (14)	191 (23)		
2 or 3	132 (7)	102 (12)		

IPTW, inverse probability of received treatment weighting.

[a] White, black, or Native American.

[b] According to each site's reference range.

Table 3

Simple Associations of Baseline Characteristics With Development of HCC in Cox Proportional Hazard Modeling in the Overall HBV Cohort

	Hazard ratio (95% CI)	*P* value
Age category, *y*		
<40	1 (Reference)	<.001
>40–50	5.93 (1.33–26.50)	
>50–60	6.18 (1.40–27.29)	
≥60	19.33 (4.66–80.22)	
Gender		
Female	1 (Reference)	<.001
Male	3.32 (1.81–6.11)	
Race		
Asian/Pacific Islander	1 (Reference)	.166
Other[a]	1.02 (0.56–1.85)	
Unknown	0.15 (0.02–1.08)	
Median household income		
<$15,000	1 (Reference)	.122
≥$15,000 to < $30,000	4.91 (0.65–37.19)	
≥$30,000 to <$50,000	2.47 (0.33–18.40)	
≥$50,000 to <$75,000	2.53 (0.33–18.98)	
≥$75,000	1.91 (0.23–15.59)	
HIV coinfection		
HIV	1.06 (0.42–2.66)	.901
Charlson/Deyo comorbidity index score		
0	1 (Reference)	<.001
1	2.60 (1.49–4.54)	
2 or 3	3.54 (1.83–6.84)	
Insurance status		
Not insured	1 (Reference)	.130
Insured	0.85 (0.12–6.25)	
Unknown	2.48 (0.26–23.63)	
ALT		
ALT normal[b]	1 (Reference)	<.001
ALT abnormal[b]	4.44 (2.46–8.01)	
Antiviral HBV treatment[c]	0.50 (0.35–0.72)	<.001

[a] White, black, or Native American.

[b] According to each site's reference range.

[c] After adjustment for inverse probability of received treatment weighting.

Table 4

Final Multiple Cox Regression Models for Prediction of HCC in the Overall HBV Cohort, the Serum Fibrosis Marker Subgroup, and the DNA Viral Load Subgroup

	Overall cohort		Serum fibrosis marker subgroup		DNA viral load subgroup	
	Hazard ratio[a] (95% CI)	*P* value	Hazard ratio[a] (95% CI)	*P* value	Hazard ratio[a] (95% CI)	*P* value
Age, *y*		<.001		.055		<.001
>40–50 vs <40	5.51 (1.74–17.42)	.004	7.67 (1.33–44.10)	.023	3.53 (1.17–10.49)	.025
>50–60 vs <40	5.55 (1.78–17.28)	.003	7.96 (1.40–45.20)	.019	4.37 (1.51–12.66)	.007
≥60 vs <40	13.77 (4.54–41.76)	<.001	9.94 (1.78–55.69)	.009	8.78 (3.08–25.03)	<.001
Male vs female gender	2.29 (1.46–3.59)	<.001	4.70 (2.34–9.42)	<.001	1.60 (1.00–2.56)	.051
Charlson/Deyo comorbidity index		<.001		<.001		<.001
Score of 1 vs 0	2.15 (1.44–3.21)	<.001	2.11 (1.30–3.43)	.003	2.16 (1.36–3.43)	.001
2 or 3 vs 0	2.55 (1.62–4.02)	<.001	2.91 (1.78–4.78)	<.001	2.58 (1.54–4.31)	<.001
ALT						
Abnormal vs normal	4.41 (2.81–6.90)	<.001	—	—	4.88 (2.90–8.23)	<.001
$_{\log}$FIB4[b]	—	—	1.97 (1.65–2.34)	<.001	—	—
$_{\log}$APRI	—	—	1.43 (1.28–1.61)	<.001	—	—
Antiviral HBV therapy						
Received vs not received	0.50 (0.35–0.72)	<.001	0.24 (0.15–0.39)	<.001	—	—
Antiviral HBV therapy * DNA level (interaction)						.072
Treatment effect:						
Treated vs untreated: >20,000 IU/mL	—	—	—	—	0.17 (0.06–0.52)	.002
Treated vs untreated: 2000–20,000 IU/mL	—	—	—	—	0.45 (0.14–1.47)	.185
Treated vs untreated: <2000 IU/mL	—	—	—	—	0.72 (0.43–1.20)	.206
Viral load effect: treated group						
>20,000 vs <2000 IU/mL	—	—	—	—	0.46 (0.15–1.40)	.170
2000–20,000 vs <2000 IU/mL	—	—	—	—	1.10 (0.35–3.39)	.876
Viral load effect: untreated group						
>20,000 vs <2000 IU/mL					1.92 (1.16–3.17)	.011
2000–20,000 vs <2000 IU/mL					1.75 (0.94–3.25)	.077

[a] After adjustment for propensity score and study site.

[b] The estimated APRI effect was derived from the second multiple Cox regression when FIB4 was absent. The other covariates, including antiviral HBV therapy, had similar effects across the two multivariable models.