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Original Article

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Association of Baseline Hepatitis B Virus DNA and On-Treatment Risk of Cirrhosis and Hepatocellular Carcinoma

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Abstract

Background: Recent studies suggest an inverse relationship between baseline levels of hepatitis B virus (HBV) DNA and on-treatment risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). However, data are limited to Asian cohorts, and it is unclear if similar associations hold true for non-Asians with CHB. We aimed to evaluate association of baseline HBV DNA with long-term risks of cirrhosis and HCC among a predominantly non-Asian cohort of CHB patients in the USA.

Methods: Using longitudinal data from the national Veterans Affairs database, we evaluated the risk of cirrhosis or HCC among adults with non-cirrhotic CHB who are on continuous antiviral therapy, stratified by moderate levels of baseline HBV DNA (4.00 - 6.99 $\log_{10}$ IU/mL) vs. high levels of baseline HBV DNA (7.00 $\log_{10}$ IU/mL or higher). Propensity score weighting was applied, and competing risks cumulative incidence functions and Cox proportional hazards models were utilized.

Results: Among 1,129 non-cirrhotic CHB patients (41% non-Hispanic White, 36% African American, mean age 57.0 years, 62.2% hepatitis B e antigen (HBeAg) positive), 585 had moderate levels of baseline HBV DNA and 544 had high HBV DNA. After propensity score weighting, no significant difference in risk of cirrhosis was observed between moderate vs. high baseline HBV DNA (4.55 vs. 5.22 per 100 person-years, hazard ratio (HR): 0.87, 95% confidence interval (CI): 0.69 - 1.09, P = 0.22), but risk of HCC was significantly higher in patients with moderate vs. high baseline HBV DNA (0.84 vs. 0.69 per 100 person-years, HR: 1.33, 95% CI: 1.09 - 1.62, P < 0.01).

Conclusions: Among a national cohort of predominantly non-Asian US veterans with non-cirrhotic CHB on antiviral therapy, moderate levels of baseline HBV DNA was associated with higher risk of HCC than high HBV DNA.

Keywords: HBV; Cirrhosis; Hepatocellular carcinoma; Veterans; Antivirals

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Introduction

Chronic hepatitis B (CHB) remains a major contributor to liver related morbidity and mortality globally [1, 2]. In the USA, recent data estimate that nearly 2.4 million adults are affected by CHB [1]. Delays in diagnosis, timely linkage to care, and appropriate antiviral therapy can lead to liver disease progression to cirrhosis and hepatocellular carcinoma (HCC) [3-7]. While CHB antiviral therapy is associated with significant reductions in long-term risks of HCC, it remains unclear whether baseline factors contribute to differences in HCC risk despite patients being on antiviral therapy [8-10]. Understanding differences in baseline factors and their impact on HCC risk may guide discussions regarding early initiation of antiviral therapy or closer monitoring of high-risk patients while on antiviral therapy.

Recent data suggest that baseline hepatitis B virus (HBV) DNA is associated with long-term on-treatment risks of HCC [11]. Choi et al [11] evaluated 2,073 patients with CHB across three centers in Korea who were maintained on entecavir or tenofovir therapy. The investigators observed an inverse relationship between baseline HBV DNA and long-term risk of HCC. For example, compared to CHB patients with 8.00 $\log_{10}$ IU/mL or higher HBV DNA at baseline, the adjusted hazard ratios (HRs) for HCC risk were 2.48 for patients with HBV DNA levels of 7.00 - 7.99 $\log_{10}$ IU/mL, 3.69 for HBV DNA levels

of 6.00 - 6.99 $\log_{10}$ IU/mL, and 6.10 for HBV DNA levels of 5.00 - 5.99 $\log_{10}$ IU/mL [11]. In another study of 4,693 CHB patients on antiviral therapy across multiple centers in Korea, the investigators observed significant differences in risk of HCC by baseline HBV DNA, with the highest risk observed in patients with moderate baseline viral loads (5.00 - 7.99 $\log_{10}$ IU/mL) and the lowest risk observed in patients with high viral loads (8.00 $\log_{10}$ IU/mL or higher) [12].

However, both of these studies were conducted in Asian cohorts from a single country, and it remains unclear if similar patterns would be seen in non-Asian cohorts. Data among predominantly non-Asian populations, and specifically data evaluating both risks of HCC and cirrhosis while on CHB antiviral therapy, are lacking. The current study utilizes a large longitudinal cohort of predominantly non-Asian veterans in the USA with CHB to investigate the association between baseline HBV DNA and long-term risks of cirrhosis and HCC while on antiviral therapy.

Materials and Methods

We utilized data from the 2010 - 2022 Veterans Affairs (VA) Corporate Data Warehouse (CDW). The VA CDW is a national longitudinal database of all veterans receiving care at VA healthcare facilities in the USA. The VA CDW allows for longitudinal assessment of patient outcomes, laboratory data, and clinical encounters, and captures important demographic data and comorbidities. The VA health system is the largest integrated health system in the USA, caring for more than 9 million individuals.

Adults with CHB were identified by at least two positive results for hepatitis B surface antigen (HBsAg), HBV DNA, or hepatitis B e antigen (HBeAg) at least 6 months apart, or at least one positive result for HBsAg, HBV DNA, or HBeAg, and one International Classification of Diseases, 9th/10th Revision (ICD-9/10) code for chronic HBV (ICD-9: 070.2x, 070.3x, V02.61; ICD-10: B16.x, B18.0-1, B19.1x). CHB patients were excluded if there was evidence of concurrent human immunodeficiency virus (HIV), hepatitis C, or hepatitis delta infection. The current study focused on differences in on-treatment risks of cirrhosis or HCC by baseline HBV DNA. Each patient with CHB was retrospectively evaluated to determine the first start date of CHB antiviral treatment documented in the medical record, which was set as the index date for assessing outcomes in the follow up period. Comprehensive review of pharmacy data ensured continuous antiviral therapy prescription, and patients were followed until the last date of antiviral therapy prescribed, development of study outcomes (i.e., cirrhosis, HCC), death, or until end of the study period. Patients with cirrhosis or HCC at index date or within 12 months of starting antiviral therapy were excluded to ensure that we are capturing incident events. Cirrhosis and HCC were identified using established definitions based on ICD-9/10 codes [13]. Race/ethnicity in the VA CDW was based on self-reporting and included non-Hispanic White (NHW), Black or African American (AA), Asian or Pacific Islander (API), Hispanic, and American Indian or Alaska Native. Alcohol use was assessed based on documented AUDIT-C scores [14] closest to the time of first start of antiviral therapy and were categorized as: 1) no alcohol use (AUDIT-C = 0); 2) mild levels of alcohol use (AUDIT-C 1 - 2 for women and 1 - 3 for men); and 3) moderate-high levels of alcohol use (AUDIT-C $\geq$ 3 for women and $\geq$ 4 for men). Baseline fibrosis-4 (FIB-4) scores at index date were calculated and grouped into three categories based on established criteria: FIB-4 < 1.45, FIB-4 1.45 - 3.25, and FIB-4 > 3.25 [15].

Our initial cohort included 2,510 patients with CHB. From this cohort, we specifically focused on patients with baseline HBV DNA $\geq$ 4 $\log_{10}$ IU/mL, and categorized patients into moderate levels of baseline HBV DNA (4.00 - 6.99 $\log_{10}$ IU/mL) and high levels of baseline HBV DNA (7.00 $\log_{10}$ IU/mL or higher). Propensity score weighting was applied to these two groups, which was subsequently used to analyze cirrhosis and HCC outcomes. Baseline demographics and disease characteristics are presented as frequencies and proportions for categorical variables and mean and standard deviation or median and interquartile range (IQR) for continuous variables. The standard mean difference was utilized to compare differences in patient's characteristics before and after propensity score weighting. Incidence of cirrhosis or HCC was presented as incidence per 100 person-years. Comparisons of univariate unadjusted outcomes were compared between groups using Chi-square testing as well as the Z statistic using standard equations. Overall incidence of cirrhosis or HCC was also evaluated using the Nelson-Aalen methods for estimating cumulative hazards rate, and competing risks methods were applied with death as a censoring event. The log-rank testing was used to compare cumulative incidence curves between groups. Statistical analyses were performed using SQL and SAS® Studio 3.6 on SAS® 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a two-tailed P value < 0.05. This study was approved by the Stanford University Institutional Review Board and the VA Palo Alto Healthcare System Research and Development Committee. Waiver of informed consent was granted by the aforementioned institutional review board.

Results

A total of 585 CHB patients were in the moderate HBV DNA level group, and 544 patients were in the high HBV DNA level group (Table 1). Median follow-up time was 57 months (IQR: 29 - 106). The majority of patients were men and were on entecavir antiviral therapy. Among patients with moderate HBV DNA, 41.3% were HBeAg positive, whereas 85.0% were HBeAg positive in the high HBV DNA group. Race/ethnicity distribution was similar between both groups, with the majority being non-Asian (mostly NHW and Black/AA). Patients in the high HBV DNA were slightly older than those in the moderate HBV DNA group (58.1 vs. 55.9 years). Table 1 also describes alcohol use and tobacco use between the two groups. When evaluating by baseline FIB-4 scores, 21.1% of patients with moderate HBV DNA had FIB-4 > 3.25, compared to 27.7% of patients in the high HBV DNA group (Table 1).

Table 1. Characteristics of the Study Cohort

Variables	Moderate HBV DNA (4.00 - 6.99 log_{10} IU/mL)		High HBV DNA (7.00 log_{10} IU/mL or higher)		SMD (before weighting)	SMD (after weighting)
	Proportion (%)	Frequency (n)	Proportion (%)	Frequency (n)		
Total	100	585	100	544		
Antiviral treatment					0.05004	0.07214
Entecavir	62.74	367	64.89	353		
Tenofovir alafenamide	7.35	43	5.7	31		
Tenofovir disoproxil fumarate	29.91	175	29.41	160		
HBeAg status					1.0264	0
HBeAg positive	41.32	188	84.98	345		
Sex					-0.01885	-0.00992
Female	4.62	27	4.23	23		
Male	95.38	558	95.77	521		
Race/ethnicity					0.33475	0
American Indian or Alaska Native	0.18	1	0.19	1		
Asian or Pacific Islander	21.15	118	10.29	54		
Black or African American	37.99	212	36.95	194		
Hispanic	2.51	14	4.38	23		
Non-Hispanic White	38.17	213	48.19	253		
Age					0.15735	0.06375
Age (mean ± SD)	55.92 ± 13.91		58.11 ± 13.38			
18 - 39 years	15.04	88	11.03	60		
40 - 59 years	39.32	230	36.21	197		
60 years and over	45.64	267	52.76	287		
BMI categories					0.10212	0.16677
BMI (mean ± SD, kg/m^2)	(28.23 ± 5.34)		(28.60 ± 6.18)			
18.0 - 24.9	28.27	162	28.76	153		
25.0 - 29.9	37.35	214	34.77	185		
30.0 - 34.9	24.08	138	21.99	117		
35.0 and over	10.3	59	14.47	77		
Comorbidities						
Diabetes	27.52	161	30.51	166	-0.06599	-0.0522
Hypertension	60.17	352	66.73	363	-0.13648	-0.01316
Alcohol use categories					0.11127	0.02222
No alcohol[a]	42.88	223	48.36	236		
Low-risk drinking[b]	38.85	202	34.43	168		
High-risk drinking[c]	18.27	95	17.21	84		
Tobacco use categories					0.21708	0.04502
Never	41.55	209	32.13	142		
Past history of tobacco	20.48	103	21.04	93		
Active current tobacco	37.97	191	46.83	207		
FIB-4 categories					0.21459	0.04146
FIB-4 score < 1.45	42.67	224	32.67	163		
FIB-4 score 1.45 - 3.25	36.19	190	39.68	198		
FIB-4 score > 3.25	21.14	111	27.66	138		

[a]No alcohol use: AUDIT-C = 0. [b]Low-risk alcohol: AUDIT-C = 1 - 2 for women and 1 - 3 for men. [c]High-risk alcohol: AUDIT-C > 3 for women and > 4 for men. HBV: hepatitis B virus; HBeAg: hepatitis B e antigen; FIB-4: fibrosis-4; SMD: standard mean difference; AUDIT-C: Alcohol Use Disorders Identification Test.

Table 2. Incidence and Risk of Cirrhosis Before and After Propensity Score Weighing by Baseline Levels of HBV DNA

	Incidence of cirrhosis	HR	95% CI	P value
Before propensity weighting				
Moderate HBV DNA[a]	4.15 per 100 person-years	0.87	(0.69, 1.11)	
High HBV DNA[b]	4.84 per 100 person years	Reference		0.28
After propensity weighting				
Moderate HBV DNA	4.55 per 100 person-years	0.87	(0.69, 1.09)	
High HBV DNA	5.22 per 100 person-years	Reference		0.22

[a]Moderate HBV DNA: 4.00 - 6.99 $\log_{10}$ IU/mL. [b]High HBV DNA: 7.00 $\log_{10}$ IU/mL or higher. HBV: hepatitis B virus; HR: hazard ratio; CI: confidence interval.

The incidence of cirrhosis was 4.15 per 100,000 person-years (95% confidence interval (CI): 3.49 - 4.93) in the moderate HBV DNA group vs. 4.84 per 100,000 person-years (95% CI: 4.08 - 5.74) in the high HBV DNA group (Table 2). After propensity score weighting, no significant difference in the incidence of cirrhosis was observed between the two groups (4.55 per 100,000 person-years in the moderate HBV DNA vs. 5.22 per 100,000 person-years in the high HBV DNA) (Table 2, Fig. 1). On Cox regression analyses, when compared to CHB patients with high baseline HBV DNA, no significant difference in risk of cirrhosis was observed in the moderate HBV DNA group both before propensity score weighting (HR: 0.87, 95% CI: 0.69 - 1.11, P = 0.28) and after propensity score weighting (HR: 0.87, 95% CI: 0.69 - 1.09, P = 0.22) (Table 2).

The incidence of HCC was 0.55 per 100,000 person-years (95% CI: 0.35 - 0.85) in the moderate HBV DNA group vs. 0.50 per 100,000 person-years (95% CI: 0.31 - 0.82) in the high HBV DNA group (Table 3). After propensity score weighting, the incidence of HCC was 0.84 per 100,000 person-years in the moderate HBV DNA and 0.69 per 100,000 person-years in the high HBV DNA) (Table 3, Fig. 1). On Cox regression analyses, when compared to CHB patients with high baseline HBV DNA, no significant difference in risk of HCC was observed in the moderate HBV DNA group before propensity score weighting (HR: 1.12, 95% CI: 0.58 - 2.17, P = 0.73). However, after propensity score weighting, patients with moderate HBV DNA had significantly higher risk of HCC compared to patients with high HBV DNA (HR: 1.33, 95% CI: 1.09 - 1.62, P < 0.01) (Table 3).

Discussion

In a national population-based analysis of US veterans with CHB, we observed that patients with moderate levels of baseline HBV DNA had a significantly higher risk of HCC compared to those with high levels of baseline HBV DNA, but no difference in risk of cirrhosis was observed. Our findings confirm what has been recently observed in predominantly Asian populations with CHB. For example, in a previous study of 2,073 HBeAg-positive CHB patients across three centers in Korea who were maintained on CHB antiviral therapy (entecavir or tenofovir), an inverse relationship between baseline HBV DNA and long-term risk of HCC was reported [11]. Compared to CHB patients with 8.00 $\log_{10}$ IU/mL or higher HBV DNA, the adjusted HRs for HCC risk were 2.48 for patients with HBV DNA levels of 7.00 - 7.99 $\log_{10}$ IU/mL, 3.69 for HBV DNA levels of 6.00 - 6.99 $\log_{10}$ IU/mL, and 6.10 for HBV DNA levels of 5.00 - 5.99 $\log_{10}$ IU/mL [11]. In a more recent multicenter study of 4,693 CHB in Korea maintained on CHB antiviral therapy, the highest risk of HCC was observed in patients with moderate baseline viral loads (5.00 - 7.99 $\log_{10}$ IU/mL), and the lowest risk observed in patients with high viral loads (8.00 $\log_{10}$ IU/mL or higher) [12]. Our current study observed similar findings but is unique in demonstrating similar patterns in the association of baseline HBV DNA and risk of HCC in a predominantly non-Asian population with CHB. This is particularly important given the overall paucity of CHB data in non-Asian cohorts, and these observations support the suggestion for earlier initiation of CHB antiviral therapy tailored to HBV viral load to reduce long-term risks of HCC even among non-Asian populations. However, it is important to interpret the findings of our study in the context that the overall distribution of HBV DNA levels was lower than in previous Korean cohorts. Hence the thresholds we used for defining moderate and high levels of baseline HBV DNA were slightly different from previous studies. Nevertheless, the overall similar trends observed in the relationship between baseline HBV DNA and risk of HCC demonstrate consistent findings.

In addition, our study also evaluated incidence of cirrhosis as an outcome, which has not been extensively evaluated in prior studies. While we did not observe significant differences in risk of cirrhosis between those with moderate vs. high levels of baseline HBV DNA, the data seem to suggest a trend towards higher risk of cirrhosis in those with high HBV DNA vs. moderate HBV DNA. While cirrhosis certainly modulates the risk of long-term HCC, it is also important to emphasize that nearly a quarter of patients with CHB-related HCC do not have evidence of cirrhosis [16-18]. This emphasizes the point that the HBV itself is carcinogenic and even in the setting of non-cirrhosis, can induce mutations contributing to the higher risk of developing HCC. While the exact reasons for this inverse relationship between baseline HBV DNA and HCC and cirrhosis risk are not clear, several hypotheses have been discussed. Prior studies have suggested that high HBV DNA is usually associated with HBeAg positive stage of disease, whereas patients with a lower HBV DNA may reflect HBeAg negative patients, who have longer duration of infection. Studies have

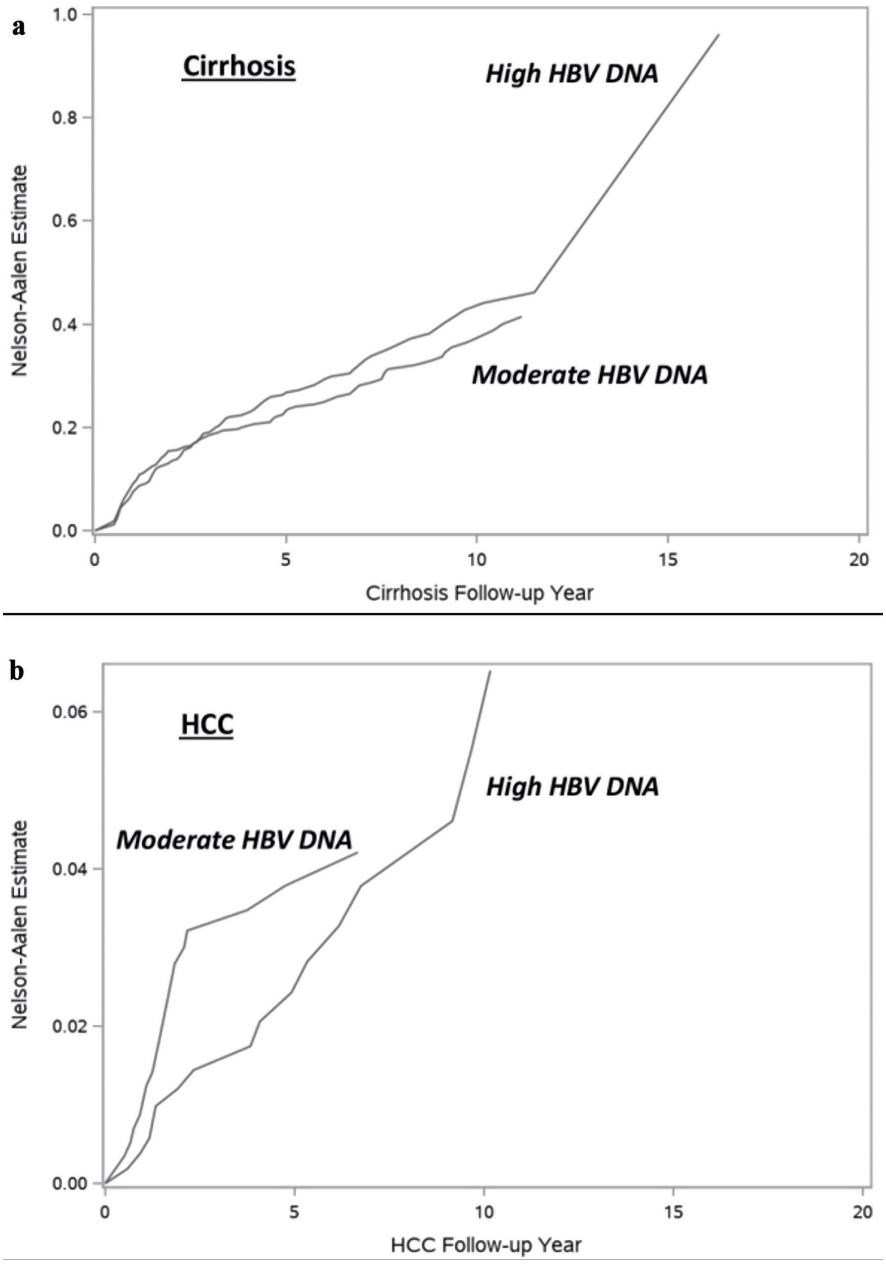

Figure 1. Figure 1. Incidence of (a) cirrhosis and (b) hepatocellular carcinoma by baseline HBV DNA. HBV: hepatitis B virus; HCC: hepatocellular carcinoma.

Table 3. Incidence and Risk of Hepatocellular Carcinoma Before and After Propensity Score Weighing by Baseline Levels of HBV DNA

	Incidence of HCC	HR	95% CI	P value
Before propensity weighting				
Moderate HBV DNA[a]	0.55 per 100 person-years	1.12	(0.58, 2.17)	
High HBV DNA	0.50 per 100 person-years	Reference		0.73
After propensity weighting				
Moderate HBV DNA[b]	0.84 per 100 person-years	1.33	(1.09, 1.62)	
High HBV DNA	0.69 per 100 person-years	Reference		< 0.01

suggested that the low level persistent immune-mediated killing of HBV-infected hepatocytes, by the infiltration of cytotoxic T lymphocytes, may contribute to adaptive responses in the liver along the development of HBV-resistant hepatocytes. While this leads to overall declines in HBV DNA, this may represent progressive injury of hepatocytes through attempted immune mediated viral clearance, clonal hepatocyte repopulation, and a subsequent increase in the risk of HCC. Along the same lines, those with lower baseline HBV DNA likely reflect longer duration of potential HBV DNA integration into the host's genome, and hence greater risk of HCC.

The strengths of this study include the utilization of a large, established, longitudinal cohort, which allows for accurate assessment of long-term CHB outcomes. In particular, there are generally limited data on CHB epidemiology among non-Asian populations, especially as it relates to evaluating baseline factors contributing to long-term risk of cirrhosis and HCC while maintained on CHB antiviral therapy. Thus, our cohort of predominantly non-Asians adds important data to the CHB literature. Furthermore, we applied propensity score weighting to balance potential differences in baseline factors that may confound the assessment of outcomes. However, certain limitations should be acknowledged. The mode of HBV transmission and hence the duration of CHB infection, is likely to be different between Asian and non-Asian cohorts. The majority of veterans with CHB likely acquired CHB infection during adulthood rather than vertical transmission, and hence the overall risk of HCC due to less duration of chronic infection may be lower in veterans with adult acquired CHB. Our cohort was predominantly men, and thus may have limited generalizability to women and non-veterans. However, this limitation should be balanced with the fact that veterans receive most, if not all, of their healthcare within VA health systems. Given the integrated nature of the national VA healthcare system, accurate assessment of long-term health outcomes is ensured. Along similar lines, our sample size had limited statistical power to perform sub-group analyses by patient characteristics. For example, when attempting to stratify the cohort by race/ethnicity, the sample size of some groups, especially in the high baseline HBV DNA group, became much smaller and limited the power to be able to evaluate differences in HCC or cirrhosis outcomes. While we utilized established definitions and previously validated algorithms to identify out study population and to define our study outcomes, there is a possibility of misclassification bias, although we would not necessarily expect any bias to be differential in nature. For example, there may be some misclassifications present such that patients with FIB-4 > 3.25 may have undiagnosed cirrhosis. However, we used established definitions and algorithms that have been previously used with the current dataset to accurately identify cirrhosis and thus we believe the misclassification was likely minimal. As previously noted, while we attempted to adjust for important baseline confounders using propensity score weighting, we acknowledge that unmeasured confounders may have affected the study outcomes as with all observational studies. Finally, one common limitation of observational studies is lost to follow-up or challenges in ascertaining outcome assessment for patients that utilize different healthcare systems. However, we believe the integrated nature of the VA health system is a strength in this regard, given that most veterans will continue longitudinal care within VA healthcare systems.

In conclusion, among a national longitudinal cohort of predominantly non-Asian veterans in the USA, with non-cirrhotic CHB on antiviral therapy, we observed that patients with baseline moderate levels of HBV DNA had significantly higher risk of HCC compared to patients with high levels of baseline HBV DNA. We did not observe differences in risk of cirrhosis by baseline HBV DNA. These data validate previous Asian studies showing the inverse relations of HBV DNA and risk of HCC in a predominantly non-Asian Western CHB population. Our findings taken together with recent data from Asian cohorts suggest that earlier initiation of CHB antiviral therapy targeting HBV DNA may further help reduce long-term risks of HCC.

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None to declare.

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Conflict of Interest

ZY and RC report no disclosures. JHJ has received grants from Gilead. JKL has received grants from Gilead, Intercept, Inventiva, Novo Nordisk, Pfizer, and Viking. YSL is an advisory board member of Gilead Sciences and receives investigator-initiated research funding from Gilead Sciences. RJW has received funding (to his institution) from Gilead Sciences, Exact Sciences, Theratechnologies, Durect Corporation and has served as a consultant for Gilead Sciences (without compensation).

Informed Consent

This study was approved by the Stanford University Institutional Review Board and the VA Palo Alto Healthcare System Research and Development Committee. Waiver of informed consent was granted by the aforementioned institutional review board.

Author Contributions

Study concept and design: all authors. Acquisition of data: ZY and RJW. Analysis and interpretation of the data: all authors. Statistical analyses: ZY and RJW. Drafting of the manuscript: ZY and RJW. Critical revision of the manuscript for important intellectual content: all authors. Study supervision: RJW. All authors had full access to the data in the study and take

responsibility for the integrity of the data and accuracy of the data analysis

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

AA: African American; API: Asian or Pacific Islander; CDW: Corporate Data Warehouse; CHB: chronic hepatitis B; FIB-4: fibrosis-4; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; NHW: non-Hispanic White; VA: Veterans Affairs

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