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Past Exposure to Hepatitis B: A Risk Factor for Increase in Mortality?

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Abstract

Background—Chronic hepatitis B has been shown to increase mortality, but association of past exposure to hepatitis B and mortality has not been studied well. The aim of this study is to evaluate the risk of overall and liver-related mortality in individuals with past exposure to hepatitis B.

Methods—The National Health and Nutrition Examination Survey III (NHANES III) and its related public linked mortality files were used for this study. The participants with presence of anti-HBc ± anti-HBs, in absence of HBsAg were considered to have previous exposure to hepatitis B. The overall mortality from past exposure to hepatitis B was assessed in participants without any chronic liver diseases (CLD) and in participants with chronic hepatitis C (CHC), alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD). The cox proportional regression analysis was used to calculate adjusted hazard ratios.

Results—15650 individuals were included in the analyses. Past exposure to hepatitis B was an independent predictor of increase in overall mortality in individuals without CLD (aHR = 1.29, 95% CI 1.06–1.56, $p=0.012$) and those with ALD (aHR = 2.25, 95% CI 1.20–4.23, $p=0.013$). It was also an independent predictor of liver-related mortality in ALD cohort (aHR = 7.75, 95% CI 2.56–23.48, $p<0.001$). Past exposure to hepatitis B did not correlate with a significant increase in overall or liver-related mortality in CHC or NAFLD cohorts.

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Conclusion—Past exposure to hepatitis B is associated with significant increase in overall mortality among individuals with ALD and those without CLD.

Keywords

Past exposure to hepatitis B; Mortality; NHANES III; Chronic liver disease

Background

The World Health Organization has estimated that around 2 billion people have been infected with hepatitis B virus worldwide, of which 350 million live with chronic infection. Even though chronic hepatitis B is not as endemic in the United States as compared to other regions of the world, it still contributes to a substantial healthcare burden with an estimated prevalence of around 1.25 million.¹ According to the International Agency for Research on Cancer and the US National Toxicology Program, hepatitis B has been considered a group 1 human carcinogen.² Many studies have shown chronic hepatitis B as a well-established risk factor for the increase in liver related complications and mortality. But the role of past exposure to hepatitis B, which is defined as presence of antibody to hepatitis B core antigen (anti-HBc) in the absence of surface antigen (HBsAg), in the development of liver-related complications or hepatocellular carcinoma still remains controversial. Despite seroclearance of HBsAg, a few patients continue to have persistently detectable HBV DNA in their serum and most in their hepatocytes. Prevalence of this occult infection varies widely and depends mainly on the prevalence of hepatitis B virus infection in that geographic location.

The studies looking at clinical aspects of occult hepatitis B infection suggested poor outcomes to antiviral treatments for chronic hepatitis C (CHC)^{3, 4}, and increased risk of hepatocellular carcinoma in alcoholics and CHC patients^{5–7}. Some studies also demonstrated occult hepatitis B as an independent predictor of hepatocellular carcinoma in the absence of other chronic liver diseases.^{8–10} Though the exact mechanism for development of liver-related complications is not well understood, some studies suggested that a persistently low level of hepatitis B virus in hepatocytes causes progressive liver injury, while others postulated reactivation of hepatitis B during immunocompromised states such as in individuals receiving hepatitis C treatment may be responsible for these effects. The evidence regarding implications of these effects of past exposure to hepatitis B on mortality remains scarce.

The aim of this study is to evaluate the risk of mortality from past exposure to hepatitis B from a large US population database, the third National Health and Nutrition Examination Survey (NHANES III). We hypothesized that past exposure to hepatitis B in the absence of a chronic state leads to an increase in mortality among individuals with and without chronic liver disease.

METHODS

The NHANES III is a program designed to assess the health and nutritional status of adults and children in the United States. It was conducted in the United States from 1988 through 1994 by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention. It used complex, multistage, stratified, clustered samples of civilians, age 2 months and older to collect information about their health and nutrition. It did not include institutionalized, incarcerated and homeless populations. The survey consisted of questionnaires, physical examination data and laboratory tests from blood samples collected during examination. The details of survey design and sampling methods are available elsewhere.¹¹

Study selection criteria and Definitions

Individuals age 17 years or older were eligible for mortality follow-up and were included for our study. We included those who are of the following ethnicities: Non-Hispanic white, non-Hispanic black, and Mexican American. We excluded those with missing values for baseline characteristics including demographic and social data for age, gender, race/ethnicity, education, smoking and alcohol status. The observations with person-month follow-up of zero were considered ineligible for the study.

The etiologies of chronic liver disease were defined from available hepatitis markers, serum transaminases levels and alcohol use. Chronic hepatitis B was defined as the presence of HBsAg, while past exposure was defined as anti-HBc positivity with or without anti-HBs in the absence of HBsAg. The individuals with positive hepatitis C virus RNA were defined as those with CHC. Individuals with excessive alcohol use and elevated serum transaminases (ALT > 40 U/l in men and > 31 U/l in women, or AST > 37 U/l in men and > 31 U/l in women) in the absence of chronic hepatitis B or C were considered to have alcoholic liver disease (ALD). Excessive alcohol use was defined as more than 2 drinks per day in men and more than 1 drink per day in women.¹² The average alcohol consumption was calculated using responses to two survey questions that queried about the number of days of drinking over the past 12 months and the number of drinks on a given drinking day. Those with moderate to severe hepatic steatosis on ultrasound in the absence of chronic hepatitis B, CHC, excessive alcohol use, and transferrin saturation > 50% were considered to have nonalcoholic fatty liver disease (NAFLD). The subjects without chronic hepatitis B, CHC, ALD, NAFLD and transferrin level >50% were considered as individuals without chronic liver diseases. Additionally, individuals with excessive alcohol use despite normal enzymes were excluded from non-chronic liver diseases group. The observations with missing values for CHC, ALD, NAFLD and transferrin level were excluded from the study analysis.

Laboratory measurements

The laboratory procedures followed in the NHANES III are described in detail elsewhere.¹³ All blood samples were immediately centrifuged and transported weekly to a central laboratory at -20 °C temperature. Solid-phase competitive immunoassay method was used to measure antibodies against Hepatitis C virus and hepatitis B core antigen while determination of hepatitis B surface antigen was performed using sandwich radioimmunoassay.

Mortality data

In 2009, the National Center for Health Statistics completed a mortality update for NHANES III survey participants (1988–1994), by linking participants to death certificate data found in the National Death Index (NDI) through probabilistic record matching process. These data provided mortality follow-up for NHANES III participants from the date of survey participation (1988–1994) through December 31, 2006. Individuals with age 17 years or older were considered eligible for this mortality follow-up. Two versions of the NHANES III linked mortality files including public-use file and restricted-use file were released. Only public-use mortality file was used in the analysis. Details of these NHANES III linked mortality files and NDI record matching process has been provided elsewhere.¹⁴

According to NDI database, coding for cause of death for all deaths occurring prior to 1999 followed the 9th revision of the International Statistical Classification of Disease, Injuries and Cause of Death (ICD-9) guidelines, while deaths during and after 1999 were coded according to ICD-10 guidelines. In order to have same cause-of-death codes across all years in the study period, deaths occurring prior to 1999 were recoded into ICD-10 codes.

The liver-related mortality included death from viral hepatitis (ICD-10, B15–B19), primary liver cancer (ICD-10, C22), and chronic liver disease and cirrhosis (ICD-10, K70, K73–K74).

Statistical analysis

Basic descriptive statistics, including mean, standard errors, ranges, and weighted percentages were used to characterize the study population. Appropriate comparison tests including chi-square test and student t-test were used for comparison between groups for categorical variables and continuous variables respectively. To evaluate the independent predictors of overall mortality and liver-related mortality, the Cox proportional hazards model was used. To account for effects from socio-demographic variables; age, gender, race, smoking status, and excessive alcohol use were included in the hazard models as covariates. The hazard models used calculated person-months of follow-up time provided in the public-use mortality file from the time of enrollment into NHANESIII study until December 31, 2006.

The risks of overall and liver-related mortalities from past exposure to hepatitis B were assessed separately in the cohorts of CHC, ALD, NAFLD, and in those without chronic liver diseases. A separate risk analysis was conducted for individuals with only anti-HBc positive in the absence of anti-HBs. All analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina, USA), using survey procedures to take into account appropriate sample weight, clustering and strata to control for unequal selection probabilities, designing, multi-staging and complexity of survey data.

RESULTS

After implementing study selection criteria, a total of 15,650 individuals constituted our study cohort. The mean age was 43.7 ± 0.5 years. The detailed demographics of study participants showed 48% male, 83% non-Hispanic white, 28% smokers and 9% excessive alcohol users. The prevalence of CHC, ALD, and NAFLD was 1.4%, 1.4%, and 14.4%, respectively. The prevalence of past exposure to hepatitis B (anti-HBc positivity regardless of anti-HBs status in absence of HBsAg) was 4.5%, while prevalence of anti-HBc positivity only was 0.8%. Further details of the baseline characteristics are provided in table 1.

Overall and liver related mortality of individuals among total study cohort

During follow-up period, a total of 3,710 individuals died. The overall and liver-related mortalities during the follow-up period (167.9 ± 2.7 person-months) were 17.1% and 0.3%, respectively. The multivariate cox proportional hazard model revealed that past exposure to hepatitis B (aHR = 1.27, 95% CI 1.05–1.55, $p=0.016$) and CHC (aHR = 2.76, 95% CI 1.82–4.17, $p<0.001$) were the independent predictors of overall mortality. As expected, the risk of liver-related mortality was increased in individuals with CHC (aHR = 26.48, 95% CI 4.84–145.03, $p<0.001$), and ALD (aHR = 6.90, 95% CI 1.13–42.38, $p=0.037$).

Mortality of individuals without chronic liver disease with previous exposure to hepatitis B

Past exposure to hepatitis B was found in 4% among subjects without chronic liver disease ($n=11,410$). Exposed individuals were older (50.4 ± 1.0 years vs 42.3 ± 0.5 years, $p<0.001$) and had higher rates of smoking (34% vs. 25.9%, $p=0.007$) (Table 2). A total of 2,819 died during follow-up period (overall mortality = 17.3%). The past exposure to hepatitis B was found to be an independent predictor of increased overall mortality in these individuals (aHR = 1.29, 95% CI 1.06–1.56, $p=0.012$). In addition, older age, male gender, non-Hispanic black and smoking were found to be independent factors affecting overall

mortality. Age (aHR = 1.05, 95% CI 1.01–1.08, $p=0.006$) was the only independent factor affecting liver-related mortality in this cohort (Table 3).

Mortality of individuals with specific types of chronic liver disease and previous exposure to hepatitis B

Thirty four percent of subjects with CHC had past exposure to hepatitis B. The overall and liver-related mortality rate was 24.9% and 6.7%, respectively. Age was the only independent predictor of overall mortality (aHR = 1.09, 95% CI 1.07–1.11, $p<0.001$). Age (aHR = 1.06, 95% CI 1.03–1.09, $p<0.001$) and male gender (aHR = 4.10, 95% CI 1.57–10.67, $p=0.004$) were the predictors for liver-related mortality in this cohort. Previous exposure to hepatitis B did not significantly affect neither overall (aHR = 0.88, 95% CI 0.49–1.56, $p=0.643$) nor liver-related mortality (aHR = 0.58, 95% CI 0.10–3.35, $p=0.535$) (Table 3).

Ten percent of subjects with ALD had past exposure to hepatitis B. The overall and liver-related mortality rate during the follow-up period was 17.6% and 4.0% respectively. Past exposure to hepatitis B was an independent predictor of both overall (aHR = 2.25, 95% CI 1.20–4.23, $p=0.013$) and liver-related (aHR = 7.75, 95% CI 2.56–23.48, $p<0.001$) mortality in individuals with ALD (Table 3).

Four percent of subjects with NAFLD had past exposure to hepatitis B. The rates for overall mortality and liver-related mortality were 17.7% and 0.24% respectively. The independent predictors of overall mortality in this cohort were age (aHR = 1.09, 95% CI 1.08–1.11, $p<0.001$) and non-Hispanic black race (aHR = 1.44, 95% CI 1.10–1.88, $p=0.009$). The increased risk of overall and liver-related mortality from past exposure to hepatitis B among NAFLD individuals was not found to be statistically significant (overall aHR = 1.41, 95% CI 0.90–2.22, $p=0.130$; liver-related = 0.12, 95% CI 0.01–1.22, $p=0.072$).

Finally, separate analyses for individuals with only core antibody positivity were performed for non-CLD, CHC, ALD and NAFLD cohorts. Isolated core antibody positivity was found to be an independent predictor of overall mortality (aHR = 1.91, 95% CI 1.20–3.06, $p=0.008$) but not liver-specific mortality in subjects without chronic liver diseases. However, it was an independent predictor for both overall mortality (aHR = 4.58, 95% CI 1.67–12.57, $p=0.004$) and liver specific mortality in those with ALD (Table 3).

DISCUSSION

Our study suggests that past exposure to hepatitis B is an independent predictor of overall mortality in individuals without chronic liver diseases and those with ALD. The liver-related mortality was only affected by past exposure to hepatitis B in ALD individuals. These risks were found to be higher with loss of surface antibody positivity. Past exposure to hepatitis B did not affect overall or liver-related mortality in CHC or NAFLD individuals. Similar results were observed for individuals with only core antibody positivity.

Studies evaluating long term mortality in individuals with past exposure to hepatitis B are limited. The study by Norman et al. determined liver-related mortality in army personnel exposed to hepatitis B during 1942 epidemic from yellow fever vaccine. Most of the individuals involved in their study had antibodies to HBV in the absence of HBsAg. Their study did not show excess mortality from liver disease of all kinds including hepatocellular carcinoma among individuals exposed to hepatitis B.¹⁵ Similarly, our study did not find an increase in liver-related mortality among different cohorts except for those with alcoholic liver disease. Though conclusive evidence is scarce, previous studies have suggested a higher incidence of hepatocellular carcinoma in individuals with alcoholic cirrhosis along with past exposure to hepatitis B.⁶

Some studies have suggested an increased risk of liver related complications in those exposed to hepatitis B in the absence of chronic carrier state.^{8–10} Many studies have postulated hypothesis regarding mechanisms of liver related complications in individuals with this occult HBV infection. It is plausible that low levels of HBV still persist in hepatocytes leading to hepatic injury and increased risk of hepatocellular carcinoma in the animal model. The possible mechanism may be related to propensity of virus to act as an insertional mutagen of the host's myc family genes among the hepatocytes leading to production of X and truncated preS-S proteins leading to cell transformation and hepatocellular carcinoma.^{16–19} Apart from affecting host DNA, the virus may persist as episomal DNA even after seroclearance which may induce mild inflammation over longer duration of time.²⁰ This may lead to progression towards cirrhosis and thus hepatocellular carcinoma in occult hepatitis B patients. In individuals with preexisting liver disease like HCV, ALD or NAFLD, occult hepatitis B infection may have more deleterious effects and may hasten the progression of hepatic injury.

Despite the above mentioned hypothesis and findings, the long term implication of these effects on mortality has not been studied well. Many studies have shown a relatively higher incidence of liver related complications in individuals with pre-existing chronic liver disease in the presence of occult HBV infection.^{5–7} Our study provided long term follow-up effect of the exposure to hepatitis B in the absence of chronic carrier state and we did not observe a higher liver-related mortality in individuals with or without pre-existing liver disease except for those with ALD.

Our study results showed an overall increase in mortality in individuals with past exposure to hepatitis B in absence of any other chronic liver diseases but the liver related-mortality difference was not significant. This may have been due to a slower rate of liver fibrosis in occult hepatitis B individuals compared to chronic carriers which may not affect liver related mortality or might not have been evident during the follow-up period. The lack of occult hepatitis B infection confirmation in our study by HBV DNA levels or liver biopsy may have some impact on results. Our large US population sample also differed significantly from Asian population with aspects of endemicity and age of acquiring hepatitis B, which may be responsible for the differences in our study results compared to previous studies. Similar results were also evident in a recent large cohort study of US population from the HALT-C trial which did not show significantly higher prevalence of occult and previous hepatitis B virus infection in hepatocellular carcinoma individuals with chronic hepatitis C.²¹

An alternative explanation for higher overall mortality but no change in liver-related mortality may be related to high risk behaviors in those individuals exposed to hepatitis B. Hepatitis B is not endemic in the United States and is usually acquired during adulthood through intravenous drug use or sexual transmission^{22–24} and these high risk behaviors may have led to death from causes other than liver-related complications (e.g. HIV, illicit drug related complications etc. in those exposed to HBV).

The NHANES III database allowed us to follow the individuals with a past exposure to hepatitis B over an average of more than 10 years period in a large US population sample. Despite of this strength, our study had many potential limitations. The NHANES III database does not provide information on HBV DNA and liver biopsy. The survey did not include homeless, incarcerated or institutionalized individuals which may account for a significant burden of hepatitis B. Our study did not evaluate the incidence of cirrhosis or hepatocellular carcinoma in previously exposed hepatitis B individuals but rather evaluated the risk of mortality. Some patients could have developed liver related complications but they may have responded well to treatment and may not have died during follow-up period.

Furthermore, lack of data regarding autoimmune liver diseases did not allow us to control for their effects on mortality in our hazard models.

In conclusion, we identified past exposure to hepatitis B as a risk factor for increase in overall mortality in individuals with ALD and more importantly those without chronic liver disease. It also had an influence on liver-related mortality among individuals with ALD. Our study did not identify exposure to hepatitis B as a risk factor for increase in mortality in CHC or NAFLD individuals.

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List of Abbreviations

NHANES	National Health and Nutrition Examination Survey
CLD	chronic liver diseases
CHC	chronic hepatitis C
ALD	alcoholic liver disease
NAFLD	nonalcoholic fatty liver disease
Anti-HBc	antibody to hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
Anti-HBs	antibody to hepatitis B surface antigen
ICD	International Classification of Diseases
aHR	adjusted hazard ratio

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Table 1

Baseline characteristics of total study population

	Unweighted n (n= 15,650)	Weighted percentage (Std Error)
Age (years), mean		43.68 ±0.49
Age groups		
17–44	8343	58.3% (±1.23)
45–64	3671	25.2% (±0.59)
65–84	3260	15.3% (±0.85)
85+	376	1.2% (±0.16)
Gender		
Male	7379	47.9% (±0.45)
Female	8271	52.1% (±0.45)
Race/Ethnicity		
Non-Hispanic white	6678	83.0% (±0.82)
Non-Hispanic black	4443	11.4% (±0.68)
Mexican American	4529	5.6% (±0.46)
Education level		
Less than high school	6491	25.3% (±1.05)
High school	4807	34.4% (±0.76)
More than high school	4257	40.3% (±1.34)
Body mass index		
Less than 25	6382	45.5% (±0.87)
25 to 29.9	5365	32.5% (±0.57)
30 or more	3903	22.0% (±0.73)
Alcohol status		
No	14480	91.1% (±0.59)
Yes	1170	8.9% (±0.59)
Smoking status		
No	11704	71.6% (±0.85)
Yes	3946	28.4% (±0.85)

Table 2

Comparison of socio-demographic characteristics of exposed (anti-HBc ± anti-HBs) and non-exposed to hepatitis B individuals in CLD and non-CLD cohorts

	Chronic hepatitis C n = 257			Alcoholic liver disease n = 225			Nonalcoholic fatty liver disease n = 2465			Non-CLD n = 11410		
	Exposed to hepatitis B (n=99)	Non- exposed to hepatitis B (n=158)	p value	Exposed to hepatitis B (n=39)	Non- exposed to hepatitis B (n=186)	p value	Exposed to hepatitis B (n=62)	Non- exposed to hepatitis B (n=916)	p value	Exposed to hepatitis B (n=861)	Non- exposed to hepatitis B (n=12,908)	p value
Age (years), mean	39.7±1.19	39.5±1.18	0.908	38.6±1.09	40.9±1.58	0.304	43.2±3.11	42.0±0.81	0.720	50.4±1.00	42.3±0.51	<0.001
Gender (weighted %)												
Male	75.3±7.67	65.9±5.60	0.331	77.7±5.22	60.5±5.16	0.008	51.2±6.64	52.8±1.44	0.822	51.6±3.36	44.8±0.72	0.056
Female	24.7±7.67	34.1±5.60	0.331	22.3±5.22	39.5±5.16	0.008	48.8±6.64	47.2±1.44	0.822	48.4±3.36	55.2±0.72	0.056
Race/Ethnicity (weighted %)												
Non-Hispanic white	55.3±9.30	72.7±4.06	0.028	41.4±10.07	82.7±2.20	<0.001	57.0±6.18	83.5±1.31	<0.001	59.4±2.88	83.9±0.86	<0.001
Non-Hispanic black	37.6±8.45	19.8±2.95	0.028	43.8±10.69	8.4±1.20	<0.001	35.5±5.49	8.2±0.91	<0.001	35.8±2.85	11.0±0.71	<0.001
Mexican American	7.1±2.38	7.5±1.70	0.028	14.8±4.03	8.9±1.39	<0.001	7.5±1.82	8.3±0.87	<0.001	4.8±0.88	5.2±0.45	<0.001
Excessive alcohol (weighted %)												
No	61.3±7.07	74.0±6.24	0.170	-	-	-	100.0±0	100.0±0	-	100.0±0	100.0±0	-
Yes	38.7±7.07	26.0±6.24	0.170	100.0±0	100.0±0	-	-	-	-	-	-	-
Smoking (weighted %)												
No	23.8±6.60	40.4±6.36	0.035	42.1±6.68	53.5±4.83	0.168	78.5±1.28	69.4±2.28	0.139	66.0±3.22	74.1±0.89	0.006
Yes	76.2±6.60	59.6±6.36	0.035	57.9±6.68	46.5±4.83	0.168	21.5±1.28	30.6±2.28	0.139	34.0±3.22	25.9±0.89	0.006
CLD- chronic liver disease												

Table 3

Hazard ratio of Overall and liver-related mortality from past exposure to hepatitis B in CLD and non-CLD cohorts

Cohorts	Anti-HBc with or without Anti-HBs				Anti-HBc only			
	Overall mortality		Liver-related mortality		Overall mortality		Liver-related mortality	
	aHR* (95% CI)	p-value	aHR* (95% CI)	p-value	aHR* (95% CI)	p-value	aHR* (95% CI)	p-value
Non-chronic liver disease	1.29 1.06–1.56	0.013	3.29 0.76–14.18	0.108	1.91 1.20–3.06	0.008	2.17 0.25–19.0	0.477
Chronic hepatitis C	0.88 0.49–1.56	0.643	0.58 0.10–3.35	0.535	0.95 0.33–2.74	0.915	1.94 0.23–16.54	0.534
Alcoholic liver disease	2.25 1.20–4.23	0.013	7.75 2.56–23.48	<0.001	4.58 1.67–12.57	0.004	41.32 14.23–119.99	<0.001
Nonalcoholic fatty liver disease	1.41 0.90–2.22	0.130	0.12 0.01–1.22	0.072	2.08 0.82–5.26	0.121	-	-

CLD – chronic liver disease, anti-HBc – antibody to hepatitis B core antigen, anti-HBs – antibody to hepatitis B surface antigen

- insufficient data for analyses

* aHR - adjusted hazard ratio for age, gender, race, smoking, and excessive alcohol use