



## Latent hepatitis B is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C

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### Abstract

**AIM:** To study the potential association between hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC), cirrhosis and latent hepatitis B (LHB) infection, defined as the absence of detectable serum hepatitis B surface antigen (HBsAg) and the presence of hepatitis B core antibody (HBcAb).

**METHODS:** This retrospective analysis is comprised of 185 cirrhotic patients with HCC who were hepatitis C virus antibody (HCV Ab) (+) and HBsAg(-) at Wayne State University between 1999 and 2008. From these, 108 patients had HCV polymerase chain reaction confirmation of viremia while the remaining (77) were considered to have CHC on the basis of a positive HCV Ab and the absence of any other cause of liver disease. Controls were drawn from our institutional database from the same time period and consisted of 356 HBsAg(-) age, race and gender matched patients with HCV RNA-confirmed CHC and without evidence of HCC. A subgroup of controls included 118 matched patients with liver cirrhosis.  $\chi^2$  test and *t* test were used for data analysis.

**RESULTS:** Seventy-seven percent of patients in all 3 groups were African Americans. Patients with HCC

had a significantly higher body mass index ( $P = 0.03$ ), a higher rate of co-infection with human immunodeficiency virus (HIV) ( $P = 0.05$ ) and a higher prevalence of alcohol abuse ( $P = 0.03$ ) than the controls. More patients with HCC had LHB than controls (78% vs 39%,  $P = 0.01$ ). Sixty three percent of patients with HCC were both hepatitis B surface antigen (HBsAb)(-) and HBcAb(+) compared to 23% of controls ( $P < 0.01$ ). When compared to cirrhotic controls, the frequency of HBcAb(+) remained higher in patients with HCC (78% vs 45%,  $P = 0.02$ ). Patients with HCC were more likely to be both HBsAb(-) and HBcAb(+) than the cirrhotic controls (63% vs 28%,  $P = 0.01$ ). Although not statistically significant, 100% of CHC and HIV co-infected patients with HCC ( $n = 11$ ) were HBcAb(+) when compared to controls (44%;  $n = 9$ ).

**CONCLUSION:** These data suggest that LHB occurs at a significantly increased frequency in patients with CHC and HCC than in patients with CHC without HCC.

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**Key words:** Hepatocellular carcinoma; Chronic hepatitis C; Latent hepatitis B; Hepatitis C virus

**Core tip:** Latent hepatitis B (LHB) has recently received significant attention among researchers and clinicians managing chronic liver disease. It is defined as a combination of hepatitis B surface antigen negative and hepatitis B core antibody positive. The potential association of LHB with hepatocellular carcinoma among patients with chronic hepatitis C infection has been studied and reported in this manuscript.

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## INTRODUCTION

Emerging data suggest that the mortality rate in cirrhotic patients with hepatocellular carcinoma (HCC) is rising whereas the mortality rate from other complications of cirrhosis is either stable or declining<sup>[1]</sup>. In the United States, chronic hepatitis C (CHC) accounts for the majority of cases of HCC. Among patients with CHC, factors such as older age, male gender, severity of liver disease, metabolic syndrome and poor response to interferon therapy are established risk factors for hepatocarcinogenesis<sup>[1]</sup>. “Latent hepatitis B (LHB)”, defined as the presence of detectable hepatitis B core antibody (HBcAb) with undetectable hepatitis B surface antigen (HBsAg)(-) in serum and usually with detectable HBV DNA in hepatocytes, has not been studied as a risk factor for HCC in the United States<sup>[2]</sup>. Patients with previous exposure to hepatitis B virus but with no evidence of chronic infection are HBsAg(-) and HBcAb(+). This finding alone is now considered as unrecognized LHB<sup>[3]</sup>. In a large study, the majority of patients with LHB had detectable hepatitis B DNA (HBV DNA) in serum as well as in liver tissue<sup>[4]</sup>. Various other studies have also confirmed the same findings<sup>[5,6]</sup>. This led to the identification of a unique group of patients who are HBcAb(+) and at risk for latent hepatitis B.

Early studies from the 1990s suggested that patients with HCC in the absence of chronic hepatitis B and C had detectable covalent closed circular hepatitis B DNA (ccc DNA) in liver parenchyma although they were HBsAg(-) in serum. These patients were considered to have “occult hepatitis B”<sup>[7]</sup>. A single prospective study by Squadrito *et al*<sup>[8]</sup> revealed that among HBsAg(-) patients with CHC, patients with occult hepatitis B with ccc DNA in liver biopsy specimens were at a higher risk for the development of HCC. With the availability of highly sensitive real-time polymerase chain reaction (PCR) assays for the measurement of HBV DNA, tissue analysis for HBV DNA is largely unnecessary to make a diagnosis of latent hepatitis B<sup>[2]</sup>. Patients with cirrhosis from alcoholic and non-alcoholic fatty liver disease are also at a significantly higher risk for developing HCC when associated with LHB particularly in those who were HBcAb(+) but HBsAg(-)<sup>[9]</sup>. Injection drug users, patients on hemodialysis, patients with CHC and human immunodeficiency virus (HIV)-infected patients are at increased risk for LHB<sup>[10]</sup>. In patients with CHC, occult hepatitis B seems to be associated with rapid progression of liver disease<sup>[11]</sup>. Studies from areas with high prevalence of chronic hepatitis B have associated occult hepatitis B with HCC among patients with CHC<sup>[12,13]</sup>. This association is much stronger among CHC patients who are non-responders to currently available therapy<sup>[14]</sup>. Another study reported that although occult hepatitis B may not have a significant impact on response of CHC to interferon, it does increase

the risk for HCC among non-responders but not among responders<sup>[15]</sup>.

A large multicenter Japanese study concluded that CHC patients with LHB are at a significantly higher risk for developing HCC<sup>[16]</sup>. In the same study, interferon was less effective in preventing HCC in patients with LHB when compared to those without evidence of previous HBV exposure. This association was independent of the presence of HBV DNA in serum and therefore, LHB is clinically and prognostically more relevant than serum DNA status.

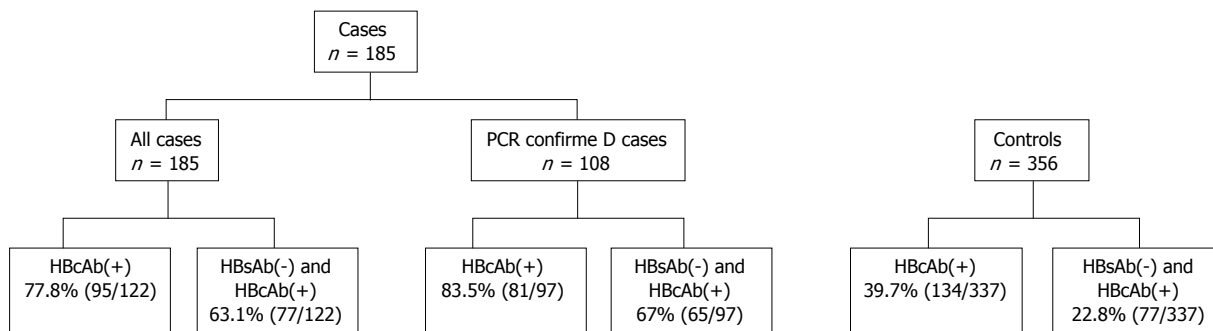
The above referenced studies establishing LHB as a risk factor for development of HCC are from countries with high endemicity for chronic hepatitis B infection. We studied this potential association among predominantly African American patients with CHC and cirrhosis in an area with low endemicity for chronic hepatitis B.

## MATERIALS AND METHODS

This retrospective study, included patients with CHC who were diagnosed with HCC between January 1999 and December 2008 at the Detroit Medical Center, Detroit, Michigan. The primary sites were the Wayne State University Gastroenterology clinic and the Department of Pathology at Harper University Hospital in Detroit. Patients with a diagnosis of HCC who were > 18 years old, hepatitis C Ab(+) and HBsAg(-) were included in our study. The diagnosis of HCC was made either by histopathology or by non-invasive criteria *i.e.*, alpha fetoprotein (AFP) > 200 ng/mL and a mass lesion in the liver with radiological features typical for HCC observed on two or more imaging modalities (European Association for the Study of the Liver, EASL criteria)<sup>[17]</sup>. The study group consisted of both inpatients and outpatients although the majority were outpatients.

A control comparison group consisted of patients with CHC who were HBsAg(-) without evidence of HCC. These patients were drawn from our institutional database of CHC patients. They were age, race and gender matched to the cases and were from the same time period. Patients with HIV and CHC coinfection were included in the study and were part of a subset analysis. The study was approved by the Institutional Review Board at Wayne State University and the Detroit Medical Center.

A total of 185 patients fulfilled the selection criteria and were evaluated for inclusion in the study. Of these, 108 had serum RNA confirmation of CHC by PCR, while CHC viremia was presumed in the remaining 77. A total of 356 matched (1:2) non-HCC controls with CHC were selected from our database. All controls had PCR confirmation of CHC, were HBsAg(-) and were selected from the same time period. Non HCC controls included 118 matched patients with cirrhosis diagnosed by histopathology or by clinical criteria. Since the majority of patients with CHC who develop HCC have underlying advanced liver disease<sup>[10]</sup>, a selected sub-group of matched



**Figure 1** Hepatitis B serology in cases and controls. HBcAb: Hepatitis B core antibody; HBsAb: Hepatitis B surface antigen; PCR: Polymerase chain reaction.

**Table 1** Baseline characteristics of hepatocellular carcinoma cases

	HCV Ab(+), HCV RNA(+) (n = 108)	HCV Ab (+) (n = 77)	P value
Age (yr), mean ± SD	60.88 ± 8.6	59.42 ± 7.4	0.88
Males	73.10%	67.53%	0.32
African American	75.90%	72.70%	0.22
	n = 70	n = 52	0.20
BMI (kg/m <sup>2</sup> )	29.56 ± 6.11	27.88 ± 5.2	
HIV coinfection	10.20%	7.60%	0.16
Heavy alcohol use	37.03%	48.05%	0.04

HCV Ab: Hepatitis C virus antibody; HCV DNA: Hepatitis C DNA; BMI: Body mass index; HIV: Human immunodeficiency virus.

controls with cirrhosis and CHC was utilized in the analysis (Figure 1). In addition to demographic data, alcohol intake was assessed by chart review. Patients were classified into three categories based on alcohol consumption. Those who consumed 1 to 2 servings of liquor or wine a week or ≤ 6 beers (12 oz) a week were categorized as “mild drinkers”. Patients with alcohol consumption that exceeded this amount were considered “heavy drinkers”. The third group was designated as “non drinkers”. Lab values closest to the date of the diagnosis of HCC were collected. In controls, lab values at the time of their initial evaluation were recorded.

**Statistical analysis**

Data was analyzed using SPSS version 12.  $\chi^2$  test was used to analyze nominal data while *t* test was used to compare means among groups. Univariate analysis was then performed after controlling for covariates in the final analysis. Among cases, baseline characteristics were compared in patients with PCR confirmation of CHC and in those without PCR confirmation (Table 1). Since these groups were identical in baseline characteristics, they were combined for subsequent analysis. Additionally, subset analysis of African-American patients, patients with PCR confirmation of CHC, and cirrhotic patients was performed.

**RESULTS**

The mean age of patients with HCC was 60 years, and

71% were male (Table 2). More than seventy five percent of patients in each group were African-American. HCC was diagnosed by biopsy in 129 patients and by non-invasive (EASL) criteria in the remainder. Patients with HCC had a significantly higher body mass index (BMI), AFP, aspartate aminotransferase, alanine aminotransferase and a more prolonged prothrombin time (PT), but they had a lower albumin and platelet count. HIV-HCV coinfection was seen more commonly in patients with HCC (8.1%) than in controls (2.5%, *P* = 0.05). While mild alcohol consumption was not different in both groups, patients with HCC were more likely to be heavy drinkers (42% *vs* 27%; Table 2). Furthermore, HCV patients without HCC were more likely to be non-drinkers (32%) compared to patients with HCC (11%, *P* < 0.01; Table 2).

HBcAb was positive in 78% of patients with HCC but in only 40% of controls (*P* = 0.01). When hepatitis B surface antibody (HBsAb) status was determined, 63% of HCC cases were both HBsAb(-) and HBcAb(+) as compared to only 23% of controls (*P* < 0.01). When analysis was restricted to patients with cirrhosis, the prevalence of HBcAb was higher in cirrhotic controls at 42%, and the combination of HBsAb(-) and HBcAb(+) was also more prevalent when compared to total controls (27.6% *vs* 63.1%, *P* < 0.01). Despite this difference in prevalence of HBsAb and HBcAb among control groups, overall prevalence remained significantly higher in patients with HCC (63.1% *vs* 22.8%). Although statistical significance was not achieved, 100% of HIV-HCV coinfecting patients with HCC (44.4%) were HBcAb(+) when compared to < 50% among coinfecting controls.

Univariate analysis predicting HCC showed that HBcAb(+) status had an odds ratio of 1.9 (95%CI: 1.28-3.04, *P* = 0.02) where as a combination of HBsAb(-) and HBcAb(+) had a higher odds ratio of 3.24 (95%CI: 2.28-4.62, *P* < 0.01). In this analysis, BMI, albumin, PT, alcohol consumption and HIV coinfection were identified covariates. When regression analysis was performed after controlling for these covariates, these odds ratios were 1.84 (95%CI: 1.22-3.08, *P* = 0.01) and 2.98 (95%CI: 2.12-5.08, *P* < 0.01) respectively. Analysis of cirrhotic patients when controlled for covariates showed that HBcAb(+) had an odds ratio of 1.66 and a combination of HBsAb(-) and HBcAb(+) was at 2.10 (95%CI: 2.12-4.04, *P* < 0.01).

**Table 2** Comparison of variables in cases and controls

	CHC with HCC (n = 185)	CHC without HCC (n = 356)	P value
Age (yr), mean ± SD	60.3 ± 9.71	59.72 ± 9.2	
Males	70.80%	71.10%	
Race AA	74.60%	78.70%	
CAU	21.60%	18.50%	
Other	3.80%	2.80%	
BMI (kg/m <sup>2</sup> )	n = 122	n = 320	
	28.8 ± 6.01	27.26 ± 5.9	
Albumin	n = 178	n = 289	
	2.67 ± 0.7	3.88 ± 0.6	< 0.01
PT (s)	n = 171	n = 242	
	16.69 ± 8.6	11.57 ± 2.5	< 0.01
AFP (ng/mL)	n = 163	n = 284	
	99035.1 ± 263605.5	21.12 ± 90.4	
Platelets	n = 172	n = 337	
	176.5 ± 127	202.98 ± 83.4	0.04
ALT (IU/L)	n = 166	n = 345	
	263.8 ± 518.2	78.19 ± 58.3	< 0.01
AST (IU/L)	n = 160	n = 324	
	283.8 ± 63.5	75.2 ± 55.9	< 0.01
HIV co-infection	8.10%	2.50%	0.05
Alcohol			
Mild	29.7%	27.50%	NS
Heavy	41.60%	27%	0.03
Non drinkers	10.80%	31.70%	< 0.01

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HIV: Human immunodeficiency virus; BMI: Body mass index; PT: Prothrombin time; AFP: Alpha fetoprotein; NS: Not significant.

Subset analysis of African-American patients with cirrhosis when controlled for covariates resulted in an odds ratio of 2.08 (95%CI: 1.42-3.60,  $P < 0.01$ ) when HBcAb was positive and 2.58 (95%CI: 1.82-4.44,  $P < 0.01$ ) when HBsAb was negative in addition to a positive HBcAb.

## DISCUSSION

In this study, HCC and advanced liver disease, shown by higher transaminases, lower albumin and platelet count and prolonged prothrombin time were associated with increased frequency of HBcAb(+) among patients with CHC. Previous studies have also noted an increased association of HBcAb(+) with advanced liver disease and HCC<sup>[1,11,12,14,16,18]</sup>. However, these data, as well as a prospective study<sup>[16]</sup>, originated from regions of relatively high prevalence for both chronic hepatitis B and HCC. Our study presents findings from an area of relatively low endemicity in a population comprised predominantly of urban African-Americans, yet the prevalence of HBcAb(+) was even higher in our study (74%) than previously reported<sup>[11,14]</sup>. Multivariate analysis restricted to this group of patients revealed a much stronger association of LHB with HCC (Table 3). Our study included a total of 418 African-American patients and is by far the largest analysis studying this association in a select group.

Certain potential limitations to our study need further discussion. A majority of patients with HCC (66%) were diagnosed by histopathology. This is largely due to inclusion of patients before the EASL non-invasive criteria

**Table 3** Univariate analysis predicting the following

	OR (95%CI)	P value
HCC in patients with CHC		
HBcAb(+)	1.90 (1.28-3.04)	0.02
HBsAb(-) and HBcAb(+)	3.24 (2.28-4.62)	< 0.01
HCC in cirrhotic patients with CHC		
HBcAb(+)	1.54 (1.18-2.54)	0.02
HBsAb(-) and HBcAb(+)	2.14 (1.68-3.82)	0.01
HCC in patients with CHC when controlled for covariates <sup>1</sup>		
HBcAb(+)	1.84 (1.22-3.08)	0.01
HBsAb(-) and HBcAb(+)	2.98 (2.12-5.08)	< 0.01
HCC in cirrhotic patients with CHC when controlled for covariates <sup>1</sup>		
HBcAb(+)	1.66 (1.22-3.24)	0.01
HBsAb(-) and HBcAb(+)	2.10 (1.72-4.04)	< 0.01
HCC in cirrhotic African American patients with CHC when controlled for covariates <sup>1</sup>		
HBcAb(+)	2.08 (1.42-3.6)	< 0.01
HBsAb(-) and HBcAb(+)	2.58 (1.82-4.44)	< 0.01

<sup>1</sup>Body mass index, albumin, prothrombin time, human immunodeficiency virus co-infection and alcohol consumption. HCC: Hepatocellular carcinoma; CHC: Chronic hepatitis C; HBcAb: Hepatitis B surface antibody; HBsAb: Hepatitis B core antibody.

for diagnosis of HCC were proposed<sup>[17]</sup>. One could argue that lack of RNA confirmation of CHC viremia in 40% of our cases detracts from our conclusions. However, patients with or without RNA confirmation of HCV viremia had similar baseline characteristics and no other etiology for their liver disease, and were therefore appropriately grouped together. Alcohol consumption is a well established risk factor for HCC among patients with chronic liver disease. In the present study, details pertaining to alcohol consumption were not available in some patients despite extensive review of both inpatient and outpatient medical records. Every effort was made to classify patients based on alcohol consumption when information was available. Controls, who were drawn from a prospectively maintained institutional database were more likely to have reliable information regarding alcohol intake. Nevertheless, in concurrence with previous literature, our results suggest that BMI and alcohol consumption play an important role in the progression to HCC in cirrhotics with CHC.

Although the majority of patients with HCC were drawn from an outpatient setting, some were hospitalized and likely sicker. Controls were selected from a predominantly outpatient database. This may account for the significantly higher AFP and transaminases in the CHC patients with HCC. Although PCR measurement of serum HBV DNA assessment was not accomplished in our patients, we do not consider this as a significant limitation. In previous studies, HBcAb had a stronger association with HCC than serum HBV DNA among patients with CHC<sup>[5,6]</sup>. Latent hepatitis B, defined as a previous exposure to hepatitis B [HBcAb(+) and HBsAg(-)] is a clinically more relevant tool for predicting risk for HCC than is the assessment of HBV DNA in serum or liver tissue.

Another limitation to the study is that the frequency

of smoking, injection drug use and diabetes was not analyzed. Patients with HIV-HCV co-infection have rapid progression of liver disease and development of HCC. Liver disease is the leading cause of mortality in these patients<sup>[19-21]</sup>. Of 20 patients with HIV-HCV coinfection, 11 patients had HCC and all 11 were HBcAb(+) compared to 40% among coinfecting controls. Although this difference did not achieve statistical significance, due to low numbers, this raises the intriguing observation that HIV-HCV coinfecting patients with HCC may have an increased frequency of LHB.

Our study is consistent with previous studies from areas with high prevalence of hepatitis B that suggests that LHB increases the risk for HCC. Furthermore, patients sero-negative for HBsAb are at even higher risk, which may suggest longer time since acquisition of HBV. Our data also suggest that African-Americans have a greater risk of HCC when associated with LHB. There is additional data from our institution (preliminary) to support the observation that patients with CHC and LHB are more likely to have advanced liver disease and respond poorly to Interferon-based therapies. The current study takes this concept further by associating LHB with HCC.

In conclusion, LHB occurs at a significantly increased frequency in patients with CHC and HCC than in patients with CHC without HCC. This association is even stronger in African Americans. It is important to recognize this risk during surveillance for HCC in these patients.

## COMMENTS

### Background

Patients with chronic hepatitis C (CHC) and cirrhosis have an increased risk of developing hepatocellular carcinoma (HCC). Several risk factors for this progression have so far been identified. The authors studied the potential association between HCC in patients with CHC, cirrhosis and latent hepatitis B (LHB) infection, defined as the absence of detectable serum hepatitis B surface antigen (HBsAg) and the presence of hepatitis B core antibody (HBcAb).

### Research frontiers

LHB has recently received significant attention among researchers and clinicians managing chronic liver disease. It is defined as a combination of HBsAg(-) and HBcAb(+). The potential association of LHB with HCC among patients with chronic CHC has been studied and reported in this manuscript.

### Innovations and breakthroughs

Interestingly, subset analysis among human immunodeficiency virus-CHC co-infected patients showed a 100% association of HCC with LHB suggesting much higher association in this group. This identifies a unique group of CHC patients at much higher risk for development of HCC.

### Peer review

Risk factors for HCC in patients with chronic hepatitis C are only partially understood. Here the authors showed that there is a clear association between latent hepatitis B infection and HCC development in an area with low endemicity for chronic hepatitis B.

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