Journal of Primary Care & Community Health
Volume 15: 1–7

DOI: 10.1177/21501319241259413
journals.sagepub.com/home/jpc
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Risk Factors and Comorbidities Associated With Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Virus Infection

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Abstract

Introduction/Objectives: Chronic hepatitis B virus infection (CHBVI) is a major public health problem affecting about 296 million people worldwide. HBV infects the liver, and when it becomes chronic, may cause cirrhosis and hepatocellular carcinoma (HCC). The aim of our study was to identify the risk factors and comorbid medical conditions that were associated with HCC in patients who had CHBVI. **Methods:** We performed a retrospective electronic medical record review of adult patients diagnosed with CHBVI, who presented to our primary care office between October 1, 2017 and October 21, 2022. Selected variables in patients with CHBVI with HCC (HCC group) were compared to those without HCC (NoHCC group). **Results:** Among 125 patients with CHBVI, 24% had HCC and 76% did not have HCC. There were higher frequencies of association of certain comorbidities in the HCC group compared to NoHCC group, such as anemia (63.3% vs 26.3%; $P < .001$), ascites (53.3% vs 1.1%; $P < .001$), portal hypertension (43.3% vs 0.0%; $P < .001$), chronic kidney disease (40.0% vs 13.7%; $P = .002$), and HCV coinfection (13.3% vs 7.4%; $P < .001$). The logistic regression model showed increased odds of HCC for each year of increase in age (OR = 1.06, 95% CI = 1.01-1.11; $P = .014$), and increased odds in men (OR = 5.96, 95% CI = 1.71-20.73; $P = .005$). Although Asians represented the racial majority in both the groups, there was no significant difference in the race distribution between the two groups. **Conclusion:** In patients with CHBVI, increasing age and male sex are factors associated with increased odds of having HCC. Patients with CHBVI and HCC have higher frequencies of association of tobacco use, recreational drug use, anemia, ascites, portal hypertension, chronic kidney disease, and co-infection with HCV.

Keywords

hepatocellular carcinoma, chronic hepatitis B virus infection, HCC in HBV, hepatoma in HBV, Risk of hepatoma in chronic HBV infection

Dates received: 20 March 2024; revised: 15 May 2024; accepted: 17 May 2024.

Introduction

Chronic hepatitis B virus infection (CHBVI) is a major public health problem affecting about 296 million people worldwide.[1] CHBVI represents HBV infection lasting for more than 6 months. The hepatitis B virus (HBV) is a double stranded DNA virus that infects the liver, and in some cases may progress to cirrhosis and/or hepatocellular carcinoma (HCC), eventually causing premature death. HBV, along with hepatitis C virus (HCV), is the most important global risk factor for HCC.[2] The World Health Organization estimated that hepatitis B resulted in 820 000 deaths from cirrhosis and hepatocellular carcinoma in 2019.[1] Previous research studies have shown that CHBVI accounts for approximately 50% of HCC cases globally, which is the leading cause of death in those with chronic HBV.[3] Despite long-standing viral suppression medications, HCC

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continues to occur at a significantly increased rate in patients with chronic HBV infection.

Many non-modifiable and modifiable risk factors are believed to be associated with progression to HCC in patients with CHBVI. Among those factors are demographic characteristics, such as sex, age, ethnicity, and a family history of CHBVI; viral factors, such as elevated HBV DNA levels, coinfection with HCV or HIV; and environmental factors, such as alcohol use, tobacco use, obesity, and diabetes mellitus.[2,3] Most previous studies have looked at particular risk factors by themselves, but did not consider their relative importance compared to others not included in the studies. As such, identifying additional risk factors and comorbidities associated with the progression of HBV to HCC may allow avenues to explore interventions to improve the prognosis and treatment of patients with CHBVI who are at risk of HCC. Our aim was to identify the risk factors and comorbidities that were associated with HCC in adult patients with CHBVI. We hypothesized that some of the risk factors were more strongly associated with HCC in patients with CHBVI compared to others, such as age, race, sex, alcohol use, tobacco use, obesity, acetaminophen use, hyperlipidemia, diabetes mellitus (DM), coinfection of HCV, chronic kidney disease (CKD), and ascites.

Materials and Methods

Study Design and Setting

Our study was a retrospective study that utilized convenience sampling of the existing electronic medical records of an entire cohort of adult patient population who received medical care in our suburban internal medicine primary care office, which is a part of a large urban not-for-profit tertiary healthcare system.

Participants

The inclusion criteria of our study were adult patients who were 18 years of age, or older, with a documented diagnosis of CHBVI, who received medical care between October 1, 2017 and October 31, 2022. Our exclusion criteria were patients younger than 18 years of age, and patients who had no chronic HBV infection.

Variables

We collected the following data for each patient from their existing electronic medical records: demographics, such as age, race, gender; modifiable risk factors, such as alcohol use, tobacco use, recreational use of drugs, body mass index (BMI); medication use, such as non-steroidal anti-inflammatory drugs (NSAID), treatment with tenofovir, treatment with interferons; certain comorbid medical conditions, such as hypertension, hyperlipidemia, hypothyroidism, cerebrovascular accident (CVA), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), asthma, gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD), anemia, diabetes mellitus (DM), hepatitis D virus (HDV) coinfection, HCV coinfection, human immunodeficiency virus (HIV) coinfection, ascites, portal hypertension; and laboratory parameters, such as blood / serum levels of total bilirubin, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), prothrombin time (PT), international normalized ratio (INR), albumin, hemoglobin, alpha-fetoprotein (AFP), and HBV DNA viral load. The laboratory values obtained at the time nearest to the diagnosis were utilized. We recorded the collected data into a Microsoft Excel (2016, Redmond, Washington, USA) spreadsheet.

Data Source and Access

Our study was reviewed and approved by the Institutional Review Board (IRB) of our healthcare system (IRB 22-218). Authorization was granted to utilize the materials gathered exclusively for research purposes in accordance with the Health Insurance Portability and Accountability Act (HIPPA) requirements. Informed consent waivers were granted by the IRB. The study adhered completely to the ethical standards set forth by the IRB. All investigators were granted access to the data available in the Epic healthcare software (Epic Systems Corporation, Wisconsin, USA) electronic medical records.

Bias

In order to minimize the potential for inappropriate diagnostic inclusion, we excluded patients who had HCC due to causes other than HBV, such as HCV without HBV infection, non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), alcohol without HBV infection, Aflatoxin B1, disorders associated with hepatic iron overload, glycogen storage disease, Wilson's disease, alpha-1 antitrypsin disease, Alagille syndrome, history of porphyria, and hypercitrullinemia.

Study Sample Size

In our internal medicine primary care office database we found a total of 169 patients diagnosed with HBV infection who received care between October 1, 2017 and October 31, 2022. However, we found that only 125 patient records accurately depicted the diagnosis of CHBVI and had all pertinent data variables available. Hence, we enrolled the entire population of 125 patients diagnosed with CHBVI.

Statistical methods

We performed statistical analysis by using the SPSS (Statistical Package for the Social Sciences, version 15.01, IBM, Armonk, New York, USA) software. Patients were divided into 2 groups. The first group of patients included those who had CHBVI with HCC (HCC group); and the second group of patients included those who had CHBVI without HCC (NoHCC group). For the continuous variables, we ran a test of skewness to determine whether the data is normally distributed or nonparametric. Independent *t*-test was performed on normally distributed data and Mann-Whitney *U* test was performed on the non-parametric data. For the categorical variables, Pearson chi square tests were used. Additionally, we used logistic regression where HCC was the outcome variable. The statistical significance in this study was defined as $P < .05$.

Results

We had a total of 11 507 adult patients in our practice. We identified 169 patients who had a diagnosis of CHBVI in their problem lists. However, 44 patients had neither supporting lab tests results, nor the available test results that aligned with the diagnosis of CHBVI. Hence, those 44 patients were excluded from the study. The remaining 125 patients had supporting lab test results that aligned with the diagnosis of CHBVI. All 125 patients had a diagnosis of CHBVI for more than 10 years. Among 125 patients with CHBVI, 30 patients (24%) had HCC and 95 patients (76%) did not have HCC. The mean age of the patients in the HCC group was significantly greater than the NoHCC group (63.4 ± 8.6 years vs 55.1 ± 13.3 years; $P < .001$). There were significantly more men in the HCC group compared to the NoHCC group (Table 1). Although Asian race represented the majority in both the groups, there was no statistically significant difference in the race distribution between the 2 groups. In the HCC group, there were higher frequencies of use of tobacco, alcohol, and other recreational drugs; especially, greater use of tobacco and recreational drugs were statistically significant (Table 1). Patients in both groups had their mean BMIs in the overweight categories; however, the difference was not statistically significant. There was a positive family history of HCC in 13.3% of the patients in the HCC group and in 12.6% in the NoHCC group, which was not significantly different. Compared to the NoHCC group, patients in the HCC group had significantly lower hemoglobin and serum albumin levels; and significantly higher levels of BUN, ALP, AST, ALT, total bilirubin, GGT, PT, INR, AFP, and HBV DNA viral load (Table 1).

There were higher frequencies of association of certain comorbidities in the HCC group compared to NoHCC group, such as anemia (63.3% vs 26.3%; $P < .001$), ascites (53.3% vs 1.1%; $P < .001$), portal hypertension (43.3% vs 0.0%; $P < .001$), CKD (40.0% vs 13.7%; $P = .002$), and HCV coinfection (13.3% vs 7.4%; $P < .001$; Figure 1). The frequencies of associations of comorbidities, such as hypertension, hyperlipidemia, DM, hypothyroidism, CVA, CHF, COPD, asthma, GERD, IBD, and anemia were comparable between the 2 groups (Figure 1).

Among the medication usage, Tenofovir was the most frequently administered anti-HBV therapy in both the groups followed by Entecavir, Lamivudine, and Interferon. However, the differences were not statistically significant (Figure 1). Similarly, the use of acetaminophen and NSAIDs were comparable between the 2 groups (26.7% vs 34.7%; $P = .412$) and (36.7% vs 40.0%; $P = .744$) respectively (Table 1).

The logistic regression model showed that for each year increase in the age, there was a 1.06% increase in the odds of HCC (95% confidence interval (CI) 1.01 - 1.11; $P = .014$). Compared to females, men had 5.96 greater odds of developing HCC (odds ratio (OR) 5.96, 95% CI 1.71 - 20.73; $P = .005$; Table 2).

Discussion

In our study, we found that the association of factors in patients with CHBVI and HCC were increasing age and male sex. Among the patients with CHBVI and HCC, we also found higher frequencies of association of tobacco use, recreational drug use, anemia, ascites, portal hypertension, CKD, and co-infection with HCV.

Increasing age and its association with HCC in patients with chronic HBV infection has been reported in a systematic review and meta-analysis,[4] and by a number of the studies, including some of the studies that have used age in their risk prediction models as well, such as CU-HCC,[5] GAG-HCC,[6] D2AS,[7] REACH-B,[8] REACH-B IIb,[9] and AGED.[10] Increasing age has been associated with shortening of telomeres in the liver and aberrant DNA methylation that can result in carcinogenesis.[11] Genomic instability, changes in gene expression, somatic mutations, and DNA methylation, have been observed with aging which promote the development of HCC.[12] Additionally, increasing age also reflects longer exposure to HBV.[13] Our finding of association of increasing age as a risk factor for HCC in patients with CHBVI aligns with the existing literature.

Male sex has been widely accepted as a known risk factor for the development of HCC in patients with CHBVI.[14] The risk ratio of males to females in developing HBV-related HCC is 2.9 to 3:1.[13,15] Some studies indicate a direct role of androgens in the genesis of HCC.[16] Some studies have found that estrogen is protective against the development of HCC.[17] While the exact mechanisms of such protection remains unclear, it has been found that estrogen

Table 1. Baseline Characteristics.

	Variable	HCC group (n = 95)	No HCC group (n = 30)	*P*
Age, mean (SD)	Years	55.1 (13.3)	63.4 (8.6)	<.001
Sex, n (%)	Male	40 (42.1)	26 (86.7)	<.001
	Female	55 (57.9)	4 (13.3)	
Race, n (%)	White	16 (16.8)	9 (30.0)	.268
	Black	10 (10.5)	5 (16.7)	
	Asian	56 (59.0)	13 (43.3)	
	Other	13 (13.7)	3 (10.0)	
Social, n (%)	Tobacco use	33 (34.7)	22 (73.3)	<.001
	Alcohol use	27 (28.4)	14 (46.7)	.063
	Recreational drug use	5 (5.3)	7 (23.3)	.008
Weight, mean (SD)	BMI (kg/m^2)	27.1 (6.9)	27.6 (5.0)	.716
Family Hx, n (%)	HCC	12 (12.6)	4 (13.3)	1.000
Lab values, mean (SD)	Hb (g/dL)	13.6 (1.6)	11.8 (3.2)	.006
	BUN (mg/dL)	16.4 (9.8)	27.1 (20.9)	.010
	ALP (IU/L)	77.8 (41.2)	195.9 (149.3)	<.001
	Alb (g/dL)	4.3 (0.5)	3.3 (0.8)	<.001
Lab values, (median, 25th-75th)	AST (U/L)	22.00 (18.00-27.00)	73.00 (41.00-124.75)	<.001
	ALT (U/L)	20.00 (15.00-28.00)	38.00 (24.00-58.50)	<.001
	Bilirubin (mg/dL)	0.50 (0.30-0.70)	1.25 (0.68-3.83)	<.001
	GGT (U/L)	25.50 (15.50-44.50)	45.50 (35.25-107.50)	.002
	PT (s)	11.70 (10.70-13.00)	16.80 (12.00-24.25)	<.001
	INR	1.10 (1.00-1.20)	1.55 (1.10-2.18)	<.001
	AFP (ng/mL)	2.80 (1.80-4.40)	25.50 (3.40-1346.50)	<.001
	HBV DNA (IU/mL)	0.00 (0.00-550.00)	21.00 (0.00-3385.25)	.016
Comorbidities, n (%)	Hypertension	38 (40.0)	12 (40.0)	1.000
	Hyperlipidemia	51 (53.7)	13 (43.3)	.323
	DM	18 (18.9)	4 (13.3)	.481
	Hypothyroidism	4 (4.2)	2 (6.7)	.629
	CVA	2 (2.1)	0 (0.0)	1.000
	CHF	2 (2.1)	3 (10.0)	.089
	COPD	7 (7.4)	3 (10.0)	.702
	Asthma	8 (8.4)	0 (0.0)	.197
	GERD	43 (45.3)	13 (43.3)	.853
	IBD	0 (0.0)	1 (3.3)	.240
	Anemia	25 (26.3)	19 (63.3)	<.001
	Ascites	1 (1.1)	16 (53.3)	<.001
	Portal HTN	0 (0.0)	12 (43.3)	<.001
	CKD	13 (13.7)	40 (40.0)	.002
	HDV coinfection	5 (5.3)	0 (0.0)	.200
	HCV coinfection	7 (7.4)	4 (13.3)	<.001
Medications, n (%)	Acetaminophen	33 (34.7)	8 (26.7)	.412
	NSAIDs	38 (40.0)	11 (36.7)	.744
	Lamivudine	5 (5.3)	3 (10.0)	.397
	Tenofovir	21 (22.1)	10 (33.3)	.214
	Interferon	0 (0.0)	2 (6.7)	.056
	Entecavir	11 (11.6)	4 (13.3)	.755

Abbreviations: AFP, alpha fetoprotein; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GERD, gastroesophageal reflux disorder; GGT, gamma-glutamyl transferase; Hb, hemoglobin; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HCV, Hepatitis C virus; HDV, hepatitis D virus; IBD, inflammatory bowel disease; INR, international normalized ratio; NSAIDs, non-steroidal anti-inflammatory drugs.; Portal HTN, portal hypertension; PT, prothrombin time; SD, standard deviation

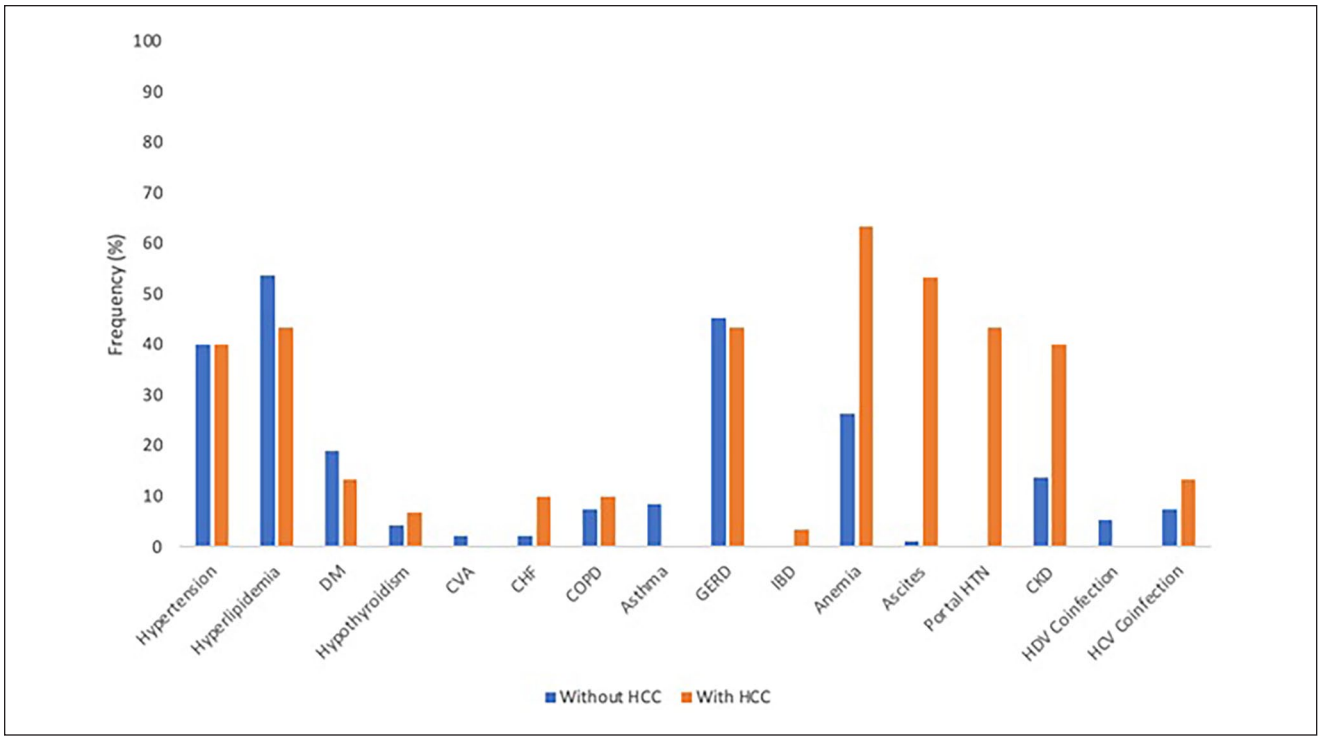

Figure 1. Frequencies of comorbidities.

Table 2. Influence of Risk Factors on HCC.

				95% CI for Exp(*B*)	
Risk factor	*B*	*P*	Exp(*B*)	Lower	Upper
Age	.056	.014	1.058	1.011	1.106
Sex male	1.785	.005	5.959	1.713	20.731
Body mass index	.007	.895	1.007	0.910	1.114
Black vs White	.111	.900	1.117	0.199	6.267
Asian vs White	−.484	.483	0.616	0.159	2.384
Other races vs White	−.732	.408	0.481	0.085	2.723
Tobacco use	.244	.199	1.276	0.880	1.850
Alcohol use	.045	.937	1.046	0.349	3.130
Recreational drug use	1.003	.225	2.726	0.540	13.764

Abbreviations: *B*, beta weight; CI, confidence interval; Exp(*B*), odds ratio; P, significance

inhibits interleukin-6, which may be casual or contributory to HCC in patients with chronic HBV infection.[18,19] Estrogen also up-regulates ER-alpha receptor, which alters the binding of hepatocyte nuclear factor-4 alpha to the HBV enhancer I, repressing the transcription of HBV genes.[20] This is consistent with the findings observed in some of studies in which women had a lower HBV viral load compared to men.[13] Moreover, an active androgen pathway regulates the host's immune response to HBV which influences the expression of HBV-targeting micro-RNAs, and assists in HBV chromosomal integration.[21]

We found significant association of tobacco use and recreational drug use with HCC in patients with CHBVI. There is sufficient evidence in the literature to support a causal relationship between smoking and HCC,[22] and our results are consistent with those results. Experimental studies have identified 2-acetylaminofluorene, 4-aminobiphenyl, and other constituents in inhaled tobacco as hepatocarcinogens.[22] We found no significant difference in the use of alcohol, which does not align with the existing literature. A meta-analysis of more than 340 000 patients found that alcohol use significantly increased the incidence of HCC in

patients with chronic HBV infection (relative risk = 2.1; 95% CI = 1.0–4.6).[23] Other studies have shown only a modest correlation between light-to-moderate alcohol intake and HCC, whereas heavy alcohol consumption significantly hastened the progression to HCC.[24] The lack of association with alcohol consumption in our patients with CHBVI and HCC could be attributed to patients being classified as alcohol users based on documentation in the patients' social history, without distinguishing between social or hazardous use of alcohol.

In our study, anemia was strongly associated with the group of patients with CHBVI who had HCC. It has been shown that the degree of anemia correlates with the severity of liver insufficiency, as well as the prognosis of HCC patients, as anemia has the potential to trigger tumor hypoxia, which makes it more chemo-resistant to chemotherapeutics.[25] The study also reported that low hemoglobin levels were associated with mortality, independent of differing patient parameters. The study concluded that anemia should be considered a risk factor for HCC.[25]

Portal hypertension, increased pressure within the portal venous system, has been found to be an independent predictor of HCC development.[26] This is consistent with the findings in our study, which showed higher frequencies of association between portal hypertension and HCC in patients with CHBVI. Additionally, ascites has many etiologies, including portal hypertension, liver cirrhosis, and long-term alcohol overuse. Studies have found that 80% of ascites cases result from portal hypertension secondary to liver cirrhosis.[27]

Association of CKD has been commonly reported in patients with cirrhosis, and is usually associated with ascites, which indicates a more complex course of liver disease.[27] A longitudinal study evaluating comorbidities in patients with chronic HBV infection over a 15 years period found a 4.5 fold increase in the risk of CKD.[28] Another study reported the relationship between HCC and CKD, and proposed several mechanisms of CKD leading to HCC, which include uremia, long-term use of dialysis, use of immunosuppressive agents, and hormonal alterations.[29] The study investigators also examined the possibility of HCC leading to CKD, which involved mechanisms, such as tumor invasion and hepatorenal syndrome.[29] Our finding of CKD with HCC in patients who had CHBVI aligns with these reports. Further research is warranted to determine the exact nature of the association between HCC and CKD.

Independently, HCV is a causative factor in the development of HCC,[2] hence it was expected that coinfection with HBV would result in greater association with HCC, which was congruent with our study.

Our study had some limitations. Although the majority of the patients' medical records had the documentation of the date of HBV infection by more than 10 years prior to the date of the diagnosis of HCC; nevertheless, the date of HBV infection was not clearly mentioned in some patients who had HCC, and they only had a documentation in the progress notes which stated that they had been diagnosed with chronic HBV infection without the documentation of a specific date. The data regarding sexual activity, injection versus inhalation drug use, educational level, and income were not consistently available in the medical records, hence we had to exclude those variables. Our patients in this study represent a suburban population, hence our findings cannot be generalized. The major strength of our study was that all the patients followed with the same internal medicine practice for more than 2 decades which allowed the care team to document comorbidities and other variables chronologically over a long period of time.

Conclusion

In patients with CHBVI, increasing age and male sex are factors associated with increased odds of having HCC. Patients with CHBVI and HCC have higher frequencies of association of tobacco use, recreational drug use, anemia, ascites, portal hypertension, CKD, and co-infection with HCV.

Acknowledgments

The authors thank Christine Rickette, RN (study coordinator) for her contribution to this study.

Author Contributions

HW and SR made substantial contributions to the study design, drafting, data acquisition and analysis, and manuscript writing. All authors contributed in data collection and manuscript writing and review. KH analyzed the data. SR contributed in revising the manuscript critically for improved intellectual content, and final approval for the version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed Consent

Not applicable. Being a retrospective chart review study the Institutional Review Board waived the need for informed consent.

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Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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