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Original article

Incidence of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Infection: A Retrospective Cohort Study (2013–2023) in Lima, Peru

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Abstract

Introduction: Chronic hepatitis B virus (HBV) infection increases the risk of hepatocellular carcinoma (HCC). HCC-related mortality ranks as the second leading cause of cancer death worldwide. This study aimed to determine the incidence of HCC in patients with chronic hepatitis B infection within a Peruvian population. **Materials and Methods:** This was a retrospective, observational cohort study of patients with chronic HBV infection treated at the Hospital Nacional Arzobispo Loayza between 2013 and 2023. **Results:** A total of 84 patients were included. The median age was 46 years, and 29% had liver cirrhosis at the start of the study. The median follow-up period was 66 months (range: 64–87). At baseline, 87% of patients were receiving antiviral therapy. The cumulative incidence of HCC at 5 and 10 years was 1.2% and 2.5%, respectively. **Conclusions:** Over a ten-year follow-up period, the low incidence of HCC in patients with chronic HBV infection may be associated with timely treatment and individualized monitoring. Further research is needed to validate these findings.

Keywords

Chronic hepatitis B, incidence, hepatocellular carcinoma, antiviral therapy, liver cirrhosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) in Peru is not uncommon, and its capital, Lima, has the highest incidence in our continent (4.78 x 100,000 inhabitants), and the first cause is Hepatitis B infection[1,2]. Chronic hepatitis B infection has an oncogenic potential and a tendency to develop HCC in patients without liver cirrhosis[3]. In several cities in the interior of Peru, chronic Hepatitis B infection is endemic[1], which has probably contributed to the current scenario, in which HCC mortality is the second leading cause of death from cancer[4]. It is important to highlight the identification of people at high risk of developing HCC among chronic hepatitis B carriers, with an emphasis on treatment and follow-up. For this reason, different predictive models for the development of HCC have been developed and validated[5]. Potential clinical applications of these risk scores include prognosis and patient selection for antiviral therapy and individualized surveillance.

In Peru, little information is available on the incidence of HCC in patients with chronic hepatitis B infection. The importance of recognizing patients at higher risk lies in a more active follow-up, considering that only up to 40% of patients with HCC can achieve a functional cure due to late diagnosis[6].

In view of the above, the present research work aims to determine the incidence of HCC in patients with chronic

hepatitis B infection in a Peruvian population at a national referral hospital.

MATERIALS AND METHODS

It is a retrospective observational cohort study. Our study applied the STROBE checklist for observational studies. The clinical records of patients with chronic hepatitis B virus infection at the Hospital Nacional Arzobispo Loayza attended between 2013 and 2023 were evaluated. The inclusion criterion was mono-infection with hepatitis B virus, defined by the presence of positive surface antigen (HBsAg) for at least six months and a follow-up of at least five years in our center. Patients with co-infection with human immunodeficiency virus (HIV), previous diagnosis of HCC, co-infection with other viral hepatitis and patients under immunosuppressive treatment for autoimmune diseases at the start of follow-up were excluded.

Procedures and variables

The demographic and biochemical variables of the medical records that met the selection criteria were evaluated. Risky alcohol consumption was defined with consumption ≥20 g of alcohol per day or ≥140 g per week for men and ≥10 g of alcohol per day or ≥70 g per week for women[7]. The diagnosis of liver cirrhosis was made based on clinical, biochemical, imaging, and elastographic parameters, as well as liver biopsy when available[8]. A diagnosis of HCC was made with the presence of LI-RADS-5 lesions or observations on three-phase contrast-enhanced tomography[9]; diabetes mellitus was defined by two fasting glucose measurements of >126 mg/dL or glycosylated hemoglobin >6.5%; hypertension was defined as systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg on at least two occasions; obesity was considered as body mass index >30, and dyslipidemia was defined by a high-density lipoprotein (HDL) level <40 mg/dL in males, HDL <50 mg/dL in females, low-density lipoprotein (LDL) >160 mg/dL, or triglycerides >150 mg/dL.

Additionally, seven predictive indices for hepatocellular carcinoma were calculated at the beginning of the study:

- REACH-B: this score was calculated using sex, age, alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg), and HBV DNA levels, with values assigned according to the criteria established by Yang et al.[10]. Subsequently, based on the total score, the 5-year HCC risk was classified as follows: low (0-5 points), intermediate (6-11 points), and high (12-18 points).
- PAGE-B: This score was calculated using sex, age, and platelet count, with point values defined by Papatheodoridis et al.[11]. Based on the total score, the risk of HCC was classified as low (<10 points), intermediate (10-17 points), and high (>17 points).
- mPAGE-B: this score was calculated using sex, age, platelet count, and albumin levels. Points were assigned according to the method described by Kim et al.[12]. Based on the total score, HCC risk was stratified as low (≤8 points), intermediate (9-12 points), and high (≥13 points).
- aMAP: to apply the risk formula established by Fan R et al.[13], the following variables were used: sex, age, platelet count, albumin levels, and total bilirubin. Based on the resulting score, HCC risk was classified as low (0-50 points), intermediate (51-60 points), and high (61-100 points).
- CU-HCC: to calculate the total score as established by Wong et al.[14], the following variables were used: age, HBV DNA viral load, albumin levels, total bilirubin, and presence of cirrhosis. Based on the final score, patients were classified as low risk (<5 points), intermediate risk (5-19 points), and high risk (>19 points).
- GAG-HCC: In order to apply the formula described by Yuen et al.[15], the variables used were sex, age, HBV DNA viral load, and presence of cirrhosis. Based on the score, patients were classified as low risk (<100 points) and high risk (≥100 points).
- LSM-HCC: In order to estimate the risk, the variables used were age, HBV DNA viral load, albumin levels, and liver transient elastography. Scores were assigned based on the publication by Wong G et al.[16]. According to the total score, patients were classified into two groups: low risk (0-10 points) and high risk (11-30 points).

Follow-up data were collected retrospectively from medical records up to the last recorded evaluation, diagnosis of HCC, or date of death.

Statistical analysis

Qualitative variables were expressed as absolute frequencies and percentages. Quantitative variables were expressed as medians and interquartile ranges. The cumulative incidence of HCC at 5 and 10 years was evaluated. RStudio version 4.2.1 statistical software was used for the analysis.

Ethical considerations

The study protocol was approved by the ethics committee of the Hospital Nacional Arzobispo Loayza (No. 041-DG-HNAL/2023). The study was developed in accordance with the recommendations of the latest update of the Declaration of Helsinki (Fortaleza, Brazil, October 2013). The present study did not require informed consent, since

no intervention was performed. In addition, patients' personal information was encrypted to prevent identification. The data collected were stored and managed exclusively by the authors of the study.

RESULTS

Patient characteristics

A total of 135 medical records were evaluated and, after applying the selection criteria, 84 patients were included in the study (**Figure 1**).

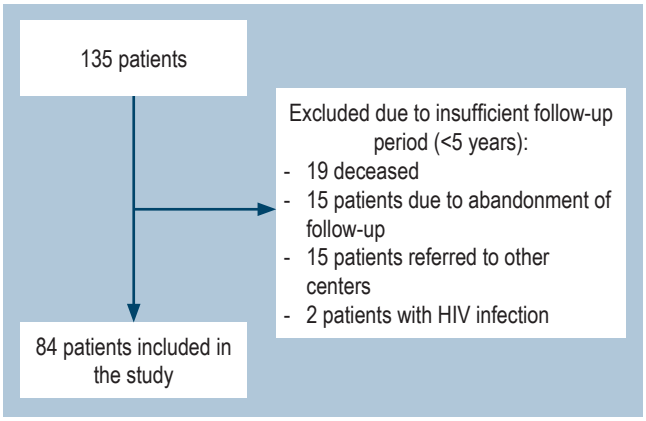

Figure 1. Flow Chart for Patient Selection in the Study. The image is the property of the authors.

The median age was 46 years, 55% of the population was male and 29% had a diagnosis of liver cirrhosis at the beginning of the study, using the Baveno VII criteria (clinical, biochemical, imaging or elastographic criteria). The median follow-up was 66 (64-87) months. Among the comorbidities, risky alcohol consumption was the most prevalent (15%), followed by dyslipidemia and obesity (8% and 6%, respectively). At the time of inclusion in the study, 87% of the patients were under medical treatment with antivirals (73 patients with tenofovir disoproxil fumarate).

Complete biochemical and elastographic data were obtained from 68 patients at baseline, which are summarized in **Table 1**. According to the HCC predictive indices, more than 50% of patients were categorized as low HCC risk for aMAP, CU-HCC, GAG-HCC and LSM-HCC indices (**Figure 2**). Mortality at the end of the study was 18% (15 patients) (**Table 2**). Of the 15 patients, seven had liver cirrhosis (five died due to cirrhosis-related decompensations and two from HCC-related complications), and only one patient did not achieve a virological response during follow-up.

Table 1. General Characteristics of the Study Population

Clinical features	n = 84
Age (years)	46 (35-60)
Sex (%)	
- Male	46 (55)
- Female	38 (45)
Arterial hypertension (%)	3 (4)
Diabetes mellitus (%)	2 (2)
Alcohol risk consumption (%)	13 (15)
Dyslipidemia (%)	7 (8)
Obesity (%)	5 (6)
Fibrosis stage (%) (evaluated in 68 patients)	
- F1	33 (49)
- F2	11 (16)
- F3	6 (9)
- F4	18 (26)
Liver cirrhosis (%)	24 (29)
- Hepatitis B	21 (88)
- Alcohol + hepatitis B	3 (12)
Hepatitis B treatment (%)	73 (87)
Stages of infection at baseline (%)	
- Chronic inactive carrier	42 (50)
- HBeAg-negative chronic hepatitis	34 (40)
- Immunotolerant	4 (5)
- HBeAg-positive chronic hepatitis	4 (5)
Immunologic profile at baseline (%)	
- HBeAg positive	29 (35)
- Anti-HBe	41 (49)
Viral response to treatment (%)	70/73 (96)
Seroconversion to anti-HBe (%)	14/29 (48)

Anti-HBe: antibody against hepatitis B antigen; HBeAg: hepatitis B virus antigen. Table created by the authors.

Table 2. Causes of Death in the Study Population

Cause of death	n = 15 (%)
Hepatic cirrhosis decompensation	
- Gastrointestinal bleeding	3 (20)
- Spontaneous bacterial peritonitis	1 (7)
- Ascites	1 (7)
Community-acquired pneumonia	2 (13)
Covid-19 pneumonia	2 (13)
Sudden cardiac arrest	3 (20)
Complicated urinary tract infection	1 (7)
Hepatocellular carcinoma	2 (13)

Table created by the authors.

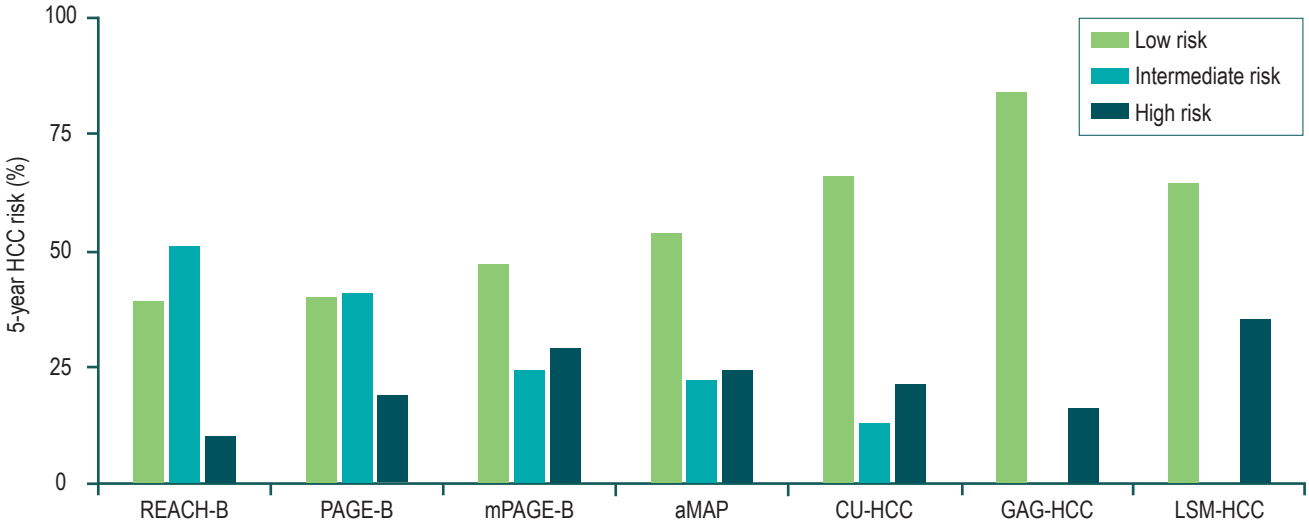

Figure 2. Categorization of Hepatocellular Carcinoma Risk According to the Predictive Index. The image is the property of the authors.

Cumulative incidence of hepatocellular carcinoma

At the end of the study, two people with liver cirrhosis since the start of the follow-up were diagnosed with HCC during the semiannual screening. The cumulative incidence of HCC at 5 and 10 years was 1.2% and 2.5%, respectively (**Figure 3**). Both cases were classified as high-risk according to the predictive indices used for cirrhotic patients at the beginning of the study. Likewise, they did not exhibit high-risk alcohol consumption or metabolic risk factors. It is important to highlight that only one patient with HCC in the follow-up achieved virological response (serum HBV DNA levels < 2000 U/mL).

DISCUSSION

To our knowledge, the present research work is the first Peruvian study that evaluates the incidence of hepatocellular carcinoma in patients with chronic hepatitis B virus infection over a ten-year period. Our result shows a long-term cumulative incidence lower than previously reported in our region[17-20]. Despite not having a control group, the present retrospective cohort demonstrates a decrease in the presence of HCC in patients under correct follow-up and treatment of hepatitis B virus infection. This result could be related to the higher percentage of patients under antiviral treatment (87%) and of patients with liver cirrhosis (29%), factors linked to the development of HCC.

The percentage of HCC is low compared to that published by Porto de Macedo et al. (2.5% vs. 3.5%)[17] and by Ferreira da Silva et al. (1.2% vs. 2.7%, cumulative incidence at 5 years)[18]. This result is related to the higher percentage of patients under antiviral treatment in our study (87% vs. 40-55%, respectively) and to an acceptable virological response (96%). Other risk factors for HCC include alcohol consumption and obesity[21]. However, these comorbidities did not prove to be the most prevalent in our follow-up cohort (15% and 6%, respectively). The two patients with HCC did not present these comorbidities and only one of them achieved a viral response. However, both patients had a diagnosis of liver cirrhosis, a proven risk factor for the development of HCC[3].

With respect to hepatitis B virus, the viral load determines a greater progression to hepatic fibrosis and greater development of HCC[22]. Antiviral treatment with tenofovir significantly reduces viral load in up to 95% of patients after twelve months of treatment, a result superior to that of entecavir[23]. In a meta-analysis by Choi Won-Mook et al.[24], which included 15 non-randomized studies and 61,787 patients, treatment with tenofovir was associated with a significant decrease in the incidence of HCC compared to entecavir (hazard ratio = 0.80 [0.69-0.93]; p = 0.003). Based on the above, the low number of patients with HCC in our study could be explained by the considerable proportion of patients treated with tenofovir (87% of patients with antiviral treatment), with a good virological response in the population studied (96%). The 13% who did not receive antiviral treatment had an HBV DNA <20,000 IU/mL at baseline follow-up, which confers a lower risk of developing HCC[25]

Regarding the distribution of the stages of chronic hepatitis B virus infection, a large percentage of patients (65%)

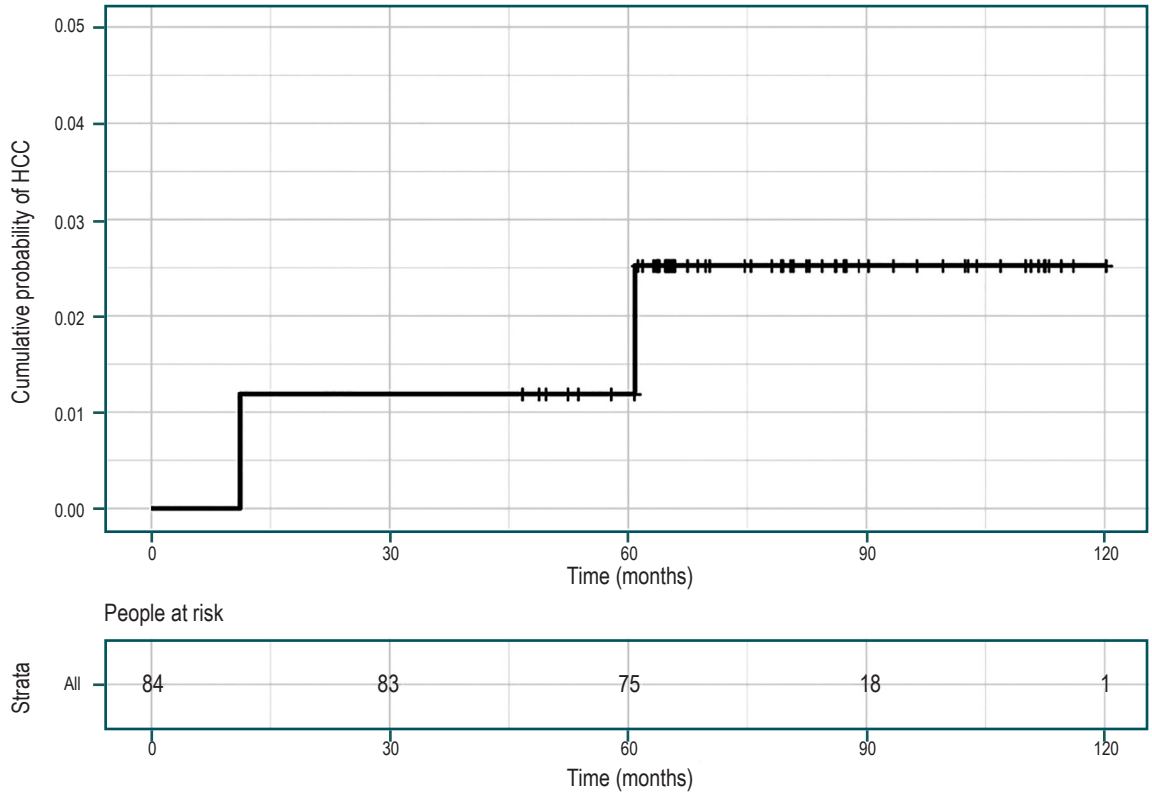

Figure 3. Cumulative Incidence of Hepatocellular Carcinoma in Patients with Hepatitis B Infection. The image is the property of the authors.

were HBeAg negative and had a seroconversion to anti-HBe under antiviral treatment of 48%. Hsu Y et al.[26], in their nine-year follow-up study in patients with HBeAg seroconversion, detected an incidence of HCC of 2.2%, a result similar to our study (2.5%). In addition, patients defined as immunotolerant have a higher risk of HCC than chronic inactive carriers[27]; however, initiation of antiviral treatment in well-selected immunotolerant patients would decrease the risk (immunotolerant patients with HBV DNA titers ≥20,000 IU/mL and older than 40 years)[25]. This characteristic of our population, added to the number of patients under treatment, could have influenced our findings.

Regarding primary prevention of HCC, the Latin American Association for the Study of the Liver (ALEH) does not specify the initiation of HCC screening in patients with hepatitis B virus infection without liver cirrhosis[28]. Currently, there are several long-term predictive indices for HCC in patients with or without liver cirrhosis and chronic hepatitis B infection[29]; however, validation of these indices in Latin American populations remains limited[17,18]. The two patients who developed HCC during follow-up had high scores on the predictive indices (PAGE-B and mPAGE-B) used in patients with liver cirrhosis. Despite this, the insufficient number of events does not allow any conclusions to be drawn regarding the usefulness of predictive indexes in other populations.

In Peru, the positive impact of hepatitis B vaccination as a national strategy for the reduction of complications of chronic infection, such as the development of HCC, has been corroborated[30]. Adding to this effort, in 2018, national guidelines for the treatment and follow-up of patients with chronic hepatitis B infection were published, recommendations based on the guideline published by the European Association for the Study of the Liver (EASL) [31]. Although the findings of the present study cannot be generalized to other populations, proper application of the guidelines would decrease the incidence of HCC, especially in patients who achieve virologic response. Based on the findings of this study, the importance of strict HCC surveillance in patients with liver cirrhosis from the time of diagnosis can be emphasized, as this risk factor may play a decisive role in the development of malignant liver lesions[3].

Limitations of the present study are associated with the retrospective nature of the investigation and the potential

incomplete data in the medical records. It is imperative to point out that the size of the population and the few events in our study (two patients with HCC) do not allow us to perform analyses to correlate variables, which could influence the explanation and inference of the findings. The small sample size was influenced by the referral of patients to their respective healthcare centers and by patient attrition during follow-up. The development of multicenter studies could reduce these limitations and biases in the future.

CONCLUSION

The low cumulative incidence of HCC, over a ten-year period, could be explained by compliance with timely treatment and follow-up of patients with hepatitis B virus infection in an independent Peruvian cohort. Further investigations with a larger sample of patients are necessary to validate the findings of the present study.

Authors' contributions

RZH, JGR and CCV contributed to the conceptualization and methodology of the study. RZH, WCC, EM and RM were in charge of data collection. RZH performed the statistical analysis. RM, WCC, JGR and CCV validated the results. All authors were involved in the transcription and approval of this manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest in this study.

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