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Hepatitis B Virus in Cirrhosis and Primary Livers Cancers

Boua-Akelelo Nathalie Philomène[1], Youssouf Oumarou[2*], Gambo Ignaleamoko Nuella Edwige[1], Yangba Kalebanga Armel[1], Elowa Jean Benoît[1], Kobelembi Mofini E[1], Bessanguem Bernard[1], Komaria Hermann[1], Service George[3], Kobelembi Armand[2], Camengo Police Serge Magloire[1]

[1]Service d'Hépato-Gastroentérologie, CHU de l'Amitié Sino-Centrafricaine, Bangui, République Centrafricaine
[2]Department of Internal Medicine, CHU Communautaire, Bangui, République Centrafricaine
[3]Department of Internal Medicine, CHU Maman Elisabeth Domitien, Bimbo, République Centrafricaine
Email: *yyoussouff@yahoo.fr

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Abstract

Introduction: Hepatitis B virus (HBV) infection is a public health problem in sub-Saharan Africa, due to its frequency and progression to complications such as cirrhosis and/or hepatocellular carcinoma (HCC). **Objective:** To help improve the management of cirrhosis and hepatocellular carcinoma. **Patients and Methods:** This was a 34-month cross-sectional study conducted in the Hepato-Gastroenterology Department of the CHU de l'Amitié Sino-centrafricaine in Bangui. It included patients of both sexes aged 18 years or older with a diagnosis of HBV-related cirrhosis and/or HCC. **Results:** During the study period, 1344 patients were admitted to hospital, 681 of them for chronic liver disease (51%). Among patients admitted for chronic liver disease, in particular cirrhosis and/or HCC, HBV was implicated in 288 cases (42.30%), of whom 170 (24.96%) met our inclusion criteria. These included 123 men (72.35%) and 47 women (27.65%). The sex ratio was 2.61. The mean age of our patients was 40 years (±11 years) with extremes of 18 and 76 years. Cirrhosis was observed in 101 cases (59.41%), HCC on cirrhosis in 59 cases (34.70%) and HCC in 10 cases (5.89%). Cirrhosis was classified as Child-Pugh B in 62 cases and C in 20 cases. HCC on cirrhosis was classified according to BCLC stage C in 7 cases and stage D in 52 cases. **Conclusion:** HBV is the leading cause of cirrhosis and HCC in the Central African Republic. Chronic liver disease is diagnosed at the advanced stage of the disease. Hence the importance of early detection, prevention through vaccination at birth, and management of infected patients.

Keywords

Hepatitis B Virus, Cirrhosis, Hepatocellular Carcinoma, Bangui

1. Introduction

Infection with the hepatitis B virus is a major public health problem, due to its frequency, complications and socio-economic consequences [1] [2] [3].

According to the World Health Organisation, 2 billion people have been infected with HBV in their lifetime, and 240 to 350 million are chronic carriers [4] [5] [6]. In Africa, the overall level of endemicity is high, with a north-south gradient. The Maghreb region, with a prevalence ranging from 2% to 8%, is described as an area of medium endemicity. The prevalence of HBsAg carriage is 4% - 7% in Tunisia, 1.66% in Morocco, 2% - 8% in Algeria and 1.3% - 5.8% in Libya [7]. The prevalence of chronic HBV infection in sub-Saharan Africa is between 8% and 20%, making it a highly endemic region [8] [9]. It is estimated at between 14.9% and 16.14% in Mali [10] [11] [12], 11% in Senegal [13] and 13.5% in Chad [14]. In the Central African Republic, the prevalence of hepatitis B varies from 10.6% to 19.8% depending on the study population [15] [16] [17] [18] [19]. Chronic hepatitis B infection carries a high risk of progression to cirrhosis and hepatocellular carcinoma (HCC). In 2010, chronic HBV infection was responsible for 786,000 deaths, 312,000 of which were attributable to cirrhosis and 341,000 to HCC. Hepatitis B is the 15^{ième} leading cause of all-cause mortality [20]. HBsAg is more frequently found in HCC in Asia, sub-Saharan Africa and Latin America. HCV is found in Europe, North America, Japan, Pakistan, Mongolia and Egypt [21]. In France, 5% of cirrhosis and 9.8% of HCC are attributable to chronic hepatitis B [22]. In Tunisia, 48% to 60% of cirrhosis and 70% of HCC are related to HBV [23]. In Mali, 71% of cirrhotic patients and 66.2% of patients with HCC are HBsAg positive [10] [11] [12]. In Senegal, HBV was the cause of cirrhosis in 82.2% of cases and of HCC in 67% of cases [13]. However, in Chad, HBV seroprevalence was 67.3% in patients with cirrhosis and 56.3% in patients with HCC [14]. In studies in Bangui, HBV was the cause of cirrhosis in 62.5% [24] and of HCC in 67.4% [25]. The aim of this study is to assess the seroprevalence of HBsAg in cirrhosis and HCC in order to help improve patient management.

2. Method Patients

We conducted a 34-month cross-sectional analytical study between 1 January 2020 and 31 October 2022. Data collection was retrospective from 1 January 2020 to 31 March 2022 and prospective from 1er April 2022 to 31 October 2022. The study population consisted of patients hospitalised in the Hepato-Gastroenterology (HGE) department of the Centre Hospitalier Universitaire de l'Amitié Sino-Centrafricaine (CHUASC) in Bangui during the study period.

We included in the study patients of both sexes aged at least 18 years, diagnosed with cirrhosis and/or primary liver cancer (PLC) and tested for HBV infection. The diagnosis of cirrhosis was based on clinical and biological signs of hepatocellular insufficiency (HCI), clinical, ultrasound and endoscopic signs of portal hypertension (PH) and, when the liver was hypertrophic, on its characte-

ristics (firm or hard consistency, regular surface, painless, with a thin or sharp lower edge). The diagnosis of FPC was made clinically if the liver was large, hard, woody, stony, with an irregular surface, tender or painful with a foamy lower margin and/or on the basis of biology if the alpha-fetoprotein level was ≥ 400 ng/ml, abdominal ultrasound if there were masses or nodules and abdominal tomodensitometry if there were hypervascularised hepatic lesions on arterial examination and late portal lavage. Infection with the hepatitis B virus was incriminated if the following serological markers were detected: positive HBS antigen, positive HBV viral load. If HBsAg was positive, the patient was tested for co-infection with HDV.

We did not include in the study patients who met the inclusion criteria and who refused to take part in the study.

Our sample was of convenience, taking into account all patients who met the inclusion criteria during the study period.

Data were collected using an individual direct-administration survey form. Data were collected from patients, medical records and hospital registers. The variables studied were sociodemographic, clinical, biological, morphological and prognostic characteristics.

The data were analysed using Epi info 7 software. We used the pearson chi² test with a significance level of 5% for the comparison.

3. Results

Epidemiological aspects: During the study period, 1344 patients were hospitalised, 681 of them for chronic liver disease (51%). The following table presents the aetiologies of chronic liver disease hospitalised during the study period (Table 1).

Among patients admitted for chronic liver disease, in particular cirrhosis and/or HCC, HBV was implicated in 288 cases (42.30%), of which 170 (24.96%) met our inclusion criteria. These included 123 men (72.35%) and 47 women (27.65%). The sex ratio was 2.61.

The average age of our patients was 40 (±11 years) with extremes of 18 and 76 years.

Table 1. Breakdown of cases of cirrhosis, HCC arising from cirrhosis and hepatocellular carcinoma by aetiology (N = 681).

Causes	Chronic liver disease			
	Cirrhosis Number (%)	HCC on cirrhosis Number (%)	CHC workforce	TOTAL workforce
Undetermined	181 (26.58)	61 (8.96)	20 (2.93)	262 (38.47)
Alcohol	42 (6.17)	31 (4.55)	14 (2.05)	87 (12.77)
Anti-HCV	28 (4.11)	3 (0.44)	13 (1.91)	44 (6.46)
HBsAg	186 (27.31)	68 (9.98)	34 (5.01)	288 (42.30
Total	437 (64.17)	163 (23.93)	81 (11.90)	681 (100)

The table below shows the breakdown by age group and gender (Table 2).

The occupation of patients with cirrhosis and/or FPC is shown in the table below (Table 3).

The patients had a good socio-economic level in 51 cases (30%) and a low socio-economic level in 119 cases (70%).

The marital status of patients is shown in the figure below (Figure 1).

Table 2. Breakdown of patients by age group and sex (N = 170).

Age range	Gender		
	Male number (%)	Female number (%)	TOTAL number (%)
18 - 27	13 (7.64)	9 (5.29)	22 (12.94)
28 - 37	35 (20.59)	8 (4.71)	43 (25.30)
38 - 47	50 (29.41)	20 (11.76)	70 (41.18)
48 - 57	15 (8.82)	5 (2.95)	20 (11.76)
58 - 67	10 (5.89)	4 (2.35)	14 (8.23)
68 - 76	0	1 (0.59)	1 (0.59)
Total	123 (72.35)	47 (27.65)	170 (100)

Table 3. Occupation (N = 170).

Profession	Workforce	%
Pupil or student	11	6.47
No profession	20	11.76
Professionals and traders	22	12.94
Farmer and stockbreeder	26	15.30
Public or private sector employee	29	17.06
Activities in the informal sector	62	36.47
Total	170	100

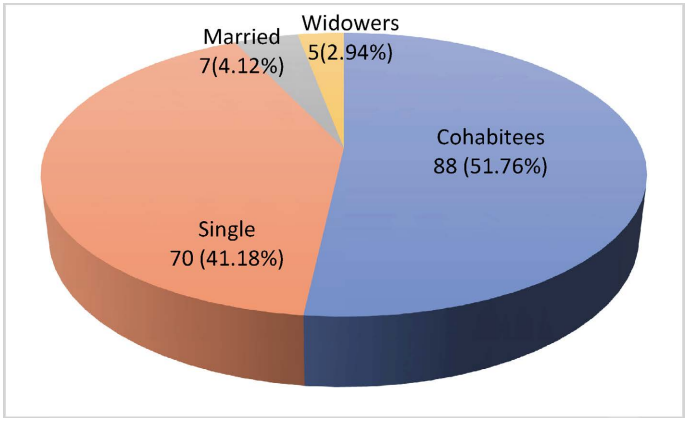

Figure 1. Marital status (N = 170).

The patient histories are presented in the table below (Table 4).

Alcohol consumption was admitted by 125 patients (73.53%). The average quantity of alcohol consumed was 60 g/d, with extremes of 20 and 160 g/l. The average duration of alcohol consumption was 10 years, with extremes of 1 and 40 years. Fourteen patients (8.82%) smoked. The average number of pack-years was 4 (extremes: 1 and 20).

None of our patients had been vaccinated against HBV.

Clinical aspects

In 145 cases (85.29%) of our patients, chronic HBV carriage was known during the course of their current disease, and in 25 cases (14.71%) it was known after an acute viral hepatitis B infection. The figure below shows the liver diseases associated with HBV (Figure 2).

The following table shows the gender distribution and average age of the patients included (Table 5).

Table 4. Patient history (N = 170).

History	Workforce	%
Drug addiction IV	1	0.59
Excision	7	14.89
Dental care	22	12.94
Tattoo	25	14.71
Multiple sexual partners	26	15.29
Scarification	28	16.47
Surgery	38	22.35
Pedicure care	40	23.53
Manicure care	40	23.53
Blood transfusion	49	28.82
Occasional sexual partner	58	34.12
Jaundice	61	35.88
Circumcision	123	72.35

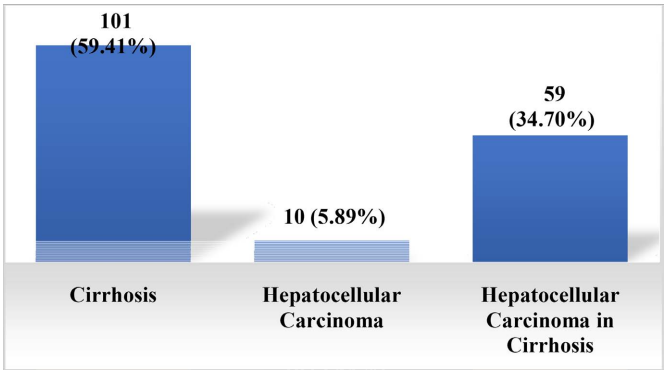

Figure 2. Diagnosis of chronic liver disease (N = 170).

68 patients (67.32%) with cirrhosis were aged between 28 and 47 years. Of the 101 patients with viral B cirrhosis, 22 (21.78%) had anti-HDV antibodies out of the 25 patients who had undergone HDV serology. Nine patients (64%) had HBV/HIV co-infection out of the 14 patients who had undergone HIV screening. HCV screening was performed in 12 patients, 6 (50%) of whom had anti-HCV antibodies.

Of the 59 patients (%) with HCC in viral B cirrhosis, 38 (64.4%) were between 28 and 47 years of age. Coinfection with the Delta virus was observed in 11 cases (18.65%). HBV/HIV co-infection was found in 5 patients (8.47%). HCV screening was performed in 8 patients, 3 of whom (37.5%) were co-infected with HBV/HCV. Of the 10 patients, 7 had HBV-related HCC aged between 28 and 47 years. One patient tested positive for HBV/HDV co-infection. HIV serology was positive in all three patients. HCV serology was positive in the 2 patients who had undergone the test.

Cirrhosis was the most common liver disease in 160 cases, followed by hepatocellular carcinoma in 59 cases (36.87%). The other modes of decompensation were ascites in 140 cases (87.50%), jaundice in 130 cases (81.25%), hepatic encephalopathy in 47 cases (29.38%), digestive haemorrhage in 42 cases (26.25%), infection of ascites fluid in 30 cases (21.43%), and hepatorenal syndrome in 9 cases (5.63%). Hepatic encephalopathy was stage 1 in 8 cases (17.02%), stage 2 in 17 cases (36.17%), stage 3 in 15 cases (31.91%) and stage 4 in 7 cases (14.9%).

The WHO performance status is shown in the figure below (Figure 3).

Biological aspects

Biologically, full HBV serology was performed in only 105 patients (61.76%).

Table 5. Breakdown by sex and average age of the various chronic liver diseases.

Variables	Men (%)	Women (%)	Sex ratio	Average age
Cirrhosis	68 (67.33%)	33 (32.67%)	2.06	40 ± 10
HCC on cirrhosis	49 (83.05)	10 (16.95)	4.9	45 ± 11
CHC	6 (60)	4 (40)	1.5	48 ± 12

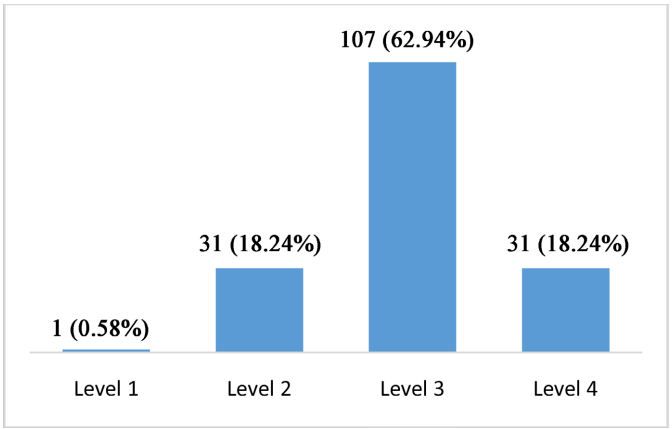

Figure 3. WHO performance status.

This enabled identification of patients carrying wild-type virus in 22 cases (20.95%) and those carrying pre-C mutants in 83 cases (79.05%). In 65 cases (38.24%), HBV infection was confirmed only by HBsAg positivity. HDV serology was carried out in only 40 patients (23.53%). It was positive in 34 cases (85%). 159 patients (93.53%) were tested for co-infection with HCV. HCV serology was positive in 11 patients (6.91%). HCV viral load was detectable in all patients. The mean viral load was 1,123,500 IU/ml. HIV serology was positive in 11 cases (6.91%). Alpha-fetoprotein was measured in 67 patients (39.41%). The mean alpha-fetoprotein value was 978 IU/ml, ranging from 1 to 840,000 IU/ml. The alpha-fetoprotein value was less than 400 IU/ml in 22 patients (32.83%) and greater than or equal to 400 IU/ml in 45 patients (67.17%).

Prognostic aspects

The severity of IHC in patients with cirrhosis and HCC on cirrhosis according to Child-Pugh is presented in the table below (Table 6).

The BCLC classification made it possible to specify the stage of severity of hepatocellular carcinoma occurring in cirrhosis in our 59 patients. They were stage C in 7 cases (11.86%) and stage D in 52 cases (88.14%).

The Okuda Classification was used to assess the severity of the 10 cases of primary liver cancer without cirrhosis. The patients were stage 2 in 4 cases (40%) and stage 3 in 6 cases.

4. Discussion

Limits of the study

The diagnosis of cirrhosis and HCC was made on clinical, biological and morphological grounds without recourse to liver biopsy. It is now accepted that when epidemiological, clinical, biological, radiological and endoscopic evidence concurs, the diagnosis of cirrhosis can be made without necessarily resorting to a liver biopsy for histological analysis, or by using other non-invasive means [26]. Blood tests for fibrosis now limit the need for PBH. CT scans can now be used to make a positive diagnosis of HCC without histological analysis of HBC specimens. The significant elevation of alpha-fetoprotein in our HCC patients was also an argument in favour of the diagnosis. We were unable to include 118 patients with hepatitis B-related chronic liver disease because of the absence of certain morphological and biological tests to support a positive diagnosis of cirrhosis and/or HCC. However, our study provided information that should be

Table 6. Child-Pugh classification (n = 160).

	Cirrhosis	HCC on cirrhosis	Total
Class A	7 (4.37%)	0	7 (4.37%)
Class B	62 (38.75%)	26 (16.25%)	88 (55.00%)
Class C	32 (20.00%)	33 (20.63%)	65 (40.63%)
Total	101(63. 12%)	59 (36.88%)	160 (100%)

compared with data in the literature.

Frequency: Chronic liver disease was the most frequent condition hospitalised in the HGE department of the CHUASC in Bangui (51.00%). The frequency of HBV during cirrhosis and/or HCC in our study is lower than that reported by authors in Ndjamena (65.5%) [14] and Pointe Noire in Congo (63%) [27]. Previous studies in Bangui reported a prevalence of 62.5% [24] for cirrhosis and 67.4% [25] for HCC. Other authors have observed a prevalence of 54.50% during cirrhosis [28] and 41% in patients with HCC [29].

Sociodemographic characteristics: The mean age of patients with cirrhosis in our study was 40 years, similar to that reported by authors in Ndjamena (41 years) [14]. However, previous studies of cirrhosis in Bangui reported an average age of 44 [24] and 45 [28]. This shows that the average age of patients with cirrhosis is falling, with younger and younger people increasingly being affected. This reduction in the average age could be encouraged by other factors, such as alcohol consumption and smoking, which favour the progression of liver disease. In Cotonou [30] and Kinshasa [31], the authors found an average age of 49 and 51 years respectively. In contrast, patients with HCC in our study had an average age of 48 years. This is lower than the 50 years reported in Bangui [25]. The mean age of our patients is similar to those observed in Dakar, Senegal [32] and Abidjan, Ivory Coast [33], which were 47.4 and 48.15 years respectively. Authors in Morocco found a mean age of 59 years [34]. HCC occurs later in the Maghreb than in sub-Saharan Africa. The age *groups* most represented in the study were 28 - 37 and 38 - 47. Authors in Ndjamena [14], Dakar [32], Côte d'Ivoire [33] and Bangui. [25] had made the same observation. The young age of patients at the time of diagnosis could be linked to vertical transmission of HBV. The male predominance of chronic viral hepatitis B (72.35%) in our study corroborates the data in the literature [14] [24] [28] [29] [30] [31] [32]. The patients in our series came from all social strata. However, 70% of our patients had a low socioeconomic level. This observation had already been made in Bangui [28] [35], as well as by other authors in Brazzaville [36] and Cotonou [30]. The low socio-economic level observed is linked to a low human development index, a characteristic of low-income countries where social inequalities are immense [37].

Daily alcohol consumption was found in 73.53% of cases. Alcohol could be one of the factors favouring the onset of complications, in particular cirrhosis and/or HCC. It has also been reported by other authors [24] [25] [28] [31] [38] [39]. Cirrhosis and/or HCC were discovered at the symptomatic stage in 163 cases (95.88%). This finding had already been made in previous studies in Bangui [24] [25] [28] [34] [35] and also by authors in Kinshasa [31], Cotonou [30], Côte d'Ivoire. [33] and Burkina Faso [36]. The delay in consulting a doctor is probably linked to the use of traditional medicine, self-medication, poverty, religious convictions and occult beliefs, as reported in the study on the therapeutic itinerary of patients with cirrhosis [37]. Cirrhosis represented 94.11% of cases

and HCC 5.89% of cases in our series. However, the authors in Ndjamena had reported 84% HBV-related cirrhosis and 16% HBV-related HCC [14]. In Pointe Noire, Congo, the authors observed 48.1% HBV-related cirrhosis and 51.8% HBV-related HCC [27]. All this shows that in our settings, cirrhosis and/or HCC are diagnosed late. This may be related to the absence of an HBV screening policy and the lack of vaccination against HBV at birth in these countries. Cirrhosis was diagnosed at the decompensation stage in 160 cases (94.11%). The most frequent modes of decompensation were ascites (87.50%), jaundice (81.25%), hepatocellular carcinoma (36.87%) and hepatic encephalopathy (29.38%). They were reported with varying frequency in other studies in Bangui [24] [28] [34] [35] [37], Bamako [11], Pointe Noire in Congo [27], Cotonou [30] and Kinshasa [31]. The majority of our patients (62.94%) had WHO performance status 3, indicating advanced disease. The presence of the PreC mutant observed in our study in 79.05% of cases was revealed in 70.7% of cases in a previous study in Bangui [35]. HBV/HDV co-infection was found in 85% of cases in our study. This frequency is higher than that reported by other authors in Bangui, who reported frequencies of 7.5% [28], 53.6% [29] and 22.5% [35]. The HBV/HDV co-infection could explain the progression of the disease. The significant elevation of alpha-fetoprotein was greater than 400 IU/ml in our patients, supporting the diagnosis of HCC reflecting the alpha-fetoprotein-secreting form, as previously reported by authors in the department [25]. In our context, alpha-fetoprotein can be used in conjunction with abdominal ultrasound to monitor cirrhosis.

In our study, cirrhosis was classified as Child-Pugh B and C in 55.00% and 40.63% respectively. This finding was made in Bangui [24] [34] [35] and by other African authors in Cotonou [30], Kinshasa [31], Libreville [38], and Ouakaa-Kchaou in Tunisia [39]. According to the BCLC classification, our patients with HCC in cirrhosis were between stage C (11.87%) and stage D (88.14%), as already reported by the authors in Bangui [25]. The same was true of studies in Dakar [32], Côte d'Ivoire [33] and Ouagadougou [36]. All these mean that HCC is diagnosed late in our regions, where curative treatment is not available.

5. Conclusion

HBV is a frequent cause of cirrhosis and HCC in the Central African Republic. The disease often occurs in young adult males. Diagnosis is made at an advanced stage, so curative treatment is not possible. It is important to raise awareness of the need for HBV screening, to introduce vaccination at birth as part of the Expanded Programme on Immunisation, and to provide care for people infected with HBV in order to reduce the severity of the disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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