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Assessment of Liver Fibrosis in HBsAg-Negative and Anti HBc Positive Patients

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Abstract

Background: Surface antigen (HBsAg) is the mean marker of hepatitis B virus infection. During the course of the infection, some patients lose the HBsAg and only the presence of anti-HBc antibody indicates previous contact with the virus. Among these patients, some have detectable viral load (occult infection) but most without viral replication. There is no guideline regarding these patients. The aim of this study was to assess hepatic fibrosis in patients with only the hepatitis B virus contact marker "total anti-HBc". Patients and methods: it was a descriptive and analytical cross-sectional study, conducted in three private hospitals from January to August 2022. Were included HBsAg-negative and HBc-positive patients, consulting in Gastroenterology departments. Noninvasive methods (APRI, FIB-4 and FIBROSCAN) were used to evaluate liver stiffness because of their easy accessibility and low-cost. The hepatic fibrosis was considered significant when the score determined by APRI, FIB-4 and FIBROSCAN® tests was respectively greater than 1.5; 2.67 and 8 kPa corresponding to fibrosis level 2 (F2). **Results:** A total of 63 HBsAg-negative/total HBcAg-positive patients were included. The mean age was 49.9 ± 13.4 years. The male/female sex ratio was 1.78. Of the 63 patients, 19 had significant liver fibrosis (30.1%) among which 9 patients had HCC. The FIB-4 score outperformed the APRI score in assessing liver fibrosis, with a sensitivity of 84.2%, a specificity of 100% and a negative predictive value of 93.6%. In univariate analysis, there was a significant association between the occurrence of significant liver fibrosis and age over 40 years, dyslipidaemia, obesity, alcohol consumption, smoking, herbal medicine, negative anti-HBs immunological status and detectable viral load. **Conclusion:** Our study revealed a high prevalence of significant to severe hepatic fibrosis in anti-HBc positive patients.

In most of the cases, the fibrosis was severe. Progression to HCC has also been possible. There is no consensus on the follow-up strategy for those patients. However, screening for hepatic fibrosis using noninvasive methods should be recommended for patients aged over 40 years, alcohol or herbal medicine users, patients with metabolic syndrome or occult hepatitis B. In HBsAg-negative/anti-HBc-positive patients, liver stiffness should be evaluated and if it is greater than F2, HCC screening should be started.

Keywords

Anti HBc Positives, Liver Fibrosis, Sub-Saharan, Hepatitis B Virus

1. Introduction

Sub-Saharan Africa is a highly endemic area for hepatitis B virus infection, with a prevalence of chronic carriers over 8% [1]. Most infections occur during the perinatal period or in early childhood. Anti-HBc represent a serological scar of HBV infection, and their prevalence is thought to exceed one-third of the general population [2]. Cirrhosis and hepatocellular carcinoma are the most feared complications of HBV-related chronic liver disease [3]. They are increasingly encountered in populations that have already lost HBsAg, and their evolution is not yet fully understood.

While some studies have shown that the level of total anti-HBc antibodies varies according to the stage of the disease in untreated chronic HBV patients. Others have shown that total anti-HBc antibodies are higher during the HBeAg-negative phase of chronic hepatitis [4], which is correlated with moderate to severe histological activity. There is certainly a prognostic value in the level of total anti-HBc that may be associated with progressive liver fibrosis, which needs to be evaluated. The aim of this study was to determine the prevalence of hepatic fibrosis and hepatocellular carcinoma (HCC) in patients with only the HBV contact marker 'total anti-HBc positive', and to identify the various factors associated with it.

2. Patients and Methods

It was a descriptive and analytical cross-sectional study conducted in the city of Ouagadougou. Ouagadougou is the political capital of Burkina Faso and is located in the central region (Kadiogo). It has a population density of more than 1000/km^2. Our study took place in three private health facilities (SANDOF polyclinic, Saint Camille Hospital of Ouagadougou, and Ilboudo Bruno Clinic). These facilities were chosen based on the large number of patients with hepatitis B infection they follow up. The study population consisted of patients in the cohort from January to August 2022 carriers of anti-HBc who were admitted for consultation. Patients over 18 years of age carrying only the HBV contact marker "anti-HBc total positive", who had given informed consent and had a concomitant measurement of amino-

transferases and platelets, as well as the measurement of liver stiffness by pulse elastometry (FIBROSCAN®), were included in the study.

Patients in the above-mentioned cohort who were HBsAg positive, patients with contraindications to pulse elastometry (large ascites and pregnancy) and patients with blood transaminases greater than 5 times the upper limit of normal were excluded from the study.

Data were collected using a survey form with sociodemographic, clinical and paraclinical variables. The files were reviewed to select patients who met the inclusion criteria, prior to the face-to-face interview with the patients. This interview was used, among other things to explain the objectives of the study, obtain informed consent, fill in any missing information on the survey form, carry out a physical examination of the patients, take blood samples to determine the biological scores for liver fibrosis and, finally, to measure liver fibrosis quantitatively using FIBROSCAN® pulse elastometry. To assess liver fibrosis, we used the APRI and FIB-4 scores and pulse elastometry (FIBROSCAN®) test. Values were therefore defined to confirm the presence or absence of significant hepatic fibrosis and in which cases it was severe.

For the APRI score, liver fibrosis was significant if the value was greater than 1.5 [5] and for the FIB-4 score if the value was greater than 2.67 [6]. The values were calculated using the medical algorithms available online at http://medicalcul.free.fr/

With FIBROSCAN® (pulse elastometry), significant fibrosis was defined as a value greater than F2 (8 kPa) and severe fibrosis as a value greater than F4 (12 kPa).

Hepatocellular carcinoma (HCC) was diagnosed on the basis of clinical and paraclinical data, in particular tumor hepatomegaly, CT scan showing nodules with vascular enhancement at arterial time and lavage at portal time, with or without elevation of alpha-fetoprotein.

The data were analyzed using R software version 4.1.2. In univariate analysis, to test the association between two qualitative variables, we used Karl Pearson's chi-square test [chi^2], Yates corrected or Fisher's exact test depending on the indicators. A difference was considered significant if the p-value was less than 0.05.

3. Results

A total of 63 patients with positive anti-HBc antibodies were included in our study. Of these patients, 30 (47.6%) were followed up at the SANDOF Polyclinic, 22 (34.9%) at the Saint Camille Hospital of Ouagadougou and 11 (17.5%) at the Ilboudo Bruno Clinic.

3.1. General Characteristics of the Study Population

Males were predominant, with a sex ratio of 1.78. The mean age was 49.9 ± 13.4 years, with extremes of 24 and 78 years. In two-thirds of cases, the serological status of patients was discovered during screening. Thus 65.1% of our patients

were asymptomatic at the time of the study. Seven patients (11.1%) were co-infected with hepatitis B and hepatitis C. A history of cirrhosis and dyslipidemia were present in 9.5% and 7.9% of cases respectively. Among our patients, 15 drank alcohol (23.8%) and 13 used herbal medicine (20.6%). Four patients smoked tobacco. Nearly a third of our patients (30.2%) were overweight, and the physical examination of patients at the time of the study was normal in 63.5% of cases.

3.2. Prevalence of Significant Liver Fibrosis and HCC

Nineteen patients had significant to severe liver fibrosis (Figure 1), representing a prevalence of 30.1%, 95% CI [19.2%; 43%]: three patients (4.7%) had significant hepatic fibrosis (F2-F3) and 16 patients (25.4%) had severe fibrosis (F4). Nine patients had hepatocellular carcinoma, a prevalence of 14.3% 95% CI [6.7%; 25.3%]. Adjusting for patients who already had significant hepatic fibrosis, this prevalence rose to 47.4% (9/19).

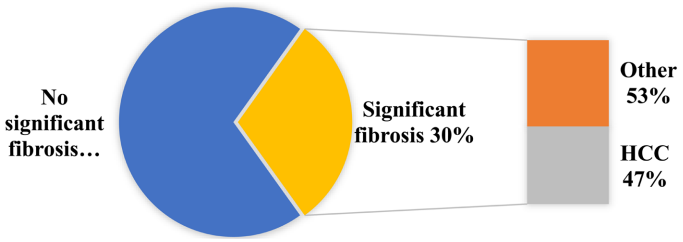

Figure 1. Prevalence of significant liver fibrosis and HCC

3.3. Performance of Biological Scores Compared with Pulse Elastometry

FIBROSCAN® (pulse elastometry) was used as the gold standard to assess the performance of biological scores in the evaluation of liver fibrosis. The APRI score had a sensitivity of 47.3%, a specificity of 100% and a negative predictive value of 81.4%. FIB-4 had a sensitivity of 84.2%, a specificity of 100% and a negative predictive value of 93.6%. The diagnostic values of the biological scores in relation to FIBROSCAN® are shown in Table 1.

Table 1. Diagnostic values of APRI and FIB-4 scores compared with FIBROSCAN® in the diagnosis of significant to severe liver fibrosis.

		Fibroscan®			
		Positive	**Negative**	**Total**	**P-value**
APRI	Positive	9	0	9	<0.001
	Negative	10	44	54	
	Total	**19**	**44**	**63**	
FIB-4	Positive	16	0	16	<0.001
	Negative	3	44	47	
	Total	**19**	**44**	**63**	

3.4. Factors Associated with Significant Liver Fibrosis in Anti-HBc Positive Patients

Table 2. Factors associated with the occurrence of significant liver fibrosis.

	Liver Fibrosis		P-valeur
	Not significant (N = 44)	Significant (N = 19)	
Age			**<0.001**
<40 years	17 (38.6%)	1 (5.3%)	
40 - 60 years	22 (50%)	8 (42.1%)	
>60 years	5 (11.4%)	10 (52.6%)	
Dyslipidaemia			**0.027**
Yes	3 (6.8%)	2 (10.5%)	
No	12 (27.3%)	11 (57.9%)	
Not sought	29 (65.9%)	6 (31.6%)	
Smoking			**0.007**
Yes	0 (0%)	4 (21.1%)	
No	44 (100%)	15 (78.9%)	
Alcoholism			**<0.001**
Yes	1 (2.3%)	14 (73.7%)	
No	43 (97.7%)	4 (21.1%)	
Withdrawal	0 (0%)	1 (5.3%)	
Herbal therapy			**<0.001**
Yes	2 (4.5%)	11 (57.9%)	
No	42 (95.5%)	8 (42.1%)	
BMI			**0.032**
Lean	1 (2.3%)	3 (15.8%)	
Normal	23 (52.3%)	12 (63.2%)	
Overweight	17 (38.6%)	2 (10.5%)	
Obese	3 (6.8%)	2 (10.5%)	
No	42 (95.5%)	8 (42.1%)	
Anti-HBs			**0.014**
Positive	22 (50%)	3 (15.8%)	
Negative	18 (40.9%)	15 (78.9%)	
Missing	4 (9.1%)	1 (5.3%)	
HBV DNA			**0.015**
Positive	1 (2.3%)	3 (15.8%)	
Negative	22 (50%)	13 (68.4%)	
Undetermined	21 (47.7%)	3 (15.8%)	

There was a significant association between the occurrence of significant hepatic fibrosis and age over 40, dyslipidemia, obesity, alcohol consumption, use of phytotherapy, immunological status linked to negative anti-HBs and detectable viral load. Table 2 shows the factors associated with the development of significant to severe liver fibrosis.

4. Discussion

The prevalence of significant to severe liver fibrosis in patients with isolated anti-HBc antibodies was 30.1%. This prevalence is close to that of a similar population of drug users attending CAARUDs and CSAPAs in the Île-de-France region, where 29.2% had moderate hepatic fibrosis [7]. In Sub-Saharan Africa, the prevalence of HBV-related liver fibrosis was estimated at 16.3% by the PROLIFICA project in the Gambia and Senegal [8]. Ntagirabiri *et al.* in Burundi found a prevalence of 17.4% [9]. This difference could be explained by the average age of our patients and by the fact that our study population consisted of patients who were only "anti-HBc positive". In endemic countries such as Burkina Faso, the prevalence of 'anti-HBc positive' is high, reaching up to a third of the general population [2]. Since the majority of infections occur in early childhood, the scarring may persist for several decades until the HBsAg is lost or not, with the corollary of possible histological activity responsible for extensive fibrosis.

HCC was present in 14.3% of patients. Nearly one in two patients with significant to severe fibrosis had HCC. This result is similar to that of a meta-analysis by Coppola *et al.* in which 14.2% of total HBcAb positive patients had HCC [10]. Of the four patients with occult hepatitis B, three had severe F4 liver fibrosis with clinical and CT scan signs of HCC. The mechanisms leading to severe fibrosis and HCC have not yet been elucidated. However, persistent occult HBV infection should be considered an adverse event because of an increased risk of progression to cirrhosis due to longer immunological damage, and also an increased risk of HCC due to prolonged exposure to HBV, which is known to be oncogenic [11].

In terms of biological scores, FIB-4 performed better than the APRI score in assessing significant to severe liver fibrosis. The better performance of FIB-4 observed in our study is corroborated by the meta-analysis of Xu *et al.* [12] which found respective areas under the curve (AUROC) of 0.75 and 0.87 for APRI and FIB-4. In a cohort of 404 patients closer to us in Senegal, Touré *et al.* [13] found that the APRI score performed better than the FIB-4 in assessing liver fibrosis, with AUROCs of 0.65 for APRI and 0.56 for FIB-4. There are several possible explanations for this difference: our study population consisted of patients who were only "anti-HBc positive", and the histobiological and age characteristics of patients are considered in calculating one of the scores and not the other. The WHO recommends using the APRI score as a non-invasive test for diagnosing cirrhosis in countries with limited resources. However, in Sub-Saharan Africa, few studies have evaluated the diagnostic yield of non-invasive markers of cirrhosis during HBV infection [14]-[17]. Studies are therefore needed to assess the contribution

of these scores in current practice.

We found no association between the presence of a co-infection and the occurrence of significant to severe liver fibrosis. Our results differ from those of Coppola *et al.* [10] who found a significant association between hepatitis C virus infection and the development of HCC in anti-HBc positive patients. Our results could be explained, on one hand by the small size of our sample and, on the other hand by the low prevalence of HCV infection in our country, which stands at 3.6% [18].

There was a significant association between dyslipidaemia, obesity and the development of liver fibrosis. These components of metabolic syndrome are involved in NAFLD and NASH, which can progress to cirrhosis and HCC. The presence of dyslipidaemia or obesity in these patients is therefore a negative factor.
Alcohol consumption and herbal medicine ($p < 0.001$) were also significantly associated with liver fibrosis. Avril [7] made the same observation regarding alcohol consumption as a factor associated with liver fibrosis. It is important to detect advanced hepatic fibrosis in alcohol consumers, who constitute a population at risk of cirrhosis and HCC without clinical monitoring. Herbal medicine has a potential hepatotoxic effect in cases of misuse or in the presence of other liver comorbidities.

There was a significant association between dyslipidaemia ($p < 0.027$) and obesity ($p < 0.032$) and the development of liver fibrosis. These components of metabolic syndrome are involved in non-alcoholic-fatty-liver Disease (NAFLD) and non-alcoholic steato-hepatitis (NASH), which can progress to cirrhosis and HCC. The presence of dyslipidaemia or obesity in these patients is therefore a negative factor.

Anti-HBs was negative in 78.9% of patients with significant to severe liver fibrosis. In univariate analysis, this variable was associated with significant liver fibrosis ($p < 0.014$). Coppola *et al.* [10] made the same observation. They also demonstrated that patients with 'isolated' anti-HBc positives had a higher risk of HCC than anti-HBs/anti-HBc positive patients. These patients were more likely to have an occult HBV infection in the liver.

HBV DNA was undetectable in 55.6% of cases, and low viral replication was observed in 6.3% of cases. In univariate analysis, there was a statistically significant association between detectable viral load and liver fibrosis ($p < 0.015$). Our results are similar to those of Coppola *et al.* [10]. However, further studies on this subject are required. Indeed, 38.1% of our patients had no HBV viral load.

5. Conclusion

Our study revealed a high prevalence of significant liver fibrosis in patients with only Anti-HBc positive. In most of the cases, the fibrosis was severe. To our knowledge, there are no guidelines on the strategies to adopt for those patients. A follow-up must be instituted to detect early significant liver fibrosis and start screening for HCC, above all in highly endemic areas for hepatitis B where, most

of viral infections occur during the perinatal period or in early childhood. Should these patients be treated with nucleotide inhibitors to prevent the risk of cirrhosis and HCC? These are questions on which a consensus needs to be reached. In HBsAg-negative/anti-HBc-positive patients liver stiffness should be evaluated and HCC screened if needed.

Conflicts of Interest

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

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