

Hepatitis B Surface Antigen Serum Level Is Correlated with Fibrosis Severity in Treatment-Naïve, Chronic Hepatitis B Patients in Côte d'Ivoire (West Africa)?

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Abstract

HBsAg serum level (quantification) may be useful for managing hepatitis B virus (HBV) infection patients. However few studies especially in Africa have evaluated the association between HBsAg serum level and liver fibrosis severity. The objective of this study was to estimate the correlation between HBsAg serum level and liver fibrosis severity with treatment naïve chronic hepatitis B patients in Côte d'Ivoire. Methodology: It is a prospective study covering from February 1st, 2014 to April 30st, 2015 at Centre Hospitalier et Universitaire de Yopougon and a private medical office in Abidjan, Côte d'Ivoire. Inclusion criteria for patients were: HBsAg positive, known HBeAg status, serum HBsAg levels, serum HBV DNA levels, complex serum markers and absence of HCV, HDV, or HIV co-infection, drinking more than 30 g/day for men and 20 g/day in women over 10 years, metabolic disease and/or hepatic overload. Pearson's Chi-square test (r^2), Anova, Spearman, T-Student, Pearson's (r) correlations and Mann Withney's Test were carried out as appropriate. A p value < 0.05 was taken as significant. Results: We recruited, 105 patients (77 men) of whom the medium age was 39.01 ± 9.72 years. Predominant hepatitis B viral genotype was E (93%). Less than 10% patients had an inactive HBV in HBeAg-negative. Patients had an average high HBsAg serum level (mean 12111.2 ± 10617.4 IU/ml) as well as the one viral load (mean $4.4 e7 \pm 7.5 e7$). Serum ALAT levels averaged at the upper limit of normal value. The average liver fibrosis score was 0.34 ± 0.22

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and the degree of viral activity was 0.19 ± 0.20 . Half of our patients had no fibrosis (35.24%) or had mild fibrosis (20.95%). No significant association was observed between HBsAg serum level and patient age ($p = 0.3994$), genre ($p = 0.8075$) or serum ALT levels ($p = 0, 0787$). In multivariate analysis, there's a significant correlation ($r = 0.239$, $p = 0.014$) between HBV DNA levels and HBsAg serum level. There's a significant correlation ($r = 0.923$, $p < 0.0001$) between HBsAg serum level and the dosage of alpha-fetoprotein. HBsAg serum level was not associated with the fibrosis stage ($p = 0.281$). HBsAg levels average with patients without fibrosis or carry a slight fibrosis (F0, F1) was higher than patients with moderate to severe fibrosis (F2, F3, F4): $13679.2 \text{ UI/ml} \pm 1956.48$ versus $10610.52 \text{ UI/ml} \pm 8998.99$ ($p = 0.29$). There's a negative correlation between HBsAg level and the liver fibrosis score was negative ($r = -0.069$, $p = 0.48$). No significant association between HBsAg level and the liver fibrosis patients that were normal ($p = 0.7965$) or elevated ($p = 0.5845$). HBV DNA level was significantly associated with fibrosis score ($r = 0.30$, $p = 0.0018$). Conclusion: This study shows that there's a negative correlation between HBsAg serum level and liver fibrosis severity treatment naïve with African chronic hepatitis B viral HBeAg-negative patients.

Keywords

Hepatitis B Surface Antigen Serum Level, Liver Fibrosis, Chronic Hepatitis B Viral, Africa

1. Introduction

Viral B cirrhosis by its complications is the leading cause of death for chronic liver diseases in Côte d'Ivoire. This cirrhosis occurs at a final stage of liver fibrosis, in our context due to hepatitis B virus (HBV) in the majority of cases [1] [2]. Fibrosis evaluation can ask therapeutic indications and improve the care of patients HBV to reduce morbidity and mortality from cirrhosis. Several methods are used to assess liver fibrosis severity: transient elastography [3], complex serum markers [4] [5] and histopathological evaluation after performing a liver biopsy [6]. This last decade has seen the birth of a new marker in the therapeutic approach of chronic HBV patients: HBsAg serum level [7].

Hepatitis B surface antigen (HBsAg), which forms the protein envelope of the virus, is generally regarded as a diagnostic for HBV infection [8]. Serum HBsAg levels have been demonstrated to be clinically useful to identify the stage of disease [9] [10], to distinguish true inactive carriers from patients with hepatitis B e antigen-negative (HBeAg-negative) disease [11] [12], and to predict response to interferon therapy [13] [14]. Recent researches have also demonstrated that HBsAg levels are associated with the risk of progression to hepatocellular carcinoma, especially with low Hepatitis B Viral deoxyribonucleic acid (HBV DNA) levels patients [15] [16]. Little is currently known about the association between HBsAg or HBV DNA levels and the severity of liver disease at any specific time point. In contrast to HBV DNA [17] [18], only one published study has investigated the potential correlation between HBsAg levels and the stage of fibrosis [19].

Few studies have evaluated in Sub-Saharan Africa interest HBsAg serum level with the treatment of chronic hepatitis B viral patients. We conducted this study in order to evaluate correlation between HBsAg serum level and liver fibrosis severity.

2. Methodology

2.1. Study Oversight

Retrospective, transversal and analytical study which took place over 14 months. From February 2014 through April 2015, we consecutively enrolled treatment-naïve chronic hepatitis B (CHB) patients who were admitted in the Centre Hospitalier et Universitaire de Yopougon and a private medical office in Abidjan, Côte d'Ivoire. No commercial support was involved in the study. All the authors vouch for the integrity and the accuracy of the analysis and for the fidelity of the study.

2.2. Selection of Patients

Selected, consecutive, treatment-naïve CHB patients were assessed at the Centre Hospitalier et Universitaire de

Yopougon and a private medical office in Abidjan, Côte d'Ivoire, between 2014 February and 2015 April. Patients inclusion criteria were: the HBsAg positive, the HBeAg status, the serum HBsAg levels, the complex serum markers and absence of Hepatitis C Virus (HCV), Hepatitis D Virus (HDV), or Human Immunodeficiency Virus (HIV) co-infection, drinking more than 30 g/day for men and 20 g/day in women over 10 years, metabolic disease and/or hepatic overload.

2.3. Studied Variables

The anthropometric variables were the age, the gender. The clinic variables were the discovery circumstances. The biological variables studied were the serum HBsAg levels, the viral markers, the HBV genotype, the alpha fetoprotein, the serum HBV DNA levels, the alanine aminotransferase (ALT) levels, the aspartate aminotransferase (ASAT) levels, the haptoglobin, the alpha 1 apolipoprotein, the macroglobulin alpha 2, the total bilirubin, the gamma-glutamyl transferase, the prothrombin rate, the triglycerid, the creatinine and the platelets. The score and liver fibrosis stage evaluated by biochemical markers of liver activity and fibrosis (Actitest®-Fibrotest®) were also been studied. These data were collected from the files of consulted patients on pre-established survey forms.

Measurement of HBsAg levels and HBV DNA levels: HBsAg levels in patient serum samples were quantified using the Cobas electro-chemiluminescence immunoassay (Roche Diagnostics) and expressed as log IU/ml. Serum HBV DNA levels were determined using the TaqMan_{assay} (Roche Diagnostics) polymerase chain reaction expressed as log IU/ml.

2.4. Statistical Analysis

Continuous variables were expressed as the mean \pm standard deviation (range) for normal distributions or the median (interquartile range, IQR) for abnormal distributions. Pearson's Chi-square test, Analysis of variance, Spearman, T-Student and Pearson's (r) correlations were carried out as appropriate. Averages comparison was made with the test of Mann Withney. All tests for significance and resulting p values were two-sided, with a level of significance of 0.05. The statistical software used for this analysis was Stata 13.1.

2.5. Ethical Approval

The analysis was conducted on anonymized data, collected aspart of routine patient care. No additional investigations were per-formed. Therefore, no prior informed consent from the patients was required.

3. Results

Over the period of our study we recruited 105 patients (77 men) with an average of 39.01 ± 9.72 years. The main hepatitis B viral genotype was E (93%). Less than 10% of chronic hepatitis B patients had HBeAg-negative inactive. Patients had an elevated average serum HBsAg levels (mean 12111.2 ± 10617.4 IU/ml) as well as the average serum HBV DNA levels (mean $4.4 \text{ e}7 \pm 7.5 \text{ e}7$). Transaminases rate averaged at the upper limit of normal value. The average liver fibrosis score was 0.34 ± 0.22 . Half of our patients had no fibrosis (35.24%) or had mild fibrosis (20.95%). Patient's characteristics are shown in **Table 1**.

No significant association was observed between serum HBsAg levels and patient age, genre or serum ALT levels (**Table 2**).

In multivariate analysis, there's a significant correlation ($R = 0.239$, $p = 0.014$) between HBV DNA levels and HBsAg serum levels (**Figure 1**). There was a significant correlation ($R = 0.92$, $p < 0.0001$) between HBsAg levels and assay of alpha feto-protein (**Figure 2**).

Serum HBsAg levels was not associated to the stage fibrosis ($p = 0.281$) (**Figure 3**). The HBsAg levels average with patients without fibrosis or carry a slight fibrosis (F0, F1) was higher than that of patients with moderate to severe fibrosis (F2, F3, F4): $13679.2 \text{ IU/ml} \pm 1956.48$ versus $10610.5 \text{ IU/ml} \pm 8998.99$ ($p = 0.29$). There was a negative correlation ($r = -0.069$, $p = 0.48$) between HBsAg levels and the liver fibrosis score (**Figure 4**). We noted a lack of significant association between HBsAg levels and fibrosis with patients with normal ALT ($p = 0.7965$) or high ($p = 0.5845$). HBV DNA levels was significantly associated with fibrosis score ($r = 0.30$, $p = 0.0018$) (**Figure 5**).

Table 1. Demographics, clinical and biological characteristics of patients included in the study.

Number of patients	(105)
Demography	
-Age	15 - 69 years (39.01 ± 9.72 years; median 38 years)
-Sex ratio (M/F)	2.74
Discovery circumstances	
	Screening (38.10%), fortuitous (56.19%), symptomatic (5.71%)
Biological variables	
-HBV genotype	E (98) NP (7)
-HBsAg quantification (N < 0.05 IU/ml)	1.69 - 6199 UI/ml (mean 12111.2 ± 10617.4; median 98.41)
-HBV HBeAg-négatif	Active (96), inactive (9)
-HBV DNA levels (N < 20 IU/ml)	154 - 1.7 (mean 4.4 e7 ± 7.5 e7; median 9685.5)
-Transaminases ALAT (N < 35 IU/ml)	9 - 422 UI/ml (mean 38.62 ± 51.12; median 26)
ASAT (N < 40 IU/ml)	10 - 313 UI/ml (mean 38.67 ± 41.88; median 27)
-Prothrombine rate (N ≥ 70%)	56% - 100% (mean 83.25 ± 8.13; median 83)
-Triglycerid levels (N < 2 gr/l)	0.12 - 2.17 mg/l (mean 0.74 ± 0.35; median 0.70)
-Creatinine (N < 15 mg/l)	6 - 16.3 mg/l (mean 9.47 ± 1.72; median 9.1)
-Platelets (N = 150 - 450 GIGA/L)	24 - 389 GIGA/L (mean 186 ± 54; median 195)
-Alpha Feto-protein (N < 8.5 IU/ml)	0.5 - 50.14 (mean 2.84 ± 5.35; median 1.51)
Complex serum markers parameters	
-Total bilirubin (N < 12.3 mg/L)	2 - 54 mg/L (mean 11.63 ± 7.71; median 9.8)
-Gammaglutamyl transferase (N < 40 IU/ml)	11 - 183 UI/L (mean 45.48 ± 34.38; median 34)
-Haptoglobin levels (N = 0.58 - 1.55 g/L)	0.1 - 1.87 g/L (mean 0.81 ± 0.5; median 0.83)
-Apolipoprotein (N = 1.08 - 2.25 g/L)	0.32 - 2.07 g/L (mean 1.30 ± 0.28; median 1.31)
-Macroglobulin α2 (N = 1.75 - 4.20 g/L)	1.02 - 5.25 g/L (mean 2.14 ± 0.71; median 1.97)
-Fibrosis stage (F0-F4)	F0 (37), F1 (22), F2 (28), F3 (9), F4 (9).
-Fibrosis score (0.00 - 1.00)	0.03 - 0.96 (mean 0.34 ± 0.22; median 0.29)
-Activity score (0.00 - 1.00)	0.01 - 0.98 (mean 0.19 ± 0.20; median 0.13)

Table 2. Serum HBsAg levels associated factors in univariate analysis.

Studied variables	P
Age (median) 38 years	0.3994
Gender: male (77)	0.8075
Transaminases	0.0787

4. Discussion

Côte d'Ivoire is a highly endemic area of viral infection B with an estimated HBsAg prevalence of 10% [1].

According to the inclusion criteria, our study population was 105 patients. This number can be explained firstly that HBsAg levels determination is expensive and other shares that review is not yet systematically requested by physicians supporting hepatitis chronic viral B patients. Martinot-Peignoux [5] had a larger cohort of patients in his study but extended to all HBV genotypes and also it came from a study that had benefited from funding. In sub Saharan Africa, few studies have investigated the correlation between serum HbsAg levels and liver diseases.

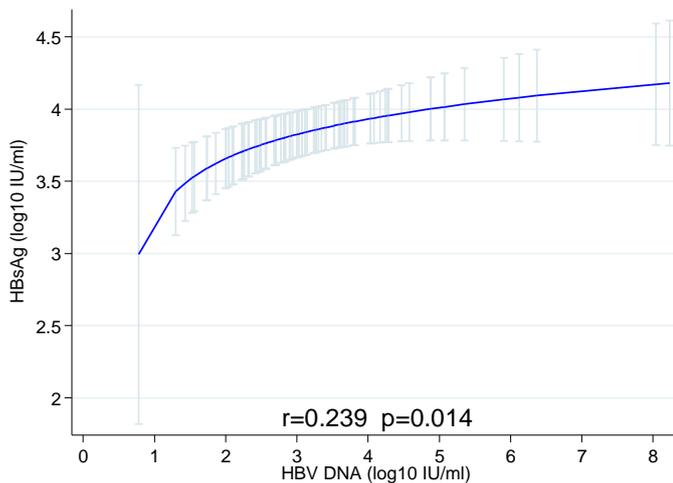


Figure 1. Correlation between HBsAg serum levels and HBV DNA levels. Method: Fractional polynomial w/CI fit plots.

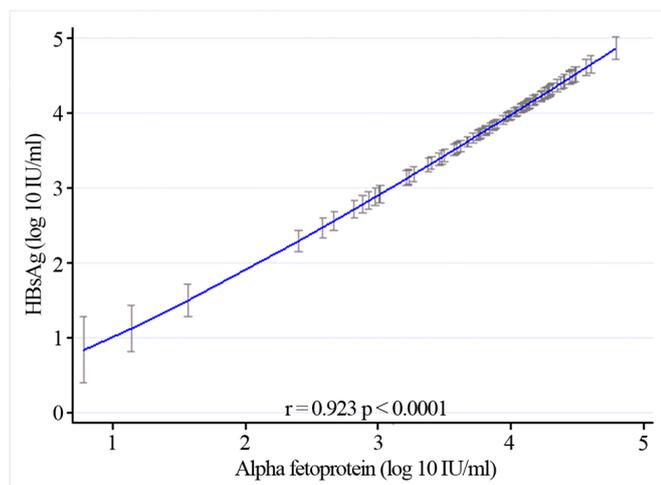


Figure 2. Correlation between HBsAg serum levels and alpha fetoprotein.

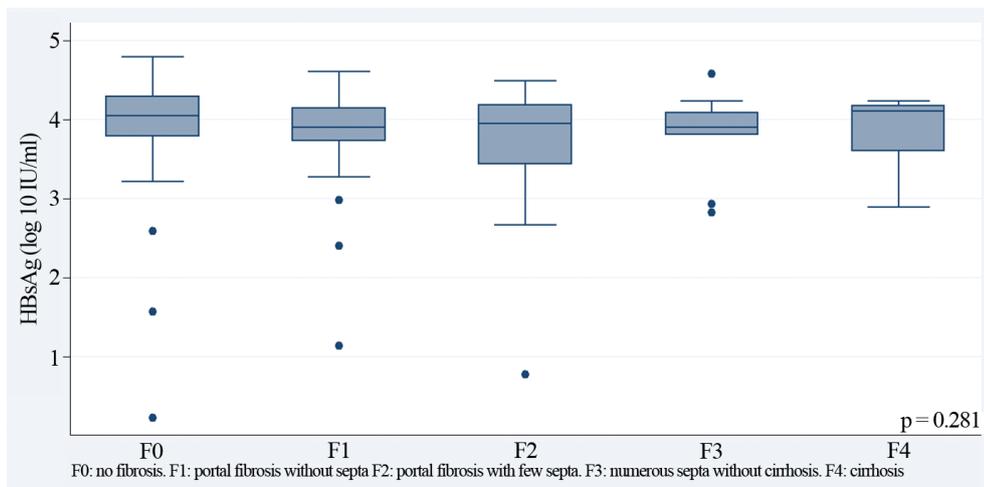


Figure 3. Distribution HBsAg levels patients by liver fibrosis stage.

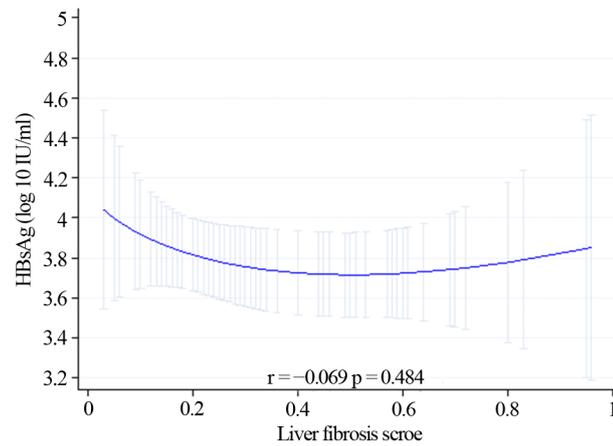


Figure 4. Correlation between HBsAg serum level and liver fibrosis score.

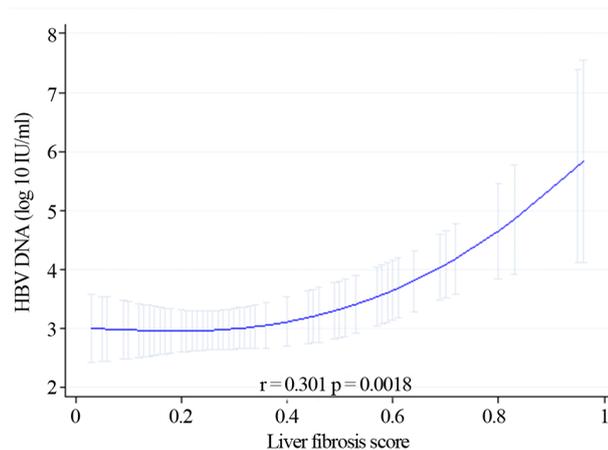


Figure 5. Correlation between HBV DNA level and liver fibrosis score.

The sex ratio in our study was 2.75 men per 1 woman. This male predominance in viral infection B is consistent with literature data [7] [20] [21]. The average age of patients was 39.17 years (extremes: 15 years - 69 years). This data is the same with those Tan [7] found a mean age of 37 ± 12 years and Sombié [21] had an average age of 32 years, ranging from 17 to 67 ans. Multiple use of contaminating materials and sexual risk behaviors were the most found risk factors in the patients' story. Kodjoh [22] made the same finding in his study.

The hepatitis mode of revelation was made fortuitous (56.19%) or during a screening (38.10%). Creach [23] noted in his series 39.4% of cases discovered during screening against 30.3% during a blood donation. Sombié [21] also showed that fortuitous discovery during blood donation (53.36%), health record (34.11%) of HBV was the most revelation common way.

The majority of chronic hepatitis viral B patients (93.33%) had genotype E. The literature also reports a high frequency of genotype E in Sub-Saharan Africa [24] [25]. Patients' proportion for which genotype was not specified is the lack of financial means and inadequate technical facilities in our work environment. All patients (100%) in the study were carriers of chronic viral hepatitis B HBeAg-negative. Creach and all [23] identified in their series 69.7% patients HBeAg-negative and 88.68% of subjects HBeAg-negative in Sombié's serie [21].

Martinot-Peignoux [5] and Tan [7] have found chronic hepatitis viral B HBsAg-negative patients in respective proportions of 75.12% and 27.46%. The high rate of carriers of HBeAg-positive in Tan's study is related to the fact that he made a study on serum HBsAg levels in the natural history HBV infection. He had a large proportion of immunotolerant treatment naïve patients.

Less than 10% of patients in our study were true inactive carriers in a study according to criteria studies Bru-

netto [26] and Jaroszewicz [9]. Tan and all [7] have rather a higher rate (32%) of inactive carrying in his study. Tan's study [7] defined inactive carriers without including HBsAg levels which certainly has overestimated the inactive carrier's number unlike ours. It took into account two parameters: alanine aminotransferase (ALT) and HBV DNA levels. It is based on persistence of the normal ALT rate (<35 IU/ml) and HBV viral load <2000 IU/ml dosed every three or four months a minimum monitoring 1 year. However, this subgroup of patients, very inactive carriers has a lower risk of developing hepatocellular carcinoma in the course of the diseases [16].

Patients have the mean serum HBsAg levels and HBV DNA levels greater than those observed in HBeAg-negative CHB in Western and Asian series [5] [7].

It is worth noting that no correlation was observed between HBsAg and HBV DNA levels or age for HBeAg-negative CHB cases. HBeAg-negative CHB may follow HBe seroconversion during the immune reactive phase or may develop after years or decades of the inactive carrier state. Furthermore, HBeAg-negative CHB patients have a high risk of progression to advanced hepatic fibrosis, cirrhosis and subsequent complications such as decompensated cirrhosis and hepatocellular carcinoma [27].

However, among HBeAg-negative patients with low viral loads, the risk of hepatocellular carcinoma is determined by HBsAg levels, ALT and age, but not HBV DNA [16]. A decline of serum HBsAg levels represents a reduction in the translation of mRNAs produced from transcriptionally active cccDNA or integrated sequences [26].

No significant correlation was observed between serum HBsAg or HBV DNA levels and patient age, sex, or serum ALT level (data not shown) [5].

In our study, there's significant correlation ($r = 0.239$, $p = 0.014$) between HBsAg levels and HBV DNA levels. A cross-sectional study demonstrated there was no significant correlation between HBsAg levels and HBV DNA levels for HBeAg negative patients [28].

Martinot-Peignoux *et al.* [ref] found significant correlation ($r = 0.438$, $p < 0.0001$) between HBsAg levels and HBV DNA levels to HBsAg-positive patients but not among HBsAg-negative. The same was found in the literature [7] [10] [29].

Our study shows a significant correlation ($p < 0.0001$) between serum HBsAg levels and especially alpha fetoprotein for levels of HBsAg levels >1000 IU/ml. This could presage the risk of developing hepatocellular carcinoma with these patients [16].

The average HBsAg levels patients without fibrosis or carry slight fibrosis (F0, F1) was elevated than that patients with moderate to severe fibrosis (F2, F3, F4) with no statistically significant difference ($p = 0.29$). There was no significant difference in serum HBsAg levels of HBeAg-negative patients with moderate to severe fibrosis compared with those with no or mild fibrosis. However, HBV DNA levels were significantly higher in HBeAg-negative patients with moderate to severe disease [5].

In our study, there was a negative correlation between HBsAg levels and fibrosis degree ($r = -0.069$, $p = 0.484$) with patients. Martinot-Peignoux [5] also found that there is no positive correlation between HBsAg levels and hepatic fibrosis in HBV to HBeAg-negative.

The decline in HBsAg levels with increasing severity of fibrosis may be due to the retention of HBsAg within cells rather than secretion, or a diminishing ability of the host to support viral replication. We observed an increasing HBV DNA levels associated with severity of fibrosis in HBeAg-negative patients, which has also been previously described [18] [30]. This is presumably due to the increasing viral load exacerbating the disease process, possibly due to a loss or lessening in the ability of the host to suppress viral replication. The authors observed a general reduction in HBsAg levels with an increasing in age [31].

Perinatally acquired HBV is the main model of chronic HBV infection in China; hence the age of patients indicates the duration of infection for the majority of the chronic HBV infection and is considered an important factor associated with the progression of HBV-related diseases. The negative correlation between HBsAg levels and age, and the decline in HBsAg levels associated with the progressive phases of the natural history of HBV infection, demonstrate that HBs Ag levels are reflective of antiviral immunity and the duration of HBV infection, particularly for HBeAg-positive patients [31].

Study limitations are the weakness of our sample expensive option because of high cost biological tests to perform particularly complex serum markers and hepatic viral markers. Furthermore, the serum samples have not always been taken on the same day in all cases. Clinicians must interpret biochemical markers of liver activity and fibrosis results with caution in patients with a significant elevation of ALT, and/or GGT and/or alpha2-macroglobulin which could overestimate hepatic injury.

5. Conclusion

The results of this study show that there is a negative correlation between HbsAg levels and liver fibrosis severity with African chronic viral hepatitis B HBeAg-negative patients.

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