

Anamnestic findings and alanine aminotransferase predict accurately chronic HBs antigen carriers among black Africans in Côte d'Ivoire (West Africa)

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To cite this article:

Alassan K. Mahassadi, Emile Allah-Kouadio, Constant Assi, Fulgence M. Y. Bathaix, Ahmad Coulibaly, Hortense Hovi, Mathieu B. Camara, Thérèse Y. Ndri. Anamnestic Findings and Alanine Aminotransferase Predict Accurately Chronic HBs Antigen Carriers among Black Africans in Côte d'Ivoire (West Africa). *Clinical Medicine Research*. Vol. 3, No. 2, 2014, pp. 12-16.
doi: 10.11648/j.cmr.20140302.11

Abstract: Background: The high burden of viral hepatitis B (HBV) remains a challenge in Côte d'Ivoire where patients are mostly seen in hospital at the end stage of the disease. Aim: This cross sectional study is aimed at assessing the usefulness of anamnestic findings, clinical and biological factors in predicting chronic hepatitis B surface antigen (HBsAg) carriers in clinical practice. Patients and methods: The study was conducted in 230 workers (median age: 39 years, female: 20%) of government press enterprise (GPE) in 2010. Socio-demographic, clinical and biological parameters were collected. Chronic HBsAg carrier was defined as serum HBsAg positivity after 2 assessments within 6 months interval. Diagnostic accuracy of predictive factors was determined by multivariate logistic regression. Results: The prevalence of chronic HBsAg was 12.6% [95%CI: 8.61-17.60]. Chronic HBsAg carriers frequently expressed a history of hepatitis (13.8 vs 2.5%, $p=0.003$), or jaundice (37.9 vs 14.3, $p=0.003$), had slightly high level of AST (33 vs 25.5 IU/L, $p=.004$) and ALT (31.5 vs 22, $p<0.0001$) compared to non-carriers. In multivariate analysis, age (OR: 0.93, $p=0.03$), history of hepatitis (OR=8.18, $p=0.005$), unsafe injection with boiled syringe (OR: 3.41, $p=0.03$), and ALT (OR=1.03, $p=0.002$) were predictive factors of chronic HBsAg carriers. The model yielded an AUROC of 0.793 ± 0.06 . With a cut-off <0.125 , the model allowed predicting chronic HBsAg carrier with a sensitivity and negative predictive value of 78.6 and 96.1% respectively. Among 28 chronic HBsAg carriers 22(78.6%) were correctly predicted and 6(21.4%) were false negative. With a cut-off >0.5 , the model showed a specificity, positive and negative predictive values of 99, 66.7 and 88.9% respectively. The model correctly classified 192(99%) workers as non-chronic HBsAg carriers and 2(1%) were misclassified. Conclusion: This study suggests that age, history of hepatitis, unsafe injection with boiled syringe combined with ALT could be used to predict chronic HBsAg carrier in Côte d'Ivoire and other endemic areas in Africa.

Keywords: HBs Antigen, ALT, Hepatitis B, Sub-Saharan Africa

1. Introduction

An estimated number of 350 million individuals are chronically infected by hepatitis B virus (HBV) worldwide, mostly in Asia and in Sub-Saharan Africa [1].

The natural course of chronic HBV infection is marked by its silent route resulting in approximately 70% of patients in

whom the disease is undiagnosed [2,3]. In these patients, chronic HBV infection is discovered at the end stage of the natural history of the disease leading to cirrhosis and hepatocellular carcinoma [3,4].

Guidelines recommend diagnosing chronic HBV infection by testing a subject for hepatitis B surface antigen (HBsAg) positivity [1,5]. Recently Eckman et al. demonstrate in United States that screening for chronic HBV

infection in foreign born subjects from endemic area is cost effective to implement treatment and prevention policies [5,6]. However testing for HBsAg to establish chronic HBV infection in subjects may be hampered in low-income sub-Saharan African countries as in Côte d'Ivoire where HBV is hyper endemic [1,7]. Therefore, a model of prediction for chronic HBsAg carriers is needed.

Most studies report the risk of being HBsAg carrier through household contact [8,9]. The magnitude of sources of contamination such as blood transfusion, sexual behaviour, surgical intervention, tattooing or unsafe injection as risk factors of HBV infection is well-documented [9-12]. The clinical usefulness of these parameters as predictors of chronic HBsAg carrier in African setting is not reported.

The most expressive clinical and biologic signs of HBV infection is jaundice and elevated alanine aminotransferase (ALT) which is common with other liver diseases [2, 13,14]. However jaundice occurs only in one third of patients with acute HBV infection or during flare-ups in those with acute on chronic HBV infection while ALT fluctuates [2,13]. The predictive values of history of jaundice and transaminases suggesting chronic HBsAg carriers are not known in Côte d'Ivoire.

This study is aimed at providing predictive factors suggesting chronic HBsAg carriers among blacks Africans in Côte d'Ivoire.

2. Patients and Methods

2.1. Setting

This study was conducted in the government press enterprise (GPE) during the annual check up of all workers in 2010. The GPE is located in Abidjan, economic capital of Côte d'Ivoire and had 300 employees in all categories (journalists, editors, managers, secretaries, photographers, office agents, factory workers, car drivers, and gatekeepers). This enterprise is engaged in editing daily newspapers, books, magazines, and brochures.

2.2. Patients

Two hundred and thirty workers were enrolled. Patients with clinically expressive liver diseases, hepatitis C antibodies positivity, sickle cell anaemia, malaria, heavy alcohol consumption [2] were excluded. All gave their consent to participate in the study that was conducted during the annual check-up implemented by the GPE's dispensary.

Methods: All GPE workers received a self-administered questionnaire comprising socio-demographic parameters and predictive factors such as a history of surgical intervention, blood transfusion, jaundice, unsafe injection with boiled syringe, family history of hepatitis or jaundice, age at first sexual activity. Clinical examination was done and blood samples were collected from all participants. HBsAg (Cobas, Roche Diagnostics, Mannheim), aspartate aminotransferase (AST) and ALT were determined

(Automate Analyzer, Hitachi Ltd, Tokyo, Japan). To confirm HBsAg positivity, a second blood test was performed 6 months later [2,3]. Chronic HBsAg carrier is defined by the presence of HBsAg in the serum of patient in two assessments within 6 months interval [2].

Further analysis were performed to those with HBsAg positivity including blood cells count, abdominal sonography, complete liver function test, viral load determination, liver biopsy or biochemical markers of liver fibrosis before treatment eventually [2,5].

3. Data Analysis

Categorical variables were expressed as number, percentage, and continuous variables as median and range. Chronic HBsAg carriers were compared to those founded negative. Univariate analysis was performed using Chi square test and Mann-Whitney test. Variables with $p < 0.30$ were included in non-conditional binary logistic regression using backward method. The area under the receiver operating characteristic curve (AUROC) of the model was calculated and the accuracy expressed as sensitivity, specificity, positive and negative predictive values, negative and positive likelihood ratios and diagnostic accuracy using the best cut-off maximising sensitivity and specificity [15]. All statistical analysis were performed using SAS with significant level set at 0.05.

4. Results

The prevalence of chronic HBsAg carriers among 230 workers (median age: 39 years, female: 20%) screened, was 12.6% [95%CI: 8.61-17.60]. In contrast 127(55.2%) of enrolled workers confirmed they had been vaccinated against HBV. Respectively, 9(3.9%), 41(17.9%) and 148(64.4%) workers had history of hepatitis, jaundice and unsafe injection with boiled syringe. The characteristics of screened workers are shown in table 1. Chronic HBsAg carriers had AST and ALT within normal range respectively in 41.4% and 62.1%. In univariate analysis, chronic HBsAg carriers frequently expressed a history of hepatitis (13.8 vs 2.5%, $p=0.003$), jaundice (37.9 vs 14.9, $p=0.001$), had slightly high levels of AST (33 vs 25.5 IU/L, $p=0.004$) and ALT (31.5 vs 22, $p<0.0001$) compared to non carriers. However neither those with history of unsafe injection with boiled syringe had significant history of hepatitis or jaundice nor those with history of hepatitis had significant history of jaundice compared to those without. Moreover, history of hepatitis was not significantly associated with an increased level of transaminases. In multivariate analysis, age (OR: 0.93, $p=0.03$), history of hepatitis (OR=8.18, $p=0.005$), or unsafe injection with boiled syringe (OR: 3.41, $p=0.03$), and ALT (OR=1.03, $p=0.002$) were predictive factors of chronic HBsAg carriers (table 2). The model of prediction was: $-1.19-0.07 \times \text{Age} + 2.1 \times \text{History of hepatitis} + 1.23 \times \text{Unsafe injection} + 0.03 \times \text{ALT}$.

The model yielded an AUROC of 0.793 ± 0.06 (figure).

With a cut-off <0.125 , the model allowed predicting chronic HBsAg carrier with a sensitivity and negative predictive value of 78.6 and 96.1% respectively. Among the 28 chronic HBsAg carriers, 22(78.6%) were correctly predicted and 6(21.4%) were false negative. With a cut-off >0.5 , the model

showed a specificity, positive and negative predictive values of 99, 66.7 and 88.9% respectively. The model correctly classified 192(99%) workers as non-chronic HBsAg carriers and 2(1%) were misclassified (table 3).

Table 1: Characteristics of screened workers

	All workers N=230	Chronic HBs antigen carriers		P
		Yes (n=29)	No (n=201)	
Age [median(range)]	39(35)	37(29)	39(35)	0.1
Sex [female (%)]	46(20)	3(10.3)	43(21.4)	0.2
Blood transfusion [n(%)]	12(5.2)	1(3.5)	11(5.5)	0.6
History of hepatitis [n(%)]	9(3.9)	4(13.8)	5(2.5)	0.003
History of jaundice [n(%)]	41(17.9)	11(37.9)	30(14.9)	0.003
History of surgical intervention [n(%)]	70(30.4)	7(24.1)	63(31.3)	0.4
Unsafe injection with boiled syringe [n(%)]	148(64.4)	22(75.9)	126(62.7)	0.2
History of jaundice in the household [n(%)]	57(24.8)	9(31.0)	48(23.9)	0.4
Family history of hepatitis [n(%)]	25(10.9)	4(13.8)	21(10.5)	0.6
Vaccination against hepatitis B [n(%)]	127(55.2)	14(48.3)	113(56.2)	0.4
ALT (IU/L) [median (range)]	23(466)	31.5(457)	22(98)	<0.0001
ALT (>1.5 ULN) [n(%)]	12(5.4)	5(17.9)	7(3.6)	0.002
AST(IU/L)[median(range)]	26(380)	33(380)	25.5(91)	0.004
AST (>1.5 ULN)[n(%)]	14(7)	7(24.1)	17(7)	0.003

ALT: Alanine aminotransferase (normal value <40 IU/L), AST: Aspartate aminotransferase (normal value <37 IU/L), ULN:upper limite of normal

Table 2: Factors predicting chronic HBsAg carriers: multivariate analysis

	Adjusted OR	95%CI	p
Age (years)	0.93	0.87-0.99	0.03
History of hepatitis (yes vs. no)	8.18	1.86-35.96	0.005
Unsafe injection with boiled syringe (yes vs. no)	3.41	1.13-10.27	0.03
ALT (IU/L)	1.03	1.01-1.05	0.002

C-index: 0.793, $p=0.0005$, ALT: Alanine aminotransferase, OR: odds ratio.

Model of prediction: $-1.19 -0.07 \times \text{Age} + 2.1 \times \text{History of hepatitis} + 1.23 \times \text{Unsafe injection} + 0.03 \times \text{ALT}$

Multivariate analysis performed in 28 chronic HBsAg carriers and 194 non carriers

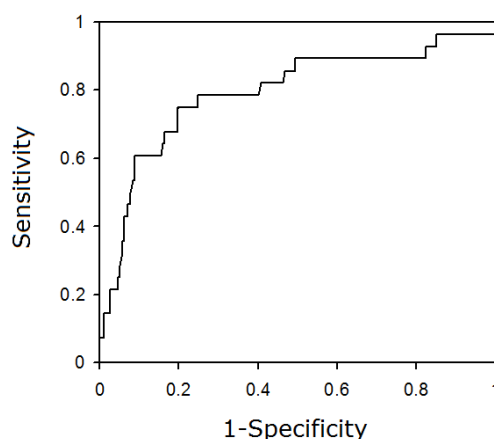


Figure1: Receiver operating characteristic curve of the model predicting chronic hepatitis B carrier based on anamnestic findings and ALT

Table 3: Accuracy of model predicting chronic HBsAg carrier based on anamnestic findings and ALT

Prediction of chronic HBsAg	Cut-off	TP (n)	TN (n)	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	DA (%)
Carrier	0.125	22	146	78.6	75.3	31.4	96.1	3.2	-	75.6
	0.136	21	151	75	77.8	32.8	95.6	3.4	-	77.5
	0.140	21	156	75	80.4	34.5	95.1	3.8	-	79.7
	0.144	20	156	71.4	80.4	34.5	95.1	3.6	-	79.2
Non carrier	0.40	6	187	21	96.4	46.2	89.5	-	0.8	86.9
	0.42	5	189	17.8	97.4	50	89.2	-	0.8	87.4
	0.48	4	190	14.3	97.9	50	88.7	-	0.9	87.4
	0.51	4	192	14.2	99	66.7	88.9	-	0.9	88.2

TP: true positive, TN: true negative, Se: sensitivity, Sp: specificity, PPV: predictive positive value, NPV: negative predictive value, LR: likelihood ratio, DA: diagnostic accuracy

Multivariate analysis performed in 28 chronic HBsAg carriers and 194 non-carriers

5. Discussion

There is a paucity of data predicting chronic HBsAg carriers among black Africans in clinical practice. This study revealed a high prevalence of chronic HBsAg carriers similar to that of general population in Côte d'Ivoire and elsewhere in sub-Saharan African countries [16,17] and demonstrated the usefulness of anamnestic findings and ALT as predictors of chronic HBsAg carriers among Ivoirians. Using the model of prediction, serological assessment of HBsAg could be avoided in nearly 100% of workers and almost 80% could be predicted as chronic HBsAg carriers with high certainty.

During the natural course of chronic HBV infection, the annual incidence of spontaneous seroclearance of HBsAg occurs in approximately 1-3% [2-3]. In Africa HBV infection occurs mainly from mother to infant at time of birth or during childhood [1,13]. Thus the longer the duration of chronic HBV infection, the higher the percentage of patients with spontaneous HBsAg seroclearance [18]. In fact, Martinson et al. demonstrate in a large population based study in Ghana that being HBsAg carrier trends down with age [8]. Our study in which the risk of being chronic HBsAg carrier declined with age reflected probably this finding.

Moreover chronic HBV carriers may have an increased level of ALT and jaundice, occurring during flare-ups related to liver impairment [3,13]. In our study the non significant effect of jaundice may be related to its confounding role as the result of the vast aetiologies of jaundice [19, 20]. Although an increasing level of ALT indicates a biological activity related to immune pressure against HBV as probably experienced by 37.9% of chronic HBsAg carriers in our study [2,3]. However, chronic HBsAg carriers may have normal level of ALT at immuno-tolerant phase and harbour liver damage [21]. In fact almost two third of chronic HBsAg carriers in our study had ALT values

within normal range that emphasized the need of model of prediction including ALT levels.

The model in our study combined in addition to age and ALT, history of hepatitis and unsafe injection with boiled syringe. History of hepatitis was significantly reported by workers in our study contrasting with the finding of Ghadir et al. made in general population in Iran [22]. This discrepancy was probably due to well-documented history of hepatitis reported by workers in our study. However we did not know whether history of hepatitis was related to acute on chronic HBV infection or acute HBV infection [2,13]. Interestingly in our study, workers reporting unsafe injection were more likely to be chronic HBsAg carriers. Unsafe injections with boiled syringes were commonly used in dispensaries in Africa [12]. This practice had probably contributed for the dissemination of HBV or others blood-borne virus among population in Côte d'Ivoire [1,12].

This study has been strengthened by the relatively high level of education of workers resulting in high reliability of all reported anamnestic findings. In addition, we did not find any colinearity between histories of hepatitis and jaundice indicating that enrolled workers have not misinterpreted the questions [15]. However, this study had these following limitations. Some parameters such as age at first sexual activity was not include in the analysis because of high missing data, and sexual behaviours, tattooing, sharing items known as risk factors were not studied [8-11]. In other hand, history of hepatitis could not be easily reported by all subjects in general population without any documented medical history because of the similarity between symptoms of hepatitis B and others viral and non viral hepatitis [13,14]. Finally, the generalizability of our results to the entire population of Côte d'Ivoire may be questionable as the study was limited to a specific population [19].

However, this study reported the diagnostic values of easily recordable parameters in clinical practice in Côte d'Ivoire for the prediction of chronic HBsAg carriers among

Ivoirians. The model could be used to select subjects when they report a history of hepatitis, unsafe injection whatever the level of ALT for a biological assessment of HBsAg and to implement treatment and prevention policies in Côte d'Ivoire [1]. Others studies are needed in others Africans countries to verify these findings.

Conflict of Interest

No potential conflict of interest relevant to this article is reported

Authors' Contributions

Alassan K. Mahassadi designed the study, wrote the protocol, managed the literature searches, collected the data, performed the statistical analysis and wrote the first draft of the manuscript. Emile Allah-Kouadio, wrote the protocol, drafted the manuscript. Constant Assi, Fulgence Mamert Yao-Bathaix, Hamad Coulibaly drafted the manuscript. Hortense Hovi collected the data and approved the final version of the manuscript. Benoit Mathieu Camara and Thérèse Ndri Yoman approved the final version of the manuscript

Acknowledgment

The authors are grateful to Dr Dogbe J.A. at the department of Child Health, SMS-KNUST/KATH, Kumasi, Ghana for correcting the manuscript

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