Journal of Gastroenterology, Hepatology and Endoscopy

Research Article
Published: 12 Jan, 2019

Random Evaluation of the Risk of Occurrence of Hepatocellular Carcinoma in Chronic Carriers of Hepatitis B Virus in a Highly Endemic Country using the REVEAL-HBV Score

Servais Albert Fiacre Eloumou Bagnaka[1,2], Winnie Tatiana Bekolo Nga[1,2], Gabin Kenfack[3], Isabelle Dissongo[2], Guy Roger Nsenga Djapa[4], Agnes Malongue[1], Christian Tzeuton[5], Oudou Njoya[3], Firmin Andoulo Ankouane[3], Henry Namme Luma[1,3] and Dominique Noah Noah[2]*

[1]Internal Medecine Unit, Douala General Hospital, Cameroon

[2]Faculty of Medicine and Pharmaceutical Sciences (FMPS), Cameroon

[3]Faculty of Medicine and Biomedical Sciences of Yaounde, Cameroon

[4]Ebolowa Regional Hospital, Cameroon

[5]Capucines Medical Center of Douala, Cameroon

Abstract

Background: Chronic Hepatitis B Viral (HBV) infection remains a public health problem worldwide. It accounts for complications such as hepatocellular carcinoma. The goal of this study was to evaluate the risk of the occurrence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B infection in a highly endemic environment.

Materials and Methods: It was a cross-sectional study, carried out at the Douala General hospital (DGH) during a period of 11 years. The risk evaluation was done using items of the Risk Evaluation of Viral Load And liver disease of Hepatitis B Virus (REVEAL-HBV) score and were classified as low, moderate and high risk of occurrence of hepatocellular carcinoma. The Khi-2 test was used to compare different groups of patients with a p-value less than 0.05 considered significant.

Results: Two-hundred and five patients were enrolled, with a male predominance (62.4%). The mean age was 34.77 ± 9.79 years. The risk of occurrence of HCC was high in 1.9% of patients, and exclusively associated to men (p=0.001). Patients aged less than 30 mainly had a low risk which accounted for 76.6% of the population (p<0.001). A low viral load was associated with a low risk of occurrence of HCC (p<0.01).

Conclusion: The risk of occurrence of HCC is slow in the majority of patients in DGH followed-up for chronic hepatitis B infection. It is related to age, sex, liver enzymes, viral load and the presence of hepatitis B e-antigen. This risk can be easily assessed during outpatient's consultations, and clinicians are encouraged to do so.

Keywords: HBV; Reveal-HBV score; Hepatocellular carcinoma; Douala; Cameroon

OPEN ACCESS

Correspondence:
Servais Albert Fiacre Eloumou Bagnaka, Internal Medecin Unit, Douala General Hospital, BP 2701, FMSP, University of Douala, Douala, Cameroun,
E-mail: eloumoug@yahoo.fr

Received Date: *26 Dec 2018*
Accepted Date: *10 Jan 2019*
Published Date: *12 Jan 2019*

Citation:
Eloumou Bagnaka SAF, Bekolo Nga WT, Kenfack G, Dissongo I, Nsenga Djapa GR, Malongue A, et al. Random Evaluation of the Risk of Occurrence of Hepatocellular Carcinoma in Chronic Carriers of Hepatitis B Virus in a Highly Endemic Country using the REVEAL-HBV Score. J Gastroenterol Hepatol Endosc. 2019; 4(1): 1054.

Introduction

Hepatitis B Virus (HBV) remains a public health problem worldwide with over two billion people infected amongst whom 240 million are chronic carriers [1,2]. Africa as well as other developing countries is highly endemic regions [1]. Cameroon, one of Africa's most endemic zones, has an overall prevalence of 11.2%, with a geographical variation ranging from 2.49% to 19% [2-5].

The HBV accounts for numerous complications generally linked to the chronic carrier status as well as other factors such as alcohol, tobacco and diet [6,7]. Continuous follow-up of chronic HBV carriers is mandatory for the prevention and early diagnosis of complications such as cirrhosis and Hepatocellular Carcinoma (HCC) [8], which quite often is diagnosed late in its course and happens to at times be the mode by which the infection is revealed [9]. Several factors contribute to the occurrence of HCC in the natural history of chronic HB infection. This can be grouped into three categories. Firstly, there are general factors which include genetic mutations such as mutation of the

P53 gene and the activation of oncogenic mechanisms (like oxidative stress, P13K-AKT-mTOR, MAPK) [8]. Next, are host related factors such as family history of HCC, diabetes, alcohol intake and massive testosterone secretion in men [8]. Last but not the least, there are viral related factors such as the genotype, viral load and the presence of hepatitis B e-antigen [8,9].

In order to prevent such complications, and most importantly to ease early detection of HCC, some models have been elaborated and used as predictive instruments for the diagnosis of HCC [10-12]. It led to the Risk Evaluation of Viral Load And liver disease of hepatitis B Virus (REVEAL-HBV), elaborated in 2007 from a Taiwanese cohort. It takes into account variations related to viral markers, sociodemographic data (sex and age) and other parameters such as liver enzymes and family history of HCC [13]. This score determines the cumulative risk of developing HCC, and classifies patients into low risk (if less than 9), moderate risk (if between 9 and 13) and high risk if above 13 [13,14]. The aim of our study was to evaluate the risk of occurrence of HCC in a hepatitis B virus highly endemic zone using the REVEAL-HBV predictif score, so as to determine how reproducible it is and be able to stage individual patients in outpatient's clinic.

Methods

It was a cross sectional study carried out at the GI unit of the Douala general hospital (which is a university teaching hepatology hospital with a capacity of 310 beds). It was carried out during a period of 11 years from January 1st 2005 to December 31st 2015. Files of chronic carriers of HBV were sampled and only those with all parameters permitting to calculate the REVEAL-HBV were included in our study [15]. Exclusion criteria were co-infection with hepatitis C virus and/or HIV, and the presence of complications such as cirrhosis and HCC. Data collected included sociodemographic data (age and sex), mode of payment of health care services, comorbidities (alcohol or tobacco intake, personal past medical history, family history of HCC, clinical presentation upon diagnosis).

Biologic data included the presence of hepatitis B e-antigen (HBeAg) or its antibodies (HBeAb), HBV viral loads using a real time PCR technique (Cobas TaqMan HBV) with a threshold of 20IU/ml considered significant, quantification of hepatitis B surface antigen (HBsAg) using an immunological automated technique (Cobas e 411) with a threshold of 0.05IU/ml considered significant, and liver enzyme tests. Liver fibrosis was evaluated using non invasive methods: Fibrotest or Transient Elastography(TE), which were correlated to the METAVIR score. When it was less than F2, was termed of non-significant fibrosis, and when it was greater or equal to 2 it was considered significant fibrosis. A file was considered complete when it had all parameters of the REVEAL-HBV score.

Concerning the risk of occurrence of HCC, we took into consideration all risk factors. Extrapolations were done when considering genotypes A and E.

Definition of terms:

Asymptomatic patient: patient without any symptom; Incomplete files: files without REVEAL-HBV baseline predictor; HBV carriers: patients with HBs antigen; Non chronic carriers: patients with clearance of HBs antigen after six months

Chronic carrier's patients with persistence of HBs antigen after six months.

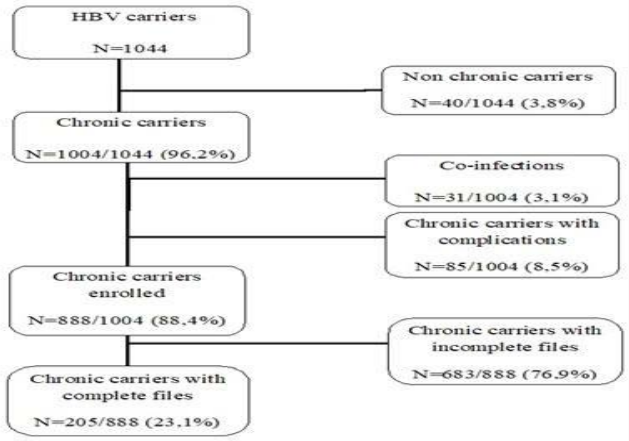

Figure 1: Flow chart of the population.

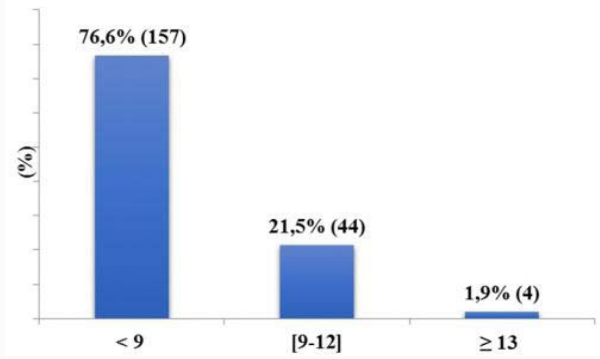

Figure 2: Distribution of the population with respect to the REVEAL-HBV score (n=205).

Microsoft Excel 2013, SPSS 20 and sphinx plus software were used for data analysis. Qualitative variables were presented as frequencies and percentages and were compared using the Khi-2 test with a confidence interval set at 95. Quantitative variables were on the other hand analyzed using means, median, standard deviation with a confidence interval set at 95%.

Results

Of the 1044 files analysed during the study, only 205 met our selection criteria (Figure 1).

The mean age of patients was 34.77 ± 9.79 years with a predominance of patients being less than 30 years old, 32.2% (Table 2). The male to female ratio was 1.6. Seventy two percent of them agreed to taking alcohol and 2.4% (n=05) had a family history of HCC (Table 2). Upon diagnosis, 75% (n=155) of them were asymptomatic (Table 2).

When considering biological data, the mean ALT level was 46.67 ± 43.72 IU/L Hepatitis B e-antigen was present in 4.9% (n=10) of patients. The mean value of quantitative HBsAg was 1.52.104 ± 1.02.104 IU/ml. The mean HBV viral load was 5.97.106 ± 4.1.106 UI/ml (Table 2). Of the 86 patients in whom liver fibrosis was evaluated, 66 (79.1%) had a non significant fibrosis (Table 2).

The mean REVEAL-HBV score was 7 ± 2.29. The risk of developing HCC was low for 76.6% (n=157) of patients (Figure 2). The risk of developing HCC was low ($p \leq 0.05$) (Table 3). Men were

Table 1: Reveal-VHB score with extrapolations of genotypes A and E [15].

Baseline Predictor	Risk score
Age(Year)	
30-34	0
35-39	1
40-44	2
45-49	3
50-54	4
55-59	5
60-65	6
Sex	
Female	0
Male	2
Levels of ATL (IU/L)	
<15	0
15-44	1
≥ 45	2
Family History of hepatocellular carcinoma	
No	0
Yes	2
HBeAg/HBV DNA (copies/ml) HBsAg (IU/ml) genotype	
Negative/<10^4/<100/any type	0
Negative/<10^4/100-999/any type	2
Negative/<10^4/ ≥ 1000/any type	2
Negative/10^4-10^6/<100/any type	3
Negative/<10^4-10^6/100-999/any type	3
Negative/<10^4-10^6/ ≥ 1000/any type	4
Negative/>10^6/any type/ B or B + C	5
Negative/>10^6/any type/C	7
Positive/any level/any level/ B or B + C	6
Positive/any level/any level/C	7
Risk levels of developing hepatocellular Carcinoma	**Sum of score**
Low risk	<9
Medium risk	9-12
High risk	≥ 13

more at risk of developing HCC than women (p<0.001). Family history of HCC and quantitative HBsAg level did not influence the occurrence of HCC (p>0.05) (Table 3). A high viral load and positive HBe-antigen increased the risk of developing HCC (p<0.001), so did raised liver enzymes (p<0.01) (Table 3).

Discussion

This study aimed at determining the risk of occurrence of HCC using a validated score in a HBV highly endemic zone. It helped us realize that chronic hepatitis B mostly affects the male youth less than 30 years old. The risk of occurrence of HCC is low in 76.6% of patients. HCC is associated to patient's age sex, liver enzymes level, viral load and the presence of HBeAg.

The major draw-backs of this study include the absence of genetic sequencing and lack of follow-up of patients. These make the risk was random.

Table 2: General characteristics of the population.

Parameters	Values
Ages (years) (<30)	66 (32.2%)
Sex (Males)	128 (62.4%)
Past Medical History	
Alcohol	70 (34.2%)
Tobacco	10 (4.9%)
Family history of HCC	05 (2.4%)
Clinical presentation	
Asymptomatic	155(75.6%)
ALAT (IU/l) (N=205)	49.67 ± 43.72
ASAT (IU/l) (N=199)	45.81 ± 14.89
GGT (IU/l) (N=71)	55.54 ± 18.84
PAL (IU/l) (N=53)	100.14 ± 58.07
PLT (G/l) (N=96)	187.82 ± 66.43
PT (%) (N=80)	87.13 ± 13.11
Albumin (g/l) (N=49)	39.97 ± 6.13
HBsAg level (IU/ml) (N=205)	1.52. 10^4 ± 1.02. 10^4
HBeAg positive (N=205)	10 (4.9%)
ADN HBV (copies/ml) (N=205)	5.97. 10^6 ± 4.1. 10^6
Fibrosis F<2 (N=86)	66 (79.1%)

The elaboration of the REVEAL-HBV score helps a better appraisal of the risk of complications in patients with chronic HBV. This score can be used easily in clinical setting as items are part and parcel of routine clinical and paraclinical evaluation of a chronic HBv carrier. However, it is worth noting that there exist a certain degree of interracial variability (Caucasians, Asians or Blacks) as well as variability related to whether the patient has cirrhosis or not [12]. As is the case with several scores, the REVEAL-HBV score has been elaborated in Asia in a cohort of non cirrhotic patients having the occurrence of HCC as the main clinical end point [9,14,16], makes this score appropriate to our study. We hence determined the risk of occurrence of HCC even though it was determined at random in our study which was retrospective and cross sectional. This risk was low in the majority of cases (76.6%). Contrary to studies carried out in Asia, namely that of Lee et al. [10], in which the risk of HCC was 60.1%, our patients had quite a better prognosis. In a study carried out by Tseng et al. [17], in a population of HBeAg negative patients, similar to ours, 15.2% of patients were at high risk of developing HCC, contrarily to 1.9% in ours. Tseng et al. found a low risk of developing HCC in 30.1% of patients, against 74.7% in ours. This discrepancy can be attributed to the geographical variability of the HBV. The B and C genotypes are more rampant in Asia, associated with high viremia and pre-core mutations increase the risk of developing HCC in Asia [1,18,19]. Our results show that age, sex, high ALAT levels, presence of HBeAg and viral load significantly influence the occurrence of HCC and the natural history of the infection. When looking at the sociodemographic characteristics, the male predominance has been reported by most studies on HBV [20], even though it is an independent risk factor as is the case in the majority of cancers [1]. Our population's youthful age, coupled to a low risk of developing HCC, makes the assertion that the risk of HCC increases with age, as it takes time for carcinogenesis to take place, which in itself is greatly influenced by fluctuations of some biological parameters during the course of the natural history of HBV [14,17]. As such, a

Table 3: Various subgroups compared with respect to the risk of occurrence of HCC.

	Low risk (%)	Moderate risk (%)	High risk (%)	p-value
Age (years)				
< 30	57 (27.8)	9 (4.4)	0 (0)	
30-34	40 (19.5)	5 (2.43)	1 (0.48)	
35-39	43 (21)	2 (0.97)	0 (0)	< 0.001
40-44	12 (5.9)	4 (1.95)	1 (0.48)	
45-49	3 (1.5)	4 (1.95)	0 (0)	
50-54	2 (0.9)	10 (4.9)	1 (0.48)	
55-59	0 (0)	7 (3.45)	1 (0.48)	
60 and above	0 (0)	3 (0.97)	0 (0)	
Sex				
Female	70 (34.1)	7(18.1)	0(0)	0.001
Male	87 (42.4)	37(3.45)	4(1.9)	
ALAT (IU/ml)				
< 15	21 (10.2)	2 (0.97)	0 (0)	
15-44	114 (55.7)	27 (13.3)	2 (0.97)	0.01
³45	22 (10.7)	15 (7.3)	2 (0.97)	
Family history of HCC				
Yes	3 (1.5)	2 (0.97)	0 (0)	0.57
No	154 (75.1)	42 (20.5)	4 (1.9)	
HBeAg				
Positive	4 (1.9)	5 (2.4)	1 (0.48)	0.009
Negative	153 (74.7)	39 (19.1)	3 (1.46)	
HBsAg level				
< 100	21 (10.3)	4 (1.9)	0 (0)	0.62
100-999	32 (15.6)	10 (4.9)	0 (0)	
³1000	104 (50.7)	30 (14.7)	4 (1.9)	
Virale load				
$< 10^4$	117 (57.1)	18 (8.8)	0 (0)	
10^4-10^6	36 (17.6)	20 (9.8)	2 (0.97)	< 0.001
$>10^6$	4 (1.9)	6 (2.9)	2 (0.97)	

rise in liver enzymes, especially ALAT is a known risk factor for the occurrence of HCC [21]. However, the mean liver enzymes level does not portray real live situation given that the study is cross sectional, as it is known to vary duty the course of the natural history of chronic HBV infection [6,8]. This is equally true for the viral load [22], which for our patients is slow, and consequently reduces the risk of HHC occurrence. Concerning viral markers, our results are similar to those of Chen et al. [10] when considering the absence of HBeAg, which in our study is associated with a low risk of HCC given that genotypes found in Africa are less virulent than those found in Asia [17]. It is worth noting that in our study, HBsAg level is mostly associated to a low risk of occurrence of HCC, though not significant. It is relevant, given that low level of HBsAg is a associated with a good prognosis especially if HBeAg negative patients with a low viral load, as is the case with most of our patients [17,23]. Though gene sequencing was not done for our patients, it plays a vital role in variations of viral load and HBsAg levels.

Conclusion

The follow-up of chronic HBV carriers remains a challenge to health care providers due to complications such as hepatocellular carcinoma. The REVEAL-HBV score in our study reveals that the risk of developing HCC in low in our setting. Predictive factors associated to this risk include age, sex, ALAT level, viral load and the presence of the HBeAg. However, our study is in cross sectional, such an evaluation should be done repeatedly given the high variability of biological parameters. We suggest that this score be used during routing outpatient clinics after its validation by other health facilities.

Acknowledgement

The authors would like to thank the external consultation staff and the archives of all health facilities that participated in this work for their contribution to the data collection.

Ethical Clearance

Ethical issues were thoroughly followed throughout this study. The management of the Douala General Hospital approved the study and it received the ethical clearance of the Douala University (code number CEI-UD/320/12/2015).

References

1. Sunbul M. Hepatitis B virus genotypes: Global distribution and clinical

importance. World J Gastroenterol. 2014;20(18):5427-34.

2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386:1546-55.
3. Bigna JJ, Amougou MA, Asangbeh, Kenne AM, Noumegni SRN, Ngo-Malabo ET, et al. Seroprevalence of hepatitis B virus infection in Cameroon: A systematic review and meta-analysis. BMJ Open. 2017;7(6):e015298.
4. Mbanya D, Takam D, Ndumbe P. Serological findings amongst first-time blood donors in Yaoundé, Cameroon: Is safe donation a reality or a myth? Transfus Med. 2003;13(5):267-73.
5. Foupouapouognigni Y, Sadeuh Mba SA, Betsem EB, Rousset D, Froment A, Gessain A, et al. Hepatitis B and C Virus Infections in the Three Pygmy Groups in Cameroon. J Clin Microbiol. 2011;49(2):737-40.
6. Hézode C. Histoire naturelle de l'hépatite B. Virologie. 2010;14(suppl1):s5-s11.
7. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-98.
8. Lin CL, Kao JH. Natural history of acute and chronic hepatitis B: The role of genotypes and mutants. Best Pract Res Clin Gastroenterol. 2017;31(3):249-55.
9. Xu W, Yu J, Wong VW. Mechanism and prediction of HCC development in HBV infection. Best Pract Res Clin Gastroenterol. 2017;31(3):291-8.
10. Lee MH, Yang HI, Lui J, Batrla-Utermann R, Jen CL, Iloeje UH, et al. Prediction Models of Long-Term Cirrhosis and Hepatocellular Carcinoma Risk in Chronic Hepatitis B Patients: Risk Scores Integrating Host and Virus Profiles. Hepatology. 2013;58(2):547-54.
11. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): Development and validation of a predictive score. Lancet Oncol. 2011;12(6):568-74.
12. Wong VW, Janssen HL. Can we use HCC risk scores to individualize surveillance in chronic hepatitis B infection? J Hepatol. 2015;63(3):722-32.
13. Iloeje UH, Yang HI, Chen CJ. Natural history of chronic hepatitis B: what exactly has REVEAL revealed? Liver Int. 2012;32(9):1333-41.
14. Chen CJ, Yang HI. Natural history of chronic hepatitis B Revealed. J Gastroenterol and Hepatol. 2011;26(4):628-38.
15. Lin CL, Tseng TC, Kao JH. What can we learn from hepatitis B virus clinical cohorts? Liver Int. 2015;35(Suppl 1):91-9.
16. Kao JH. Risk stratification of HBV infection in Asia-Pacific region. Clin Mol Hepatol. 2014;20(3):223-7.
17. Tseng TC, Liu CJ, Chen CL, Yang HC, Su TH, Wang CC, et al. Risk Stratification of Hepatocellular Carcinoma in Hepatitis B Virus e Antigen–Negative Carriers by Combining Viral Biomarkers. J Infect Dis. 2013;208(4):584-93.
18. Liu CJ, Kao JH. Global Perspective on the Natural History of Chronic Hepatitis B: Role of Hepatitis B Virus Genotypes A to J. Semin Liver Dis. 2013;33(2):97-102.
19. Shi YH. Correlation between hepatitis B virus genotypes and clinical outcomes. Jpn J Infect Dis. 2012;65(6):476-82.
20. Eloumou Bagnaka SAF, Luma Name H, Noah Noah D, Nko'Ayissi G, Malongue A, Noubiap NJ, et al. Clinicopathological Characteristics of a Group of Sub-Saharan African Patients with Chronic Hepatitis B Infection: A Gender Analysis. Gastroenterol Hepatol Open Access. 2016;5(8):00174.
21. Lin YJ, Lee MH, Yang HI, Jen CL, You SL, Wang LY, et al. Predictability of liver-related Seromarkers for the Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients. PLoS One. 2013;8(4):e61448.
22. Chen CJ, Yang HI, Iloeje UH; REVEAL-HBV Study Group. Hepatitis B Virus DNA Levels and Outcomes in Chronic Hepatitis B. Hepatology. 2009:49(5suppl):S72-84.
23. Tseng TC, Lui CJ, Yang HC, Su TH, Wang CC, Chen CL, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV Load. Gastroenterology. 2012;142(5):1140-9.