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Chronic Kidney Disease amongst Patients with Chronic Hepatitis B Virus in a Low Income Country Setting

Halle Marie Patrice[1*], Eloumou Bagnaka Servais Albert[1], Nda Mefo'o Jean Pierre[2], Kanouo Yolande[3], Djantio Hilaire[3], Fouda Hermine[4], Malongue Agnes[5], Doualla Marie Solange[4] and Luma Namme Henry[4]

[1]*Department of Internal Medicine, Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Cameroon*

[2]*Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Douala, Cameroon*

[3]*Higher Institute of Health, University of the Mountains, Cameroon*

[4]*Department of Internal Medicine, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Cameroon*

[5]*Department of Internal Medicine, Douala General Hospital, Cameroon*

[*]**Corresponding author:** Dr Halle Marie Patrice, Department of Internal Medicine, Douala General Hospital, Cameroon, Tel: 00237-699807233; E-mail: patricehalle@yahoo.fr

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Abstract

Background: Hepatitis B virus (HBV) infection and chronic kidney disease (CKD) are major public health issue. Patients with HVB are at risk of CKD. Data on the prevalence of CKD in HBV-infected patients in Sub Saharan Africa (SSA) are inexistent. This study aimed to determine the prevalence and associated factors of CKD in HBV-infected patients in Cameroon.

Methods: We carried out a cross sectional study from March to August 2017 in Cameroon, including consenting patients aged >18 years followed up for chronic HBV. Data collected in medical records were: Socio demographic, Comorbidities, HBV-related data and biological data. Morning urine and blood were collected for dipstick analysis and creatinine dosage. GFR was estimated using the four-variable MDRD and CKD-EPI equations. Patients with eGFR<60 ml/min/1.73 m² and/or urinary abnormalities underwent a second measurement 3 months later. Definition and classification of CKD were based on the KDIGO 2012. Logistic regression was used to determine factors associated to proteinuria and CKD. A p value <0.05 was considered significant.

Results: We included 272 participants, mean age of 37.33 ± 9.73 years, 65.8% males. Prevalence of proteinuria was 12.1%, 7.7% for haematuria and 3.7% for leucocyturia. Prevalence of CKD was 19.9% (54/272) using CKD-EPI-formula and 18.4% (50/272) with MDRD, with 8.1% (22/272) at CKD stage 1, 8.9% (24/272) for stage 2, 2.6% (7/272) stage 3, 0.3% (1/272) stage 4. Factors associated to proteinuria were chronic use of herbal medicine (p=0.007), haematuria (p=0.009), while age ≥50 years (p=0.004), duration of HBV infection ≥5 years (p=0.039) and chronic use of herbal medicine (p=0.040), were factors associated to CKD.

Conclusion: CKD is frequent amongst HBV patients in Cameroon. Older age, used of traditional herbs and longer duration of the infection were factors associated to CKD. There is need for renal function evaluation during follow up of HBV infected patient in our setting.

Keywords: Prevalence; Hepatitis B virus; Chronic kidney disease; Cameroon

Abbreviations: HBV: Hepatitis B Virus; CKD: Chronic Kidney Disease; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; ESKD: End Stage Kidney Disease; GFR: Glomerular Filtration Rate; SSA: Sub Saharan; KDIGO: Kidney Disease Improving Global Outcome; DGH: Douala General Hospital; NSAID: Non-Steroidal Anti-Inflammatory Drugs; Peg IFNα: Pegylated Interferon Alfa; TDF: Tenofovir Disoproxil Fumarate; HBeAg: HBe Antigen; anti-HBe: Hbe Antibody; HBV DNA: HBV Viral Load

Introduction

Hepatitis B virus (HBV) infection and chronic kidney disease (CKD) are major public health issue. Chronic HBV affects over 350 million people worldwide and the prevalence of CKD was recently estimated at 13% [1,2]. CKD is known to increase the risk of mortality of patients in general and in specific disease including chronic HBV infection [3-6]. Patients with HBV are at risk of CKD and the mechanism is multifactorial. Renal disease can be due to the virus itself and the commonest type is membranous glomerulonephritis [7-11]. Also some antiviral used for the treatments of HBV are nephrotoxic [12-14]. These patients have traditional risk factors for CKD such as diabetes mellitus, high blood pressure, human immunodeficiency virus (HIV) or hepatitis C virus (HCV) co-infection that can impact on renal function [15]. Few studies have reported the prevalence of renal abnormalities in HBV infected patients. In the majority of these studies renal abnormality was assessed once. Amet et al. reported in a multicentric study that 64.6% of untreated chronic HBV-infected patients had kidney disease with 38.1% proteinuria, 20.6% heamaturia, 9% sterile leucocyturia and 3.9% glucosuria [16]. In addition the risk of end stage kidney disease (ESKD) is reported to be high amongst HBV-infected patients [9,17,18]. In the study of YI-Chun et al. in Taiwan the

risk of ESKD was 3.85-fold higher in HBV-infected subjects than in controls after adjusting for potential confounders [18]. The prevalence of proteinuria, haematuria and glycosuria was 17%, 30% and 8% respectively amongst chronic HBV-infected patients on Adefovir in the study of Izzedine et al. in France [19]. In Taiwan Huang et al. found a prevalence of proteinuria of 6.4% among HBs antigen-positive patients [20].

In addition predictions model showed that yearly median change of glomerular filtration rate (GFR) in untreated HBV-infected patients was approximately - 2 ml/min [21]. Jung-Ho et al. identified hypertension, diabetes and underlying CKD as risk factor for renal function decline in chronic HBV-infected patients [22].

Data on the prevalence of CKD in HBV-infected patients in Sub Saharan Africa (SSA) are inexistent. CKD prevalence is high in Cameroun [23,24] and screening for renal disease in risk population is not routinely done. HBV is endemic in Cameroon with a pool prevalence estimated at 11.2% in the general population [25]. To the best of our knowledge, there are no reported data on the prevalence of CKD in chronic HBV-infected patients according to the KDIGO definition [26]. We aimed at determining the prevalence and associated factors of CKD in HBV-infected patients in Cameroon. This could help to provide basic data and also to implement strategies for better management of these patients.

Methods

Study design

This was a cross sectional study carried out from the 1st March to 30 August 2017 in the gastroenterology unit of the Douala General Hospital (DGH). DGH is one of the tertiary referral and teaching hospital in Cameroon, located in the littoral region with a population of more than 3 million at the end of the year 2015 [27].

Data collection and participants

Data were collected using patient's records and interview by a general practitioner in the routine outpatient consultation of the gastroenterology unit. We included consenting patients aged 18 years old and above followed up for chronic Hepatitis B with or without antiviral treatment. Those who had known urinary tract infection during the past 2 weeks or were during menstruation were excluded.

Data collected were: Socio demographic (age, sex), Comorbidities (diabetes, hypertension, co infection with HIV or Hepatitis C virus, alcohol consumption, chronic used of Non-steroidal anti-inflammatory drugs (NSAID), chronic use of herbal medicine, used of nephrotoxic drugs).

HBV-related data: Duration of HBV infection, usage and type of antiviral treatment, duration of treatment;

Clinical data: Body Mass Index express in kg by m^2.

Biological data: Transaminases (AST, ALT), viral markers [HBe antigen (HBeAg), Hbe antibody (anti-HBe), HBV viral load (HBV DNA)]. HBV DNA viral load was investigated through real-time PCR using the COBAS TaqMan HBV test with a lower threshold at 20 IU/ml; The viral load <2000 IU/ml was consider low and high when greater than or equal to 2000 IU/ml.

Liver fibrosis was measured through a non-invasive method, that is Fibrotest© and Actitest©, Fibrometre©, Transient Elastography (Fibroscan®). Fibrosis was correlated to the METAVIR score and stage as followed: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa, F3, septal fibrosis without cirrhosis; F4, cirrhosis. Liver fibrosis was considered insignificant when it was strictly lesser than F2 and significant if it was greater than or equal to F2.

Laboratory tests

For each patient, a sample of morning urine was collected before 9.0 am in a sterile vial for dipstick analysis using Combi Screen 10SL® Roche™ Germany, and results were reported as 0 to 4+. We collected 3ml of blood for standardized creatinine dosage using a compact automatic biochemistry analyzer Cobas 311. All patients with an eGFR less than or equal to 60 ml/min/, 1.73 m^2 and/or with urinary abnormalities underwent a second urine and/or blood analysis 3 months later.

Definitions of operational terms and calculations

Chronic HBV was defined as HBs Ag positivity for at least 6 months.

GFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [28,29].

Urinary abnormality was defined in the presence of proteinuria (≥1+), haematuria (≥1+) and/or sterile leucocyturia (≥1+ without nitrites).

CKD was defined as GFR<60 ml/min/1.73 m^2 and/or urinary abnormality persistent after 3 months and then classified in 5 stages based on the Kidney Disease Improving Global Outcomes (KDIGO) definition [26].

Hypertension was considered if a previous history of High Blood pressure, use of treatment with antihypertensive drug therapy in the files or if the systolic blood pressure>140 mmHg and/or diastolic blood pressure >90 mmHg.

Diabetes mellitus was recorded if evidence treatment with antidiabetic drug in the files.

Statistical analysis

Data analysis was performed with Statistical Package for Social Science (SPSS) version 23.0. Categorical variables were reported as frequency and percentages. Continuous variables with normal and skewed distribution were respectively reported as mean ± standard deviation (SD) and median with 25th and 75th percentiles (interquartile range). Multivariate logistic regression was used to determine factors associated with proteinuria and CKD. A p value<0.05 was considered statistically significant.

Results

A total of 300 patients were consecutively enrolled in the study. From these patients, 8 were excluded and a total f 272 patients were included in the final analysis. The general characteristic of the study population are summarized in Table 1. The participants were relatively young with a mean age of 37.33 ± 9.73 years with 179/272 (65.8%) been males. Chronic use of herbal medicine was concerning 73/272 (26.9%) patients. Median duration of the HBV infection was 3 (2-5)

years, 30/272 (11%) were on antiviral treatment mainly Tenofovir (28/30). Median viral load was 519.5 (IQR141-1779) UI/ml.

Parameters	Values
Sociodemographics	
Gender, n (%)	
Male	179 (65.8)
Female	93 (34.2)
Age (years), mean ± SDa	37.33 ± 9.73
Clinical data, n (%)	
Hypertension	20 (7.4)
Diabetes	3 (1.1)
Alcohol consumption	60 (22.1)
Hepatitis C Virus co infection	1 (0.4)
Chronic use of herbal medicine	73 (26.9)
Body mass index (kg/m^2), mean ± SDa	26.56 ± 4.46
Duration of HBVc infection (years), median (IQRd)	3 (2-5)
Being on antiviral treatment	30 (11.0)
TDFe	28 (93.3)
Peg INFf α	1 (3.3)
Peg INFf α + TDFf	1 (3.3)
Duration on treatment (years), median (IQRd)	1 (1-2)
Biological data	
ALTg (UI/L) ≥ 40 n=129, n (%)	13 (10.1)
ASTh (UI/L) ≥ 40 n=126, n (%)	16 (12.7)
HBe Antigen positive n=104, n (%)	9 (8.7)
HBV viral load (UI/ml) n=109, median (IQRd)	519.5 (141-1779)
HBV viral load (UI/ml), n (%)	
< 2000 UI/l	89 (89.0)
≥ 2000 UI/l	21 (21.0)
Fibrosis, n=59	
F0	32 (55.2)
F1	11 (19.0)
F2	11 (19.0)
F3	2 (3.4)
F4	2 (3.4)
Non-significant Fibrosis F<2	43 (72.9)

aSD: Standard Deviation; bNSAID: Non-Steroidal Anti-Inflammatory Drugs; cHBV: Hepatitis B Virus; dIQR: Interquartile Range; eTDF: Tenofovir Disoproxil Fumarate; fPeg INF: Pegylated Interferon; gALT: Alanine Aminotransferase; hAST: Aspartate Aminotransferase.

Table 1: General characteristics of the study population (N=272).

Fifty patients (18.4%) had at least 1 urinary abnormality. Among these, the prevalence of proteinuria was 12.1% (33/272), 7.7% (21/272) for haematuria and 3.7% (10/272) for leucocyturia (Table 2).

Urinary abnormalities	N (%)
At least one urinary abnormality	50 (18.4)
Proteinuria	33 (12.1)
Haematuria	21 (7.7)
Leucocyturia	10 (3.7)

Table 2: Urinary abnormalities in the study population.

The overall prevalence of CKD was 19.9% (54/272) using CKD-EPI-formula and 18.4% (50/272) with MDRD. Using CKD-EPI, the stage distribution of CKD was: 8.1% (22/272) for stage 1, 8.9% (24/272) for stage 2, 2.6% (7/272) stage 3, 0.3% (1/272) stage 4 and no patients at stage 5 (Table 3).

CKDa	GFRb estimations (ml/min/1.73 m^2)	CKD-Epi n (%)	MDRD n (%)
Stages			
1	≥90, with urine dipstick abnormality	22 (8.1)	12 (4.4)
2	60-89, with urine dipstick abnormality	24 (8.9)	28 (10.4)
3[a]	45-59, with or without urine dipstick abnormality	7 (2.6)	8 (3.0)
3[b]	30-44, with or without urine dipstick abnormality	0 (0.0)	1 (0.3)
4	15-29, with or without urine dipstick abnormality	1 (0.3)	1 (0.3)
Total		54 (19.9)	50 (18.4)

[a]CKD: Chronic kidney disease; [b]GFR: Glomerular filtration rate.

Table 3: Prevalence and stage of chronic kidney disease amongst participants.

In multivariate analysis, factors associated to proteinuria were chronic use of herbal medicine (aOR: 3.17 (1.38-7.28), p=0.007), haematuria (aOR: 4.34 (1.44-13.02), p=0.009), (Table 4) while age ≥50 years (aOR: 3.61 (1.52-8.56), p=0.004).

Characteristics	Proteinuria		Univariate analysis		Multivariate analysis	
	No N=239 n (%)	Yes N=33 n (%)	OR[a] (95% CI[b])	p	aOR[c] (95% CI)	p
Age ≥ 50 years	25 (10.5)	10 (30.3)	3.72 (1.59-8.71)	0.002	1.24 (0.38-4.07)	0.719
Female gender	82 (34.3)	11 (33.3)	0.96 (0.44-2.07)	0.912		
Hypertension	12 (5.0)	8 (24.2)	6.05 (2.26-16.22)	<0.001	2.70 (0.73-10.01)	0.136
Diabetes	2 (0.8)	1 (3.0)	3.70 (0.33-42.00)	0.291		
HIV[d] infection	3 (1.3)	2 (6.1)	5.08 (0.82-31.57)	0.082		
Body mass index ≥30 kg/m^2	45 (18.8)	11 (33.3)	2.16 (0.98-4.76)	0.058		
Chronic use of herbal medicine	56 (23.4)	17 (51.5)	3.47 (1.65-7.32)	0.001	3.17 (1.38-7.28)	0.007
Chronic use of NSAID[e]	14 (5.9)	4 (12.1)	2.22 (0.68-7.19)	0.185		
Duration of HBV[f] infection ≥ 5 years	71 (29.7)	18 (54.5)	2.84 (1.36-5.95)	0.006	2.27 (0.99-5.18)	0.052
Been on antiviral treatment	25 (10.5)	5 (15.2)	1.53 (0.54-4.32)	0.423		
Been on TDF[g]	23 (9.6)	5 (15.2)	1.68 (0.59-4.76)	0.332		
Leucocyturia	6 (2.5)	4 (12.1)	5.36 (1.43-20.11)	0.013	4.04 (0.82-19.83)	0.085
Haematuria	12 (5.0)	9 (27.3)	7.09 (2.71-18.55)	<0.001	4.34 (1.44-13.02)	0.009
GFR[h]<60 ml/min/1.73 m^2	4 (1.7)	4 (12.1)	8.10 (1.92-34.15)	0.004	3.02 (0.45-20.07)	0.254

aOR: Odds Ratio; [b]CI: Confidence Interval; [c]aOR: adjusted Odds Ratio; [d]HIV: Human Immunodeficiency Virus; [e]NSAID: Non-Steroidal Anti-Inflammatory Drugs; [f]HBV: [f]Hepatitis B Virus, [g]TDF: Tenofovir Disoproxil Fumarate; [h]GFR: Glomerular Filtration Rate

Table 4: Factors associated to proteinuria amongst the participants.

Duration of HBV infection ≥ 5 years (aOR: 2.00 (1.04-3.88), p=0.039) and chronic use of herbal medicine (aOR: 2.04 (1.03-4.05), p=0.040) were factors associated to CKD (Table 5).

Characteristics	CKDa		Univariate analysis		Multivatiate analysis	
	No N=218 n (%)	Yes N=54 n (%)	OR[b] (95% CI[c])	P	aOR[d] (95% CI[c])	P
Age ≥ 50 years	17 (7.8)	18 (33.3)	5.91 (2.20-12.54)	<0.001	3.61 (1.52-8.56)	0.004
Female gender	74 (33.9)	19 (35.2)	1.06 (0.56-1.97)	0.863		
Hypertension	8 (3.7)	12 (22.2)	7.50 (2.88-19.47)	<0.001	2.97 (0.97-9.11)	0.057
Diabetes	2 (0.9)	1 (1.9)	2.04 (0.18-22.90)	0.556		
HIV[e] infection	3 (1.4)	2 (3.7)	2.76 (0.45-16.92)	0.254		
Body mass index ≥30 kg/m^2	41 (18.8)	15 (27.8)	1.66 (0.84-3.30)	0.144		
Chronic use of herbal medicine	50 (22.9)	23 (42.6)	2.49 (1.33-4.66)	0.004	2.04 (1.03-4.05)	0.04
Chronic use of NSAID[f]	12 (5.5)	6 (11.1)	2.15 (0.77-6.01)	0.138		

Duration of HBV[g] infection ≥ 5 years	63 (28.9)	26 (48.1)	2.29 (1.24-4.2)	0.007	2.00 (1.04-3.88)	0.039
Been on antiviral treatment	24 (11.0)	6 (11.1)	1.01 (0.39-2.60)	0.983		
Been on TDF[h]	22 (10.1)	6 (11.1)	1.11 (0.43-2.90)	0.825		

[a]CKD: Chronic Kidney Disease; [b]OR: Odds Ratio; [d]aOR: Adjusted Odds Ratio; [d]CI: Confidence Interval; [e]HIV: Human Immunodeficiency Virus; [f]NSAID: Non-Steroidal Anti-Inflammatory Drugs; [g]HBV: Hepatitis B Virus, [h]TDF: Tenofovir Disoproxil Fumar.

Table 5: Associated factors to chronic kidney disease.

Discussion

The aimed of this study was to determine the prevalence and associated factors to CKD amongst patients with chronic HBV in Cameroon an endemic area. Our patients were young adults with a mean age of 37 years and more men with more than 1/4 of them using herbal medicine. Almost 1/5 patients had urine abnormalities, mainly proteinuria (12%). Also 1/5 of participants had CKD and the majority was at early stage of the disease. Factors associated to proteinuria were chronic use of herbal medicine and hematuria while older age, longer duration of the infection and chronic use of herbal medicine were associated to CKD.

Hepatitis B infection and CKD are major public health issue in Cameroon [23-25]. In the present study our participants were young, similar to most finding in the literature. It is well known that in highly endemic areas HBV infection is mostly acquired from mother to child at birth (perinatal transmission) or horizontal transmission in childhood and adolescence [18,30,31].

Patients with chronic HBV infection are at risk of CKD and renal disease can be due to the virus itself, to drugs use for the treatments of HBVor to the presence of traditional risk for CKD [9-12,13,15]. CKD can manifest either by urinary abnomalities and/or impaired renal function. Few studies have reported prevalence of renal abnormalities in HBV infected patients [16,19]. We found an overall prevalence of urinary abnormalities of 18.1%, with proteinuria accounting for 12.1%, 7.7% for haematuria and 3.7% for leucocyturia. Our prevalence is low compared to reported results in the literature. In the multicentric study of Amet et al. the prevalence of proteinuria, heamaturia and leucocyturia was 38.1%, 20.6%, and 9% respectively amongst HBV infected patient's naïve to treatment [16]. Also Izzedine et al. in France reported that prevalence of proteinuria and haematuria was 17% and 30% respectively amongst chronic HBV patients on Adefovir [19]. This reported high prevalence of urinary abnormalities can be explained by the difference in study design and population compared to the present study. Firstly in those studies urine analysis was performed once, contrary to us where patientswith abnormality was reviewed after 3 months for confirmation, reducing the risk of transitory or intermittent abnormalities and therefore the prevalence. Secondly, in the study of Amet et al. Patients were naive to treatment and Izedine included only patients on Adefovir a known nephrotoxic antiviral drug [13,14]. In our study some patients were on antiviral treatment for HBV infection, this could reduce the rate of proteinuria and hematuria secondary to glomerular disease due to the virus. Compared to the present study, Huang et al. in Taiwan reported a lower prevalence of proteinuria (6.4%) amongst HBs antigen-positive patients [20].

Reported study have shown that the risk of ESKD is high amongst HBV infected patients [9,18] and renal function is an important prognostic factor in chronic HBV patients [32]. Given the silent course of kidney disease in general, and knowing that proteinuria and impaired renal function are risk factors for increase cardiovascular mortality [6,33-35] screening for CKD amongst risk patients is necessary. Using CKD-EPI formula we found an overall CKD prevalence of 19.9% and the stage distribution was: 8.1% for stage 1, 8.9% for stage 2, 2.6% stage 3, 0.3% at stage 4 and no patients at stage 5. Studies using the same definition of CKD as in the present one are rare in the literature. Most studies used either a single measurement of renal function and urinary abnormality or patients were reviewed at 2 weeks or 1 month but not at 3 months as recommended by the KDIGO. Our rate is therefore lower compared to the HARPE study a multicentric cross sectional study of Amet et al. who reported athat 64.6% of HBV patients had CKD with 36.3%, 24.8%, and 3.5% at stages 1, 2 and 3 respectively [16]. In the HARPE study patients were naïve to treatment and renal abnormalities was evaluated only once explaining the difference. We review all patients with low eGFR and positive dipstick at 3 months reducing the rate of false positive or transitory abnormalities [36].

In our study a total of 8 patients (3%) had impaired renal function (GFR<60ml/min). Management of patients with HBV infection associated with impaired renal function is challenging mostly due to the risk of iatrogenic drug toxicity with severe clinical complications [21,37]. It is therefore necessary to evaluate systematically renal function of HBV infected patients before and during treatment because some drugs used for the treatment of these patients such as Tenofovir and Adefovir are nephrotoxic and require dose adjustment [38-41].

Data on predictors of CKD among HBV infected patients are scanty in the literature. Associated factors to CKD found in this study were older age, longer duration of the infection and chronic use of herbal medicine. Older age and exposure to traditional medicine are known independent predictors of kidney disease in various populations group [42-47]. In the study of Jung-ho Shin et al. older age was also a risk factor impaired renal function amongst HBV patients on treatment [22] while younger age and males in the contrary were associated with increased risk of CKD in untreated chronic HBV infection in Taiwan [48].

Others reported factors associated to CKD are the presence of traditional risk factors such as diabetes, hypertension [22,49,50] We found no association in this study, and the explanation could be the low prevalence of these factors in our study population.

Limitation

We acknowledge some limitations to this study. We did not have information on the HBV DNA for the majority of patients therefore

could not analyze the impact of the severity of the infection on kidney. Secondly we carried out a single center study.

The major strength is that this study is one of the rare in the literature where CKD was defined according to recommended KDGO definition and patients were reviewed twice over a period of 3 months to confirm low e GFR and urine dipstickabnormalities. Also this is the first study that reports prevalence of CKD amongst HBV infected patients in sub-Saharan Africa in general and in Cameroon and in particularendemic zone.

Conclusion

CKD is frequent amongst chronic infected HBV patients in Cameroon an endemic zone for HBV where renal function is not routinely performed. Older age, used of traditional herbs and longer duration of the infection were factors independently associated to CKD. We therefore recommend the need of renal function evaluation and dipstick analysis in HBV infected patients before initiation of treatment and during follow up. Also a collaboration between gastroenterologist and nephrologists is necessary for better management of patients with HBV associated with kidney disease, this will help to slow the progression of CKD and reduce the rate of ESKD in that population.

Declarations

Ethics approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Committee of the Bangangté University of Montagnes in Cameroon with reference number N° 2017/095/UdM/PR/CAB/CIE, and authorization was obtained from the DGH. All participants gave a written consent to participate in the study.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

On behalf of the all authors, the corresponding author states that there is no conflict of interest.

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