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Original Article

Occult Hepatitis B Infection in Patients Undergoing Haemodialysis in Yaounde (Cameroon)

Infection Occulte par l'Hépatite B Chez les Patients Hémodialysés à Yaoundé (Cameroun)

Éric Ola'a Bamzok[1], Nadège Goumkwa Mafopa[2], Juliette-Laure Ndzié Ondigui[3], Alliance-Laure Otam[2], Cindy Lobe[2], Abdel Mouliom[1], Patrick Awoumou, Puinta Peyonga[1], Solange Manju Atah[1], François Jérome Kaze[4], Judith Ndongo Torimiro[2]

Affiliations

1. Faculty of Medicine and Biomedical Sciences, Department of Biochemistry, University of Yaounde 1, Cameroon
2. Chantal BIYA International Reference Center for Research on HIV/AIDS Prevention and Management (CIRCB)
3. Faculty of Sciences, Department of Microbiology, University of Yaounde 1, Cameroon
4. [4]Faculty of Sciences, University of Ngaoundere, Cameroon,
5. Faculty of Medicine and Biomedical Sciences, Department of Public Health, University of Yaounde 1, Cameroon
6. Department of Nephrology, University Teaching Hospital of Yaounde, Cameroon
7. Faculty of Medicine and Biomedical Sciences, Department of Internal Medicine and Specialties, University of Yaounde 1, Cameroon

Corresponding Author
Éric Ola'a Bamzok
Email : e.bamzok@gmail.com

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ABSTRACT

Introduction. Occult hepatitis B is characterized by serological negative result for surface antigen (HBsAg) using available assays, detectable HBV DNA in the liver with or without HBV DNA in the blood. This condition can lead to serious liver disease and viral transmission. Despite its potential severity, occult hepatitis B has not been extensively studied in Cameroon. **Aim.** This study aimed to assess the prevalence and characteristics of occult hepatitis B infection, including genotype and HBsAg 'a' determinant mutation, in maintenance haedialysis patients. **Setting**.This was a descriptive and cross-sectional study involving 41 patients undergoing maintenance haemodialysis at Yaoundé University Hospital. **Methods.** Methods used for detection of HBV serological markers included rapid diagnosis and ELISA tests. Nested PCR was used to test for viral DNA in HBAg-negative patients. The sequencing of the samples was carried out using the Sanger method. **Results.** Findinds showed that HBsAg was detected in 7,3% (3/41) of participants while 26,32% (10/38) of the HBsAg-negative ones had HBV DNA. The genotype E was common and mutation P127L found in the HBsAg 'a' determinant. **Conclusion.** The prevalence of occult hepatitis B is high among maintenance haemodialysis patients and one mutation requiring further description have been identified. Incidence and prevalence data on hepatitis B may be underestimated due to limited access to PCR diagnosis in our context, especially in high-risk patients**.**

RÉSUMÉ

Introduction. L'hépatite B occulte se caractérise par un résultat sérologique négatif pour l'antigène de surface (HBsAg) à l'aide des tests disponibles, un ADN du VHB détectable dans le foie avec ou sans ADN du VHB dans le sang. Cet état peut entraîner de graves maladiesdufoie et une transmission virale. Malgré sa gravité potentielle, l'hépatite B occulte n'a pas fait l'objet d'études approfondies au Cameroun. **Objectif.** Cette étude visait à évaluer la prévalence et les caractéristiques de l'infection occulte par le virus de l'hépatite B, y compris le génotype et les mutations déterminantes de l'HBsAg 'a', chez les patients en hémodialyse d'entretien. **Cadre**. Il s'agit d'une étude descriptive et transversale portant sur 41 patients en hémodialyse d'entretien au CHU de Yaoundé. **Méthodes.** Les méthodes utilisées pour la détection des marqueurs sérologiques du VHB comprenaient le diagnostic rapide et les tests ELISA. La PCR nichée a été utilisée pour tester l'ADN viral chez les patients HBAg-négatifs. Le séquençage des échantillons a été réalisé par la méthode Sanger. **Résultats.** Les résultats ont montré que l'HBsAg a été détecté chez 7,3% (3/41) des participants tandis que 26,32% (10/38) des patients HBsAg-négatifs avaient de l'ADN du VHB. Le génotype E était courant et la mutation P127L a été trouvée dans le déterminant 'a' de l'AgHBs. **Conclusion.** La prévalence de l'hépatite B occulte est élevée chez les patients en hémodialyse d'entretien et une mutation nécessitant une description plus approfondie a été identifiée. Les données sur l'incidence et la prévalence de l'hépatite B peuvent être sous-estimées en raison de l'accès limité aux tests de dépistage de l'HBsAg.

INTRODUCTION

In settings where nucleic acid tests are not available, the diagnosis of hepatitis B is primarily by the detection of hepatitis B surface antigen (HBsAg) by serologic tests. These serologic tests are based on rapid diagnostic immunochromatography and enzyme-linked immunosorbent assay (ELISA) (1). Variations in the hepatitis B virus genome may lead to low expression of the surface antigen and undetectable by serologic tests.

This poses a challenge in the diagnosis of hepatitis B infection when replication-competent HBV DNA is present in the serum or the liver, but HBsAg is undetectable using serologic currently available assays. This is known as occult hepatitis B infection (2). Undiagnosed cases of hepatitis B infection can contribute to viral transmission, which can have significant public health implications. For instance, the transmission of the hepatitis B virus from mother-to-child can occur during childbirth, particularly if the mother has occult hepatitis B. In addition, occult infections may distort the accuracy of data on the prevalence of hepatitis B, resulting in misguided decisions in research, policy, and resource allocation, which may reduce the effectiveness of vaccination programs, screening protocols, educational campaigns and other preventive strategies.

Occult hepatitis B can be transmitted through blood transfusions, liver transplants from misdiagnosed donors, unprotected sex and haemodialysis. Patients with chronic renal failure may be at a higher risk of infection due to frequent transfusions and vascular access during haemodialysis sessions. Additionally, chronic renal failure is associated with a weakened immune state, making patients more susceptible to infections such as hepatitis B (3). Considering recent kidney transplants in Cameroon, it may be worthwhile to screen potential transplant recipients who will undergo immunosuppressive treatment (4). This would help to ensure that they receive the appropriate antiviral therapy to prevent reactivation in cases of occult hepatitis B infection. This measure could potentially reduce the risk of fulminant hepatitis and its diverse complications.

Several seroprevalence studies of hepatitis B infection have been conducted in Africa, mainly in Egypt, South-Africa and Nigeria. In Cameroon, blood donors, HIV-infected patients, pregnant women and other selected populations have been screened (5–7). Very few studies have reported the incidence and frequency of occult hepatitis B in Africa in the wider community, especially among vulnerable groups such as individuals with sickle cell disease, pregnant women , and people receiving maintenance haemodialysis (8). Thus, the need for more studies and provide evidence and understanding of the burden of occult hepatitis B infection in our Cameroon.

The HBsAg is detectable within 1 to 10 days following infection and thus the biomarker frequently investigated for by serology because it is more easily accessible and affordable. A positive result indicates an active hepatitis B infection, while its disappearance alongside the emergence of anti-HBs antibodies indicates recovery. However, if the antigen persists for more than 6 months, this may suggest a chronic infection (9). These serological tests use monoclonal antibodies against the 'a' determinant (amino acid 124 to 147) of the HBsAg (10).

On the other hand, occult hepatitis B can be caused by various underlying factors, including genetic variability within the 'a' determinant, as well as immunological and epigenetic mechanisms (2). Therefore, mutations in the 'a' determinant can cause conformational changes in its structure, which may reduce the affinity of monoclonal antibodies to HBsAg. These diagnostic escape mutations can make HBsAg less detectable by available serological assays. Thus, diagnosis of occult hepatitis B infection is typically based on the detection of HBV DNA in blood or liver. The HBV genome has four open reading frames, including the X gene, the pre-core/core gene, the P gene, and the S gene (which codes for HBsAg), can be amplified. However, HBV DNA levels (viral load) of patients with occult hepatitis B infection are usually very low, rarely exceeding 200 IU/l (about 1000 copies/ml) (2).

This survey is a step towards providing recent epidemiological data on occult hepatitis B infection among patients on dialysis in Cameroon. Furthermore, we sought to molecularly characterize HBV.

METHODS

Study design

This was a descriptive cross-sectional study which was carried out from October 2022 to September 2023.

Setting

Participants were recruited from the Nephrology Department where haemodialysis sessions are subsidized at 95% by state (11).

Study population and sampling strategy

The study population consisted of adult patients with chronic renal failure who are undergoing maintenance haemodialysis. Patients who had not provided informed consent and those whose documented HBsAg carriage were excluded.

Data collection

After providing a clear explanation of the study's purpose and obtaining participants' signed free and informed consent, a standardized questionnaire was administered. The questionnaire collected data on age, sex, sociodemographic information, and relevant clinical and biological data.

Ethical considerations

The study protocol was reviewed and given ethics approved by the Institutional Ethical Review Board of the Faculty of Medicine and Biomedical Sciences (N°1095/UY1/FMSB/VDRC/DAASR/CSD) and by the Centre Regional Ethics Committee for Human Health Research (N°E00495/CRERSHC/2023). Informed consent to participate in this study was obtained from patients before data and samples were collected. The identity of all participants was kept confidential, and participants were not coerced into taking part in the research. All data collected were then stored in a computer and were only accessible to the research team.

Blood sampling

Catheter blood samples were taken before the haemodialysis session and catheter lines were stopped at least 5 minutes prior to blood sampling. For patients without a peripheral venous line, venipuncture was performed at the elbow. A total of 10 ml of venous blood was collected from each patient using an anticoagulant-free tube and an EDTA tube. Samples that appeared haemolytic or visibly hyperlipemic (i.e. 'milky' in appearance) were excluded from the analysis.

Screening for serological markers

HBsAg was detected by immunochromatography (One Step HBsAg Hepatitis B Surface Antigen Rapid Test, QINGDAO HIGHTOP BIOTECH, with a detection limit of 1ng/ml) and then confirmed by ELISA (Murex HBsAg Version 3, Diasorin, with a detection limit of 0.05 IU/ml). Anti-HBs antibodies were detected by ELISA (Dia.Pro HBs Ab, Dia.Pro Diagnostics). Total anti-HBc antibodies was detected by ELISA (Murex anti-HBc Total, Diasorin).

DNA extraction

DNA was extracted from 200 ul plasma samples according to the manufacturer's instructions (QIAamp DNA Micro Kit, QIAGEN), and tested with the nanodrop spectrophotometer to assess the purity of DNA.

Nucleic acid amplification

Samples from HBsAg-negative patients were tested for HBV DNA by amplification of a 786 bp portion of the pre-S/S region by nested PCR. The sequences of specific primers used are listed in Table I. The first reaction was performed under the following conditions: initial denaturation at 94°C for 5 minutes, 35 cycles at 94°C for 15 seconds, 50°C for 45 seconds, 68°C for 90 seconds and final extension at 68°C for 10 minutes. The second reaction was carried out under the following conditions: initial denaturation at 94°C for 5 minutes, 30 cycles at 94°C for 15 seconds, 55°C for 45 seconds, 68°C for 90 seconds and final extension at 68°C for 10 minutes. For all the steps, distilled water was used as a negative control, and DNA from a chronic HBV carrier as a positive control. The position of the desired amplicons was determined by electrophoretic migration in a 1% agarose gel compared to a molecular ladder (Tableau 1).

Table I: Primers used for first (S7, S4) and nested (S11, S2) amplifications

Name	Orientation	Sequence (5'- 3')	Length
S7	Forward	GCCTCATTTTGYGGGTCA	18 pb
S4	Reverse	CATCAGCAAACACTTGGC	18 pb
S11	Forward	CTCCTGCCTCCACCAATC	18 pb
S2	Reverse	GCCCTACGAACCACTGAACAAATGG	25 pb

HBV DNA sequencing and bioinformatics analysis

Following capillary electrophoresis on a genetic analyser (3500 Genetic Analyzer, Applied Biosystems; Life Sciences, Foster City, CA; 08 capillaries), samples that yielded positive results for viral DNA detection were subsequently sequenced. The phylogenetic tree of the reported strains was constructed using MEGA (Molecular Evolutionary Genetics Analysis) software. Amino acids substitutions within the HBsAg 'a' determinant were identified by aligning the reported sequences with reference sequences from the GenBank website using the CLUSTAL W algorithm in BioEdit software version 7.7.1.

RESULTS

Initial screening

Initial HBsAg detection was done on 41 patients. Of the 41 screened, 3 patients tested positive while 38 tested negative for HBsAg. Samples that tested positive for HBsAg were not subjected to viral DNA detection.

Social and demographic profile

The analysis revealed that 56% (23/41) of the participants were male, while 44% (18/41) were female. The mean age of the cohort was 48.22 years, with a standard deviation of 15.27 years.

HBV immunisation status

9.76% (4/41) of the studied population had initiated a vaccination schedule against the hepatitis B virus, with 2.4% (1/41) patient having completed the full four-dose HBV vaccine regimen.

Patterns in serological markers

The biomarker with the highest prevalence in the study population was total anti-HBc antibodies with a seroprevalence of 68.29% (28/41), followed by anti-HBs antibody with 40.78% (20/41), while 7.32% (3/41) of the study population was HBsAg positive (Table II).

Tableau I : HBsAg, anti-HBs and total anti-HBc antibody results of study samples

Serological markers	Tested	Positive	Negative
HBsAg	41	03	38
Anti-HBs	41	20	21
Total Anti-HBc	41	28	13

Prevalence of HBV DNA in HBsAg-negative samples

Of the 38 HBsAg-negative samples, 7.89% (3/38) were positive for HBV DNA detection at the first PCR amplification, and an additional 7 during the second, giving a prevalence of 26.32% (10/38) of occult hepatitis B infection.

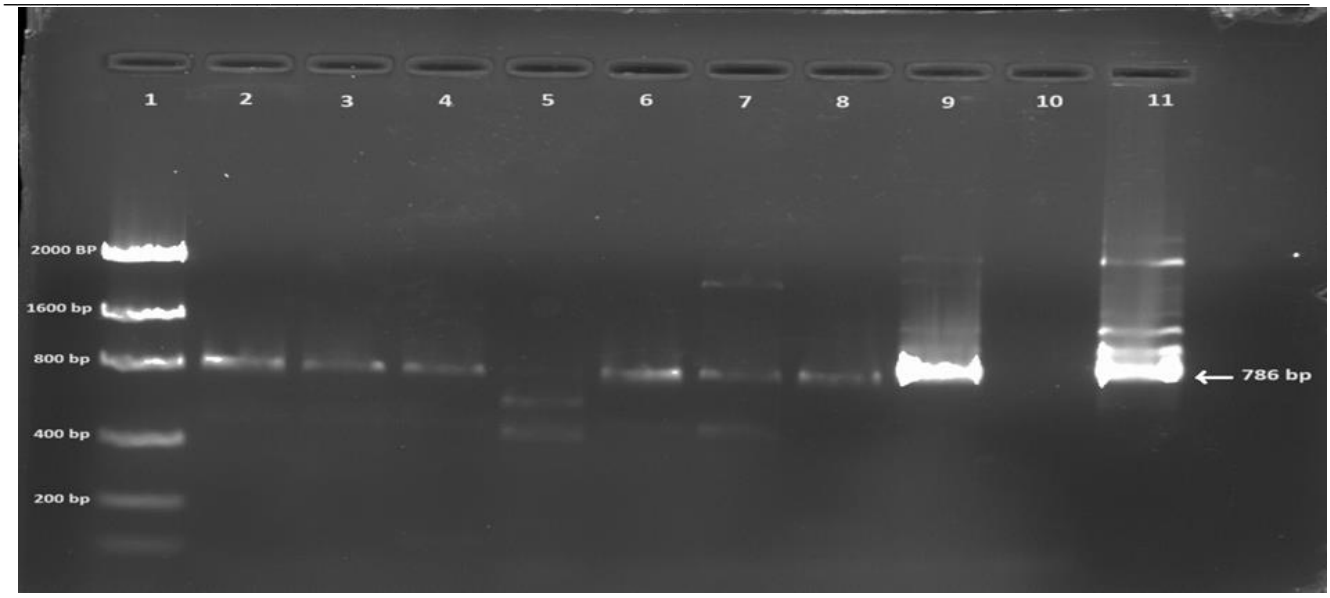

Figure 1: Electrophoretic migration of amplicons after the second amplification *(Lane 1 : Low DNA Mass Ladder; Lane 11 : Positive control with 786-800 bp; Lane 10 : Negative control; Lane 2 to 9 : samples 012OBI, 016OBI, 023OBI, 026OBI, 032OBI, 038OBI, 041OBI, 030OBI)*

HBV genotypes and frequency of mutations predictive of occult hepatitis B infection

Out of the 10 OBI samples Sanger sequenced, 3 (007OBI, 010OBI and 012OBI) had editable chromatograms. Phylogenetic analysis and BLAST search revealed that all of the 3 sequences belonged to Genotype E (Figure 2). Further amino acid sequence analysis revealed that none of the query sequences carried the sG145R mutation (predictive of occult infection). However, 3 OBI samples had the same P127L (Pro127Leu) amino acid substitution in the HBsAg 'a' determinant.

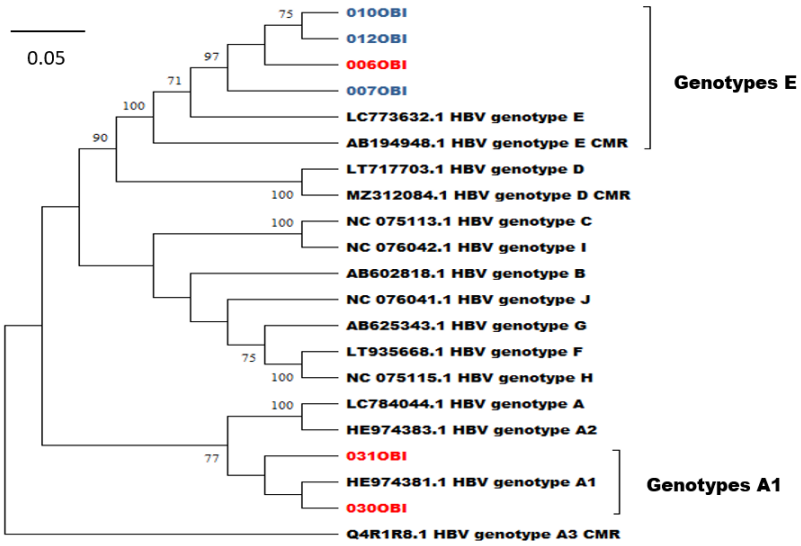

Figure 2: Phylogenetic analysis of the HBsAg-coding region sequence (nt 458–784) from OBI samples, HBsAg positive participants and HBV reference sequences.

Six sequences from 3 OBI and 3 HBsAg positive specimens were aligned with GenBank reference sequences and analyzed by maximum likelihood method. Reference sequences are shown as a GenBank accession number, followed by genotype or subgenotype and country of origin, if available.

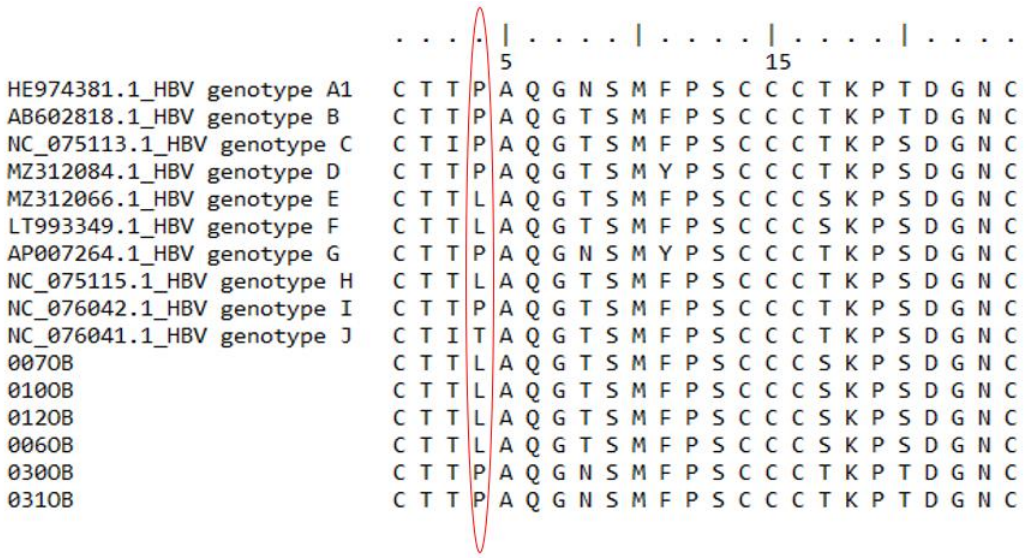

Figure 3 : Alignment of the HBsAg 'a' determinant amino acid sequences of the editable samples with those of the reference samples

DISCUSSION

Studies on the prevalence of occult hepatitis B have been extensively documented in the world but with very few carried out in Cameroon. We sought to identify patients receiving maintenance dialysis in a tertiary hospital in Yaounde, Cameroon, with occult hepatitis B infection. The patients were under age of 50 years, similar to some studies reported in Nigeria and in China (12,13). Some authors describe chronic renal failure as a disease of the young adults in Africa which may be influenced by several factors. Although we did not seek to assess the factors that may have favoured the development of chronic kidney disease in the study cohort, it is worth noting that in Cameroon, arterial hypertension, chronic glomerulonephritis, diabetes mellitus, and HIV infection can contribute to the incidence of chronic renal failure (14). In addition, the gender imbalance indicated by the data in this study has been previously reported by other authors (12,15–17).

Cameroon has a high prevalence of the hepatitis B virus infection of 11,2% in the general population (18). Patients undergoing haemodialysis may be at a higher risk of contracting hepatitis B due to their weakened immune systems and exposure to potentially contaminated blood products or objects. The frequency of anti-HBc antibodies in this study population was 62.86%, indicating a high circulation rate of HBV in the study population. However, we cannot tell whether exposure and/or contact with the virus occurred in or outside the hospital environment. From the anti-HBs antibody levels, 23 (56.1%) patients did not develop post-infectious immunity, which leaves them vulnerable to infection.

Separation from HBV-infected patients, dedicated haemodialysis machines, and mandatory vaccination are preventive measures often proposed in haemodialysis settings. The recommended vaccination protocol for patients with chronic kidney failure is a double dose of the hepatitis B vaccine, administered as part of a four-contact regimen (19). But only one (1/41) participant completed the full vaccination schedule. The poor adherence to the hepatitis B vaccination schedule among haemodialysis patients may be influenced by various factors, including poor awareness, the vaccination schedule which spans over 6 months, and other socio-economic considerations. The prevalence of occult hepatitis B varies enormously, depending on the viral epidemiology of the region concerned and the performance of the diagnostic techniques and algorithms carried out. Depending on the HBV DNA load, a second round PCR may be needed to diagnose occult hepatitis B infection, and thereby increasing the cost of diagnosis. In this study, 10 HBsAg-negative patients (26.3%) were carriers of viral DNA without their knowledge. This is a cause for concern in the management of these patients with chronic kidney disease who receive blood by transfusion.

It is frequently observed that sub-genotypes A1 and A2 are associated with occult hepatitis B infection (9). This study showed 3 samples of HBV Genotype E, which is estimated to have infected nearly 18% of chronic HBV carriers worldwide (10). It is most prevalent in West and Central Africa (11), and it is the second most prevalent genotype in Cameroon (12). The results of this study are consistent with this trend. However, it is worth noting that our knowledge of the clinical and virological characteristics of patients infected with genotype E is limited. It has been acknowledged that individuals infected with Genotype E typically exhibit high hepatitis B e antigen (HBeAg) positivity, a high viral load, and generally have a poorer response to interferon alpha treatment (20).

Although the mechanisms underlying occult hepatitis B are not fully understood, there are several widely accepted hypotheses, including immunological, genetic, and epigenetic factors. It has been noted that genetic variability in the HBsAg 'a' determinant can lead to the appearance of immune escape mutants. In our study, we did not detect the frequently identified worldwide Gly145Arg/Ala/Ile/Trp/Glu (G145R/A/I/W/E) mutants (16). However, other amino acid substitution was identified in our study which have been reported by other

studies showing mutations in the first antigenic loop (positions 124-138) of Pro127Leu (P127L).

It is important to note that the gold standard for diagnosing occult hepatitis B is the search for viral DNA in liver tissue, as viral DNA is only intermittently present in plasma are generally of very low level. It is worth considering that the prevalence of occult hepatitis B in our cohort may be underestimated. Additionally, the mechanisms by which the P127L mutation contribute to the occurrence of occult hepatitis B are not yet fully understood.

CONCLUSION

The study aimed to evaluate the prevalence of occult hepatitis B among patients undergoing maintenance haemodialysis at a tertiary hospital in Yaoundé, Cameroon. The results showed that the prevalence of occult hepatitis B was 26.32% while the rate of overt infection among the 41 patients was 7.3%. Furthermore, molecular analysis of the HBV preS/S region identified P127L mutation in the 'a' determinant in two patients of Genotype E, with unknown impact on occult hepatitis B infection.

COMPETING INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Design and study plan: Ola'a Eric, Torimiro Judith, Goumkwa Nadège, Otam Alliance-Laure, Patrick Awoumou. Data collection: Ola'a Eric, Patrick Awoumou, Puinta Peyonga. Sample collection: Ola'a Eric. Sample analysis: Goumkwa Nadège, Otam Alliance-Laure, Ondigui Juliette, Ola'a Eric. Drafting of the manuscript: Goumkwa Nadège, Otam Alliance-Laure, Ondigui Juliette, Ola'a Eric. Editing of the manuscript: Ola'a Eric, Torimiro Judith, François Jérome Kaze, Goumkwa Nadège, Otam Alliance-Laure. All authors have read and approved the final version of the manuscript.

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