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Prevalence and Determinants of Kidney Markers among Subjects with Hepatitis C Virus Infection

Mathurin Pierre Kowo[1,2*], Sylvain Raoul Simeni Njonnou[3], Murielle Sonia Mehly Ngninzeko[4], Firmin Ankouane Andoulo[1,2], Antonin Ndjitoyap Ndam[1], Michelle Tagny Sartre[5], Vicky Ama Moor[2,6], Jeanne Ngongang[2,4,6], François Folefack Kaze[1,2]

[1]Department of Internal Medicine and Specialty, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon
[2]Yaounde University Teaching Hospital, Yaoundé, Cameroon
[3]Department of Internal Medicine and Specialty, Faculty of Medicine and Pharmaceutical Sciences, University of Dschang, Dschang, Cameroon
[4]Higher Institute of Health Sciences, Université des Montagnes, Bangangté, Cameroon
[5]Medical Centre "La Cathédrale", Yaoundé, Cameroon
[6]Department of Physiological Sciences and Biochemistry, Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon

Email: *kowomathurinp@yahoo.fr, raoulsims@yahoo.fr, mmelhyngninzeko@icrc.org, ankouaneandoulo@yahoo.com, tonindam3@yahoo.fr, mtsartre@yahoo.fr, movicky@yahoo.fr, jngongang@yahoo.fr, f_kaze@yahoo.fr

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Abstract

Introduction: Hepatitis C virus (HCV) infection is a worldwide public health problem with multisystemic involvements including kidneys. We assessed the prevalence and determinants of kidney markers among HCV infected subjects. **Methods:** A cross-sectional study was conducted from March to July 2017 in two referral centers in Yaoundé. Sociodemographic, clinical and paraclinical data were collected from patient's records. Renal involvement was evaluated using estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease's (MDRD) equation, urine dipstick and albumin/creatinine ratio (ACR). An eGFR < 60 and between 60 - 89 mL/min/1.73 m^2 was defined as low and reduced respectively. Albuminuria was defined by an ACR > 30 mg/g and divided into A1 (<30 mg/g), A2 (30 - 300 mg/g) and A3 (>300 mg/g). **Results:** We included 65 (41.5% males) HCV infected patients with a mean age of 56.8 ± 10.5 years. HCV infection was diagnosed for more than 5 years in 54 (83.1%) patients. HCV viral load and genotype were available in 40 (61.5%) patients; viral load was high (>5.9 logs/mL) in 20 (50%) of them and genotypes 4 (40%), 1 (32.5%) and 2 (27.5%) were found in this population. The mean eGFR was 112.9 ± 31.9 mL/min/1.73 m^2 with 14

(21.5%) and 4 (6.2%) patients having reduced and low eGFR respectively. Albuminuria (80%), leukocyturia (24.6%) and hematuria (4.6%) were the observed dipstick abnormalities. Median albuminuria (IQR) was 542.4 (238.7 - 961.5) mg/g, with 7 (11%), 12 (18%) and 46 (71%) patients in A1, A2 and A3 respectively. Reduced/low eGFR and albuminuria were observed in 58 (89.2%) patients while low eGFR and albuminuria were found in 55 (84.6%) patients. Advanced age, female gender, HCV genotype 1 and 4, and albuminuria (all $p < 0.03$) were associated with eGFR reduction. **Conclusion:** Renal abnormalities are common in HCV infected patients leading by proteinuria and decreased eGFR. Known risk factors of kidney diseases, HCV genotype 1 and 4 and albuminuria were associated with eGFR reduction in our setting.

Keywords

Hepatitis C Virus, Chronic Kidney Disease, Prevalence, Sub-Saharan Africa

1. Introduction

Chronic viral hepatitis C (CVHC) predisposes to liver fibrosis and is a major cause of liver-related mortality and morbidity [1] [2]. With a global prevalence of 3% (71 million persons infected), CVHC infection is a major public health problem worldwide [1] [3]. Its prevalence ranges from 0.4% in Western Europe to more than 9% in Central Africa [3] [4]. Cameroon is one of the most affected countries, with a nation-wide prevalence of 6.5% [5]. This prevalence varies according to regional and temporal disparities ranging from 13% among Pygmies and Bantus in South Cameroon to 21.1% in the East region [5] [6].

Morbi-mortality of hepatitis C virus (HCV) infection is mainly related to cirrhosis and hepatocellular carcinoma [7]. Despite the HCV hepatotrophicity, it can affect other organs, leading to manifestations such as autoimmune, metabolic, renal, cardiovascular, central nervous system, and lymphoproliferative disorders [8] [9] [10] [11]. Those extrahepatic manifestations are rarely in the foreground but can reveal the disease, may be severe and require urgent management. Recent studies show a variation of extrahepatic manifestations ranging from 1.76% for ischemic stroke to 50% for neurocognitive changes, porphyria cutanea tarda and cutaneous vasculitis [9]. The renal manifestations of HCV infection are common and contribute to worsening prognosis as well as the burden of the disease; they are mainly glomerular including membranoproliferative glomerulonephritis, membranous nephropathy and cryoglobulinemia [10] [12]. They lead to chronic kidney disease (CKD) which progresses to end-stage kidney disease [13] [14] [15] [16] [17].

If renal manifestations of HCV infection have been widely assessed in Western countries, these have been poorly investigated in Africa [18] [19] [20]. A recent study in Cameroon found an anti-HCV prevalence of 19.2% among patients on maintenance hemodialysis (MHD) [21]. With the availability of direct-acting

antiviral agents (DAAA), it was therefore important for us to assess the prevalence of renal manifestations of HCV infection and identify associated risk factors. The early diagnosis will help to introduce nephroprotection measures within such a population.

2. Methods

Study design and setting: This cross-sectional study was carried out in two therapeutic centers for hepatitis management in Yaounde (Yaounde University Teaching Hospital and Medical Centre "La Cathédrale"). Yaounde University Teaching Hospital is a tertiary hospital while Medical Centre "La Cathédrale" is a private medical institution with a high technology platform; all in Yaounde, the capital city of Cameroon.

Study population: Patients seen in outpatient consultation and hospitalization ward with the diagnosis of HCV infection were recruited. Patients followed up, but not seen at outpatient consultation were invited through phone calls to participate to the study. Detection of HCV antibodies was done using a rapid diagnostic test and those who tested positive had a confirmatory ELISA test.

Variables and Measurements: All consenting HCV-infected subjects above 18 years, naïve to treatment were included. Patients with conditions that may lead to confusion at the urine test such as hypertension, diabetes, hepatitis B virus infection, HIV infection, systemic lupus, renal lithiasis or urinary tract infection, were excluded. Sociodemographic characteristics (age, gender, profession, alcohol consumption, smoking), clinical data (weight, height, signs of hepatocellular failure and/or portal hypertension), biological (serum and urinary creatinine, urine dipstick, 24 hours albuminuria) and virological parameters (HCV-viral load and genotype) were collected. Height (in m) was measured using a wooden platform and a height rule. Body mass index (BMI) was calculated as weight (kg)/height (m) × height (m).

Quantitative determination of HCV RNA and the genotyping were requested for each new patient. For followed up patients, these pieces of information were obtained from their files. Fibroscan® (Echosens, Paris, France), a noninvasive marker of fibrosis, was used and converted to the METAVIR score to categorize fibrosis in chronic hepatitis C according to a 5-stages classification: F0 (no fibrosis), F1 (portal and periportal fibrosis without septa), F2 (portal and periportal fibrosis with rare septa), F3 (numerous septa without cirrhosis), and F4 (cirrhosis). The selection process is summarized in Figure 1.

Laboratory testing

For each patient, blood and urinary samples were collected. Urine dipstick tests were conducted with CombiScreen® 7SL PLUS 7 test strips (Analyticon Biotechnologies AG, D-35,104 Lichentenfeis, Germany). Urinary pH, specific gravity and glucose were not taken into consideration for the purpose of the study.

Serum and urinary creatinine were conducted using a kinetic method called "Jaffé reaction" (with CYPRESS® reagents, CYPRESS Diagnostics, Hulshout,

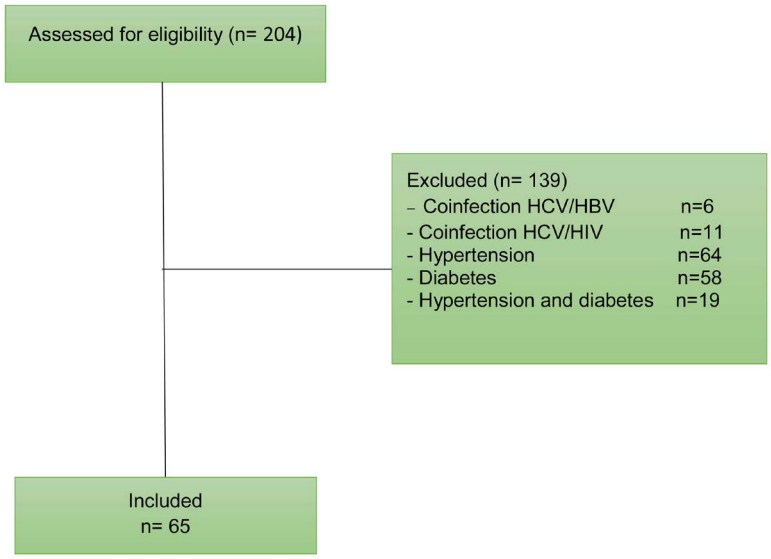

Figure 1. Patient flow chart.

Belgium). Albuminuria dosage was performed using a spectrophotometric method. Glomerular filtration rate (GFR) was estimated by The Modification of Diet in Renal Disease (MDRD) equation [15]. A urine dipstick test was conducted for evaluating albuminuria, hematuria and leukocyturia. 24 hours albuminuria was estimated using urine albumin/creatinine ratio (ACR) from the urine spot.

Definitions:

Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2, and overweight was defined as a BMI between 25 and 29.9 kg/m^2. Excessive alcohol consumption was considered for a consumption > 30 g/day for women and 40 g/day for men or more than 10 (5 for women) local beers per week. The METAVIR score also categorized activity according to a 4-grade classification: A0 (no activity), A1 (minimal activity), A2 (moderate activity), and A3 (severe activity) [22]. GFR (in mL/min per 1.73 m^2) was divided into G1 (>90), G2 (60 - 89), G3 (30 - 59) G4 (15 - 29) and G5 (<15). For this study, an eGFR < 60 mL/min per 1.73 m^2 was considered as low while between 60 - 89 mL/min per 1.73 m^2 was defined as reduced. Raised creatinine was considered for levels > 1.3 mg/dL. Albuminuria was defined by ACR ≥ 30 mg/g. It was divided into A1 (ACR < 30 mg/g), A2 (ACR (30 - 300 mg/g) and A3 (ACR > 300 mg/g). The diagnosis of urine dipstick abnormalities was based on at least 1+ confirmed by a second test two weeks later. An abnormal GPT level was defined as values greater than 35 IU/L. HCV viral load was considered as high if >800,000 IU/mL (5.9 logs/mL) [23].

Sample size and Statistical analysis: A consecutive sample of all eligible cases was considered for this study. Data were analyzed using Statistical Package for Social Sciences (SSPS Inc, Chicago, Illinois, USA) V.20.0 and EPI-INFO V.3.5 software. Discrete variables were presented as counts and percentages, and continuous variables as mean (standard deviation) or median (IQR). The Chi-square test was used, Student t-test, and ANOVA where appropriate.

3. Results

Characteristics of the study population

We included 65 (41.5% males) HCV-infected patients, naïve to treatment. Patients' mean age was 56.8 ± 10.5 years with 30 (46.2%) above 60 years old. The mean BMI was 27.1 ± 4.2 Kg/m^2 with overweight and obesity found in 35 (53.8%) and 15 (23.1%) patients respectively. Regular consumption of nephrotoxics was found in 35 (53.8%) patients. At-risk alcohol consumption was observed in 4 (6.2%) patients. There were 54 (83.1%) patients diagnosed with HCV infection for more than 5 years.

HCV viral load was performed in 40 (61.5%) patients with a mean of was 6.3 ± 3.5 logs and 20 (50%) patients had a viral load greater than 5.9 logs. Genotype: 4 (40%), 1 (32.5%) and 2 (27.5%) were found in this population. Liver fibrosis was evaluated in 50 patients with the following stage F4 (32%), F3 (10%), F2 (18%), F1 (22%) and F0 (18%). The mean GPT was 37.9 ± 24 U/L and was increased in 24 (36.9%) patients. Table 1 reports the clinicobiological characteristics of the study population.

Kidney function and urine profile

Median albuminuria (IQR) was 542.4 (238.7 - 961.5) mg/g, with 7 (11%), 12 (18%) and 46 (71%) patients classified in A1, A2 and A3 categories respectively. Association of reduced/low eGFR and albuminuria was observed in 58 (89.2%) patients while low eGFR associated with albuminuria was found in 55 (84.6%) patients (Figure 2).

The mean serum creatinine was 1.2 ± 0.3 mg/dL with 16 (24.6%) having raised serum creatinine. The mean eGFR was 112.9 ± 31.9 mL/min/1.73 m^2 with 14 (21.5%) and 4 (6.2%) patients having reduced and low eGFR respectively. Albuminuria (80%), leukocyturia (24.6%) and hematuria (4.6%) were dipstick abnormalities recorded for the purpose of the study. These abnormalities were also

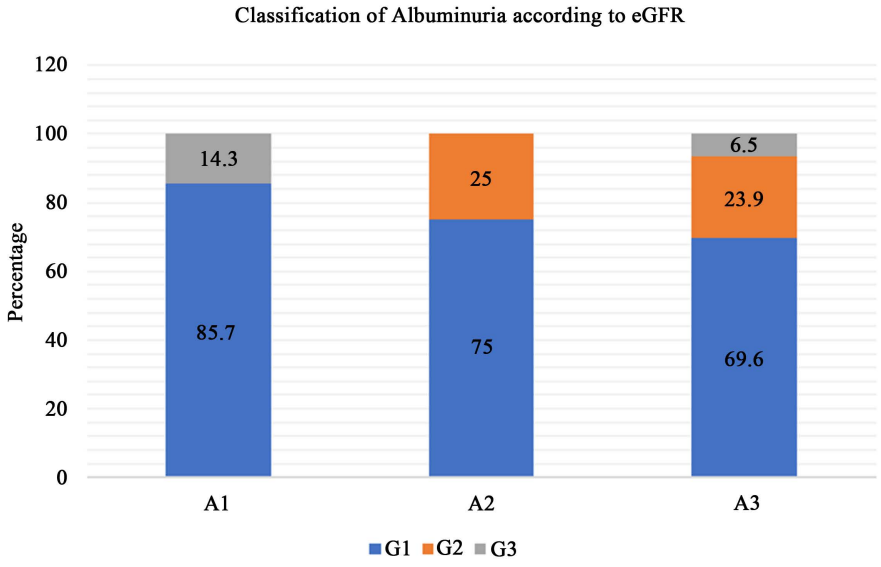

Figure 2. Classification of albuminuria according eGFR.

Table 1. Clinicobiological profile of the study population.

Variables	Frequency (n)	Percentage (%)
Gender		
Male	27	41.5
Female	38	58.5
Age group		
20 - 39	7	10.8
40 - 59	28	43.1
≥60	30	46.1
Duration of HCV infection (in years)		
1 - 5	54	83.1
6 - 10	8	12.3
11 - 20	3	4.6
Drug consumption		
Traditional medicine	12	6.1
Modern medicine	22	18.5
Modern and traditional medicine	4	33.8
None	27	41.6
Alcohol consumption		
Yes	7	10.8
At-risk	4	6.1
No	58	89.2
Body mass index		
Normal	27	41.5
Overweight	23	35.4
Obesity	15	23.1
Genotype (n = 42)		
1	13	20.9
2	11	26.1
3	2	4.8
4	16	38.1
Fibrosis staging (n = 50)		
F0	9	18
F1	11	22
F2	9	18
F3	5	10
F4	16	32

Continued

Dipstick profile		
Isolated albuminuria	35	53.8
Isolated leucocyturia	0	0
Isolated hematuria	0	0
Albuminuria + Leukocyturia	16	24.6
Albuminuria + hematuria	3	4.6
Albuminuria + Leukocyturia + hematuria	2	3.1
Albuminuria categories		
A1	7	10.7
A2	12	18.5
A3	46	70.8
Cytolysis		
Increased ALAT	24	36.9
Increased ASAT	38	58.5
Increased creatinine	16	24.6
Reduced eGFR	4	6.1

associated to each other with albuminuria-leukocyturia in 16 (24.6%) patients, albuminuria-hematuria in 3 (4.6%) patients and albuminuria-hematuria-leukocyturia in 2 (3.1%) patients.

Determinants of renal markers

We observed that advanced age ($p = 0.018$), female gender ($p < 0.001$), HCV genotype 1 and 4 ($p = 0.003$) and albuminuria ($p = 0.03$) were associated with low/reduce eGFR (Table 2). There was no factor associated with albuminuria (all $p > 0.05$) (Table 3).

4. Discussion

This cross-sectional study, assessing the prevalence and associated factors of renal markers among HCV-infected patients in a sub-Saharan African (SSA) setting, revealed that kidney abnormalities are common, leading by proteinuria (89.2%) and reduced/low eGFR (27.7%). Advanced age, female gender, HCV genotype 1 and 4, and albuminuria were associated with eGFR reduction. This study represents to our knowledge, the first published analysis of renal involvement of HCV infection in SSA.

The female predominance of HCV antibodies in this population (58.4%) was similar to reports done by other authors [24] [25]. Patients' mean age was high (56.8 ± 10.5 years), similar to that reported by Kowo *et al.* and Denniston *et al.* [6] [26]. It might be related to the age at the contamination time probably during the mass vaccination campaign before virus discovery. However, the discovery of the infection was less than 5 years old in most (83.1%) of these patients.

Table 2. Factors associated with glomerular filtration rate levels.

Variables	Mean eGFR (ml/min/1.73 m^2)	p value
Age group		
20 - 39	141	
40 - 59	115.2	0.018
≥60	104.2	
Gender		
Male	129.5	<0.001
Female	101.2	
Duration of HCv infection (in years)		
1 - 5	114.6	
6 - 10	107.7	0.565
11 - 20	96	
Traditional Medicine		
Yes	118.5	0.448
No	111.3	
Modern Medicine		
Yes	105.8	0.168
No	117.1	
Alcohol consumption		
Yes	128.3	0.094
No	111.1	
Body mass index		
Normal	114	0.815
Increased	112.1	
HCV viral load		
Increased	120.3	0.386
Low	112.8	
Fibrosis staging		
F0	119.6	
F1	120.4	
F2	113.6	0.979
F3	115.6	
F4	112.8	
Genotype		
1	110.1	
2	137.6	0.003
3	170	
4	107.9	

Continued

ALAT		
Normal	111	0.541
Increased	116.1	
ASAT		
Normal	115.1	0.640
Increased	111.3	
Dipstick albuminuria		
Yes	108.6	0.030
No	130	
Dipstick leukocyturia		
Yes	117.8	0.480
No	111.3	
Dipstick hematuria		
Yes	109.6	0.858
No	113.1	
Albuminuria categories		
A1	129.1	
A2	116.8	0.286
A3	109.4	

Table 3. Factors associated with albuminuria.

Variables	Albuminuria	p value
Age group		
20 - 39	841.3	
40 - 59	625.6	0.050
≥60	1112.2	
Gender		
Male	817.8	0.915
Female	912.9	
Duration of HCV infection (in years)		
1 - 5	709.9	
6 - 10	1510.7	0.127
11 - 20	2116.6	
Traditional Medicine		
Yes	851.1	0.937
No	880.1	

Continued

Modern Medicine		
Yes	1098.1	0.376
No	741.8	
Alcohol consumption		
Yes	610.9	0.557
No	905.1	
Body mass index		
Normal	868.8	0.980
Increased	876.6	
HCV viral load		
Increased	805.5	
Low	795.4	
Fibrosis staging		
F0	410.3	
F1	868.6	
F2	468.2	0.180
F3	1750.7	
F4	1072	
Genotype		
1	585.5	
2	895.8	0.769
3	628	
4	666	
ALAT		
Normal	683.3	0.462
Increased	1198.2	
ASAT		
Normal	639.4	0.196
Increased	1039.6	
Dipstick leukocyturia		
Yes	1385.1	0.345
No	706.3	
Dipstick hematuria		
Yes	2685.5	0.999
No	785.7	

The recent introduction of information and screening campaigns could explain this result. Unlike Caucasians, our patients had low alcohol consumption and smoking [27]. The mean BMI of this population was similar to Naga *et al.* findings [28]. This increased BMI promotes liver fibrosis and carcinogenesis, hence the need for lifestyle modifications [29] [30]. Pre-therapeutic workup shows moderate to severe fibrosis among the study population. This is probably due to long and slow evolution of the disease and late diagnosis, usually with complications, in Africa [31]. Only two over three patients performed HCV viral load, due to the high cost of this exam. Half of them had a high viral load, similar to Sonderup *et al.* reports [32]. Genotype testing revealed a type 4 predominance similar to Njouom *et al.* in south-Cameroon and Ndong-Atome *et al.* in Gabon [33] [34]. Although genotypes 1 and 4 predominate in SSA, genotype 4 is most frequent in central Africa [31] [32].

The mean eGFR was 112.9 ± 31.9 ml/min/1.73 m^2. Our findings were close to those from Saddadi *et al.* and Tsui *et al.* respectively in Iran and the United States of America (USA) [27] [35]. Reduced eGFR was found in 4 (6.2%) patients. This prevalence was higher than those from Saddadi *et al.* (0.6%) and Tsui *et al.* (2%) [27] [35]. This discrepancy could be due to the difference in population and the late diagnosis of the disease. A high prevalence of albuminuria (89.2%) was found in this population contrasting with the 4% and 8.3% found by Saddadi *et al.* and Huang *et al.* respectively [35] [36]. An explanation of this difference could be the elevated albuminuria threshold used by Saddadi *et al.* (500 mg/24 h) and the different methods for determining albuminuria. Otherwise, moderate albuminuria prevalence was similar to Liangpunsakul *et al.* findings [29]. However, severe albuminuria prevalence in our population was high. This discrepancy could be explained by the disease age (high in Africa's population) and probably increased by the intake of nephrotoxic drugs. Proteinuria and hematuria found at urine dipstick could reinforce the hypothesis of HCV-related glomerular disease, mainly membranoproliferative glomerulonephritis and membranous nephropathy [35] [37] [38]. Leukocyturia, on the contrary, seems to correlate with the interstitial involvement of HCV infection [39].

Advanced age, female gender, HCV genotype and albuminuria (all $p < 0.03$) were associated with eGFR reduction in univariate analysis. Patients with type 1 and 4 genotypes seemed to have a reduced eGFR as compared to others, but the small study population reduces our capacity to make significant associations. Tsui *et al.* found no association between age and renal manifestation, but Liangpunsakul *et al.* showed an association between albuminuria, advanced age and the black race in patients with HCV infection [27] [29]. A confounding factor could be the drug intake, responsible for renal toxicity, which was found in more than half of patients. Similarly to Iseki *et al.*, albuminuria was associated with reduced eGFR, suggesting the role of proteinuria in the progression of CKD [40]. However, no association with albuminuria was observed.

This study should be interpreted in light of some limitations. Our study pop-

ulation was small compared to other studies on this subject. We excluded many patients with confounding factors for proteinuria to avoid bias. Another limitation was biological and anatomopathological exams. Urine sediment, which is more reliable for hematuria and leukocyturia, was not performed. Due to limited financial issues, just a urine dipstick was realized. No kidney biopsy was performed in this population.

5. Conclusion

This study is the first of its type carried out in Cameroon. The prevalence of renal manifestations of HCV infection is high, led by proteinuria and reduced/low eGFR. Advanced age, female gender, HCV genotype 1 and 4, and albuminuria were associated with eGFR reduction. A regular follow-up of these patients with eGFR determination and urinalysis is necessary for the early diagnosis of renal manifestations and the implementation of nephroprotective measures.

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Availability of Data and Materials

The dataset analyzed during this study is not publicly available due to individual privacy issues. It could be available from the corresponding author on a reasonable request.

Authors' Contribution

Conception and Design: JN, MSMN, MPK, FJKF. Data collection: MSMN, MPK, FJKF, MTS. Administrative support: MTS, MPK, FJKF, JN, FAA, MTS. Data analysis and Interpretation: MSMN, MPK, SRSN, ANN. Drafting of the manuscript: SRSN, MSMN, MPK. Reviewing Manuscript: MTS, FJKF, VAM. All the authors read and approved the final draft for publication.

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Conflicts of Interest

The authors declare that they have no competing interests.

Ethical Consideration

This work was approved by the institutional review board of the Higher Institute of Health Sciences, Université des Montagnes, Bangangte, Cameroon (registration number 2014/82/UdM/PR/CAB/CIE). Administrative authorization from the Yaounde University Teaching Hospital, Medical Centre "La Cathédrale" was

obtained. This work was carried out in accordance with the declarations of Helsinki [41]. All ethical rules involving research on disadvantaged groups such as prisoners have been respected [42]. Patients were informed and a signed consent forms was collected from each participant who was equally free to attend the study without any outside constraint. This work is reported in compliance with the STROBE checklist.

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List of Abbreviations

ACR: Albuminuria/creatinuria ratio
BMI: Body mass index
CHVC: Chronic viral Hepatitis C
CKD: Chronic kidney disease
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
eGFR: estimated glomerular filtration rate
HCV: Hepatitis C virus
MDRD: Modification of Diet in Renal Disease
MHD: Maintenance hemodialysis
MPGN: Membranoproliferative glomerulonephritis
SSA: sub-Saharan Africa
SPSS: Statistical Package for Social Sciences
USA: United States of America