

Prevalence and Associated Factors of Resistant Hypertension among Patients with Chronic Kidney Disease: An Example from Cameroon

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Abstract

Background: Resistant arterial hypertension (RAH) is common in patients with chronic kidney disease (CKD). We aimed to study the prevalence and associated factors of RAH in patients with CKD in 2 referral hospitals in Cameroon.

Material and method: This was a cross-sectional and analytical study, from December 2020 to May 2021. All consenting patients over 18 years of age with hypertension and CKD stage 2-5 ND was included. Socio demographic, clinical and biological data were collected. Patients were considered to have RAH if they were on 4 antihypertensive drugs or a patient on 3 antihypertensive drugs, including 1 diuretic who presented with office blood pressure $\geq 140/90$ mmHg and BP $\geq 135/85$ mmHg after home BP self-measurement. Home BP self-measurement was performed using an OMRON brand electronic BP monitor every morning and evening for three consecutive days and the average of the 18 values was calculated. Chi-2 and exact Fischer tests was used to assess the association between variables. $p < 0,05$ was considered significant.

Results: A total of 194 patients were included, with 62.89% male. The mean age was 61.89 (13.13) years; 34.54% (67/194) had CKD stage 3a, 26.80% (52/194) stage 3b, 15.46% (30/194) stage 4 and 21.13% (41/194) stage 5. Hypertension: 47.93% (93/194), diabetes: 21.65%, (42/194) and chronic glomerulonephritis: 11.34% (22/194) were the main presumed etiologies of CKD. The prevalence of RAH was 26.29% (51/194), and age >60 years ($p=0,001$), CKD grade 5 ($p=0,000$), presence of diabetes ($p=0,000$), dyslipidemia ($p=0,006$), obesity ($p=0,001$) and smoking ($p=0,001$) were associated factors.

Conclusion: RAH is frequent amongst CKD patients, and it is associated with cardiovascular risk factors and severity of CKD. It is necessary to identify these patients and put measure to control BP especially in those with risk factors.

Keywords: Prevalence; Resistant hypertension; Chronic kidney disease; Douala

Abbreviations: BMI: Body Mass Index; BP: Blood Pressure; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; HDL: High Density Lipoprotein; HIV: Human Immunodeficiency Virus; HTN: Hypertension; RAH: Resistant Arterial Hypertension; LDL: Low Density Lipoprotein.

Background

Hypertension (HTN) is a major public health problem around the world [1]. One billion adults suffer from it, a figure which could reach 1.5 billion in 2025 [2,3]. In 13.7% to 14.7% of cases blood pressure (BP) is not controlled despite adequate treatment [4,5]. This uncontrolled BP may be pseudo-resistance to treatment or true resistant hypertension [6]. Resistant arterial hypertension (RAH) is defined as uncontrolled BP despite the use of three classes of antihypertensive drugs, including at least one diuretic, or controlled BP under four or more antihypertensive drugs [7]. The prevalence of RAH ranged from 12 to 19.7% in America [8,9], Spain [10] and in Asia [9]. Factors such as, advanced age, obesity, longer duration of HTN, dyslipidemia, diabetes, cardiovascular disease and chronic

kidney disease (CKD), are associated with a higher frequency of RAH [11-14]. In USA, 30.5% of hypertensive patients with CKD develop RAH compared to 20.1% in patients without CKD [15] and the prevalence of RAH increases with lower glomerular filtration rate (GFR) [7,15]. RAH is a risk factor of increase cardiovascular morbidity and mortality [16-19].

In sub-Saharan Africa, data are scarce. Nansseu JRN, et al. in a systematic review found a prevalence of RAH of 12.1% in the general population [20]. This prevalence was 12.8% in patients with CKD in Ghana [21]. In Cameroon a study reported that only 23% of all individuals with HTN at the community level were aware of their status, only 46% of those aware were on treatment, among which only 25% achieved expected target BP levels [22]. So BP control remains

a challenge in large part due to inappropriate treatment. Moreover, HTN is the leading cause of CKD affecting 1 in 3 patients with CKD, and their coexistence is associated with increased cardiovascular morbidity and mortality [23]. No study, to the best of our knowledge has looked at the prevalence and associated factors of RAH in patients with CKD in Cameroon.

Methods

Study setting and participants

We conducted a cross-sectional study, from 10th December 2020 to 30th May 2021 in the nephrology outpatient's unit of the Douala General Hospital (DGH), and the Douala Laquintinie hospital (DLH). These are the two main referral centers for patients with CKD in the Littoral region. The study was authorized by the General Manager of the DGH and the Director of the DLH. Ethical approval was obtained from the Douala University Ethics Committee n° 2584.

We included patients over 18 years of age, with HTN and CKD stage 2 to 5 not on dialysis (ND), and followed up for at least one month as outpatient at the nephrology unit of the two hospitals. We excluded those who refused to participate. Once their consent was obtained, we collected socio demographic and clinical data such as: age, sex, and major cardiovascular risk factor such as diabetes, dyslipidemia, obesity, smoking, history of cardiopathy, antihypertensive treatment, weight and height for the calculation of body mass index (BMI). BP was measured, using an OMRON® electronic blood pressure monitor only in patients on 3 class of antihypertensive drugs including at least one diuretic: (they were left to rest for 15 minutes, then we took their BP in both arms three times, with two minutes' intervals between each measurement). Those with office BP \geq 140/90 mmhg, benefited from a home BP self-measurement over three days and the average of the 18 values was calculated and considered.

Definition of operational terms

Hypertension: was considered in any patient on antihypertensive treatment.

Resistant hypertension: was considered in any patient on 4 antihypertensive drugs including one diuretic or a patient on 3 antihypertensive drugs including one diuretic for one month who presented with office BP \geq 140/90 mmhg and home BP \geq 135/85 mmhg after home self-measurement.

Chronic kidney disease: was defined and classified according to the KDIGO 2012 criteria [23].

Dyslipidemia: was defined as total cholesterolemia $>$ 200 mg/dl, and/or LDL-cholesterol level $>$ 130mg/dl, and/or triglyceridemia $>$ 150 mg/dl, and/or HDL-cholesterol level $<$ 40 mg/dl [24].

Diabetes: was considered in a patient with a known history of diabetes or any patient on antidiabetic treatment.

Body mass index: weight/height² (kg/m²) ratio [24].

Obesity: Body mass index greater than or equal to 30 kg/m² [24].

Statistical analysis

Data analysis was done using the statistical package software SPSS 25.0. Fischer exact and Chi-2 tests were used to assess the association between variables. Quantitative variables were expressed by mean (standard deviation), and qualitative ones by frequency and percentages. Logistic regression analysis was used to look for associated factors. A p value $<$ 0.05 was considered statistically significant.

Results

Prevalence of RAH and characteristics of the study population

A total of 194 patients were included. The overall prevalence of RAH was 26.29% (51/194) (Figure 1). In our study population, 62.89% (122/194) were male. The mean age was 61.89 (13.13) years; 34.54% (67/194) had CKD stage 3a, 26.80% (52/194) stage 3b, 15.46% (30/194) stage 4 and 21.13% (41/194) stage 5ND. Hypertension: 47.93% (93/194), diabetes: 21.65%, (42/194) and chronic glomerulonephritis: 11.34% (22/194) were the main presumed etiologies of CKD.

The prevalence of RAH increased with the stage of CKD. It ranged from 2.99% (6/194) for stage 3a to 65.85% (127/194) for stage 5 (Table 1).

Associated factors with resistant arterial hypertension in the study population

On bivariate analysis, male sex (OR: 7.95; p=0.000), diabetes (OR: 6.62; p=0.000), dyslipidemia (OR: 11.82; p=0.000), obesity (OR: 4.25; p=0.006) and smoking (OR: 3.63; p=0.005) were factors associated with RAH.

On multivariate logistic regression analysis (Table 2), factors independently associated with RAH were; age $>$ 60 years (aOR: 3.97; 95% CI: 1.81-19.53; p=0.001), CKD stage 5 (aOR: 62.68; 95% CI: 13.33-294.74; p=0.000), diabetes (aOR: 6.58; 95% CI: 2.89-13.72 ; p=0.000), obesity (aOR: 3.81; 95% CI: 1.66-16.91; p=0.001), smoking (aOR: 4.63; 95% CI: 1.38-9.54 ; p=0.005), dyslipidemia (aOR: 4.10; 95% CI: 1.56-17.9; p=0.006).

Discussion

The aim of this study was to determine the prevalence and associated factors of RAH in patients with CKD followed in nephrology consultations of two referral hospitals in Douala- Cameroon. Our study participants were more male (62.89%), their mean age was 61.89 (13.13) years and 34.54% had CKD stage 3a. The prevalence on RAH was 26.29%, and associated factors were age $>$ 60 years, CKD stage 5, presence of diabetes, dyslipidemia, obesity and smoking.

Up to 62.89% of the participants were men. Our results are similar to most studies carried out in patients with CKD [15,25,26]. Furthermore, the mean age was 61.89 years similar to that found by Thomas G, et al. in the USA (60.6 years) and Kaze FF, et al. in Cameroon (60.9 years)

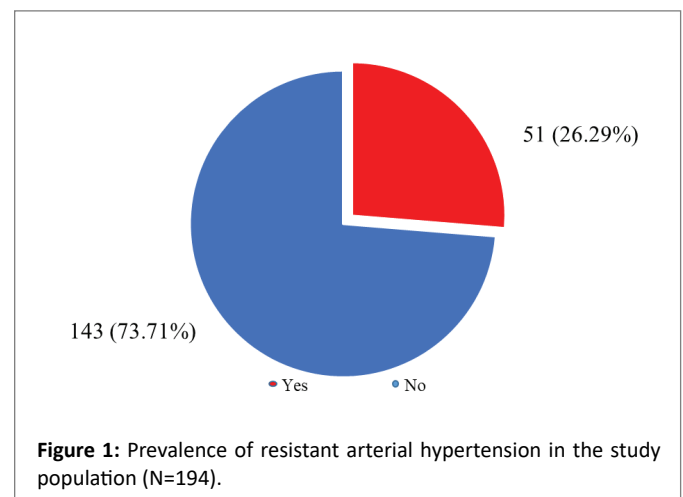


Figure 1: Prevalence of resistant arterial hypertension in the study population (N=194).

Table 1: Baseline characteristics of the study population (N=194).

Characteristics	Overall N=194	No RAH n=143	RAH n=51	P
Male sex	122 (62.89%)	87 (60.84%)	35 (68.63%)	0.322
Mean age (SD)	61.89 (13.13)	61.81 (12.75)	62.09 (14.24)	0.658
Diabetes	64 (32.98%)	31 (21.68%)	33 (64.71%)	0.000
Dyslipidemia	34 (17.52%)	10 (6.99%)	24 (47.06%)	0.000
Smoking	19 (9.72%)	09 (6.29%)	10 (19.61%)	0.005
Obesity	14 (7.21%)	06 (4.19%)	08 (15.68%)	0.006
Alcohol consumption	13 (6.70%)	08 (9.80%)	05 (5.59%)	0.301
Heart failure	33 (17.01%)	15 (10.49%)	18 (35.29%)	0.000
Stroke	12 (6.18%)	09 (6.29%)	03 (5.88%)	0.916
HIV infection	21 (10.82%)	19 (13.29%)	02 (3.92%)	0.064
Gout	16 (8.24%)	11 (7.69%)	05 (9.80%)	0.752
Auto-immune disease	13 (6.70%)	13 (9.10%)	00 (0.0%)	0.025
Hepatitis B	03 (1.54%)	02 (1.39%)	01 (1.96%)	0.779
Hepatitis C	06 (3.09%)	04 (2.80%)	02 (3.92%)	0.690
CKD grade 2	04 (2.06%)	04 (2.80%)	00 (0.00%)	0.444
CKD grade 3a	67 (34.54%)	65 (45.85%)	02 (3.92%)	0.000
CKD grade 3b	52 (26.80%)	44 (30.77%)	08 (15.69%)	0.010
CKD grade 4	30 (15.46%)	16 (11.19%)	14 (27.45%)	0.000
CKD grade 5	41 (21.13%)	14 (9.79%)	27 (52.94%)	0.000
Antihypertensive treatment				
Calcium channel blockers	122 (66.49%)	79 (55.24%)	43 (84.31%)	-
Diuretics	117 (60.30%)	66 (46.15%)	51 (100%)	-
Converting enzyme inhibitors	62 (31.95%)	34 (23.77%)	28 (54.90%)	-
Beta blockers	39 (20.10%)	14 (9.79%)	25 (49.01%)	-
Renin angiotensin aldosterone inhibitors	41 (21.13%)	16 (11.18%)	25 (49.01%)	-

CKD: Chronic Kidney Disease; HIV: Human Immunodeficiency Virus; RAH: Resistant Arterial Hypertension; SD: Standard Deviation.

Table 2: Associated factors with resistant arterial hypertension in multivariate analysis.

Variables	aOR (95% CI)	p-value
Male sex	6.89 (2.02-19.78)	0.600
Age >60 years	3.97 (1.81-19.53)	0.001
CKD grade 3b	0.80 (0.01-6.30)	0.210
CKD grade 4	20.78 (0.90-124.11)	0.589
CKD grade 5	62.68 (13.33-294.74)	0.000
Diabetes	6.58 (2.89-13.72)	0.000
Heart failure	4.45 (2.36-17.15)	0.601
Obesity	3.81 (1.66-16.91)	0.001
Smoking	4.63 (1.38-9.54)	0.005
Dyslipidemia	4.10 (1.56-17.91)	0.006

[27,28]. Age and male gender are known risk factors for CKD and Hypertension [29].

About 36.59% (71/194) had stage 4 and 5 of CKD. Oluyumbo R, et al. in Nigeria in 2017 found a prevalence which was high than ours 30.6% (grade 4) and 28.6% (grade 5) [30]. This could be explained by the silent course of the disease and late referrals of patients with CKD in nephrology in our context [30,31].

The prevalence of RAH among patients with CKD varies between studies [7,15,25,32]. We found a prevalence of 26.29% in the present

study. Tanner et al. in USA, and De Nicola et al. in Italy found a similar prevalence of 30.5% and 22.9% respectively [15,33]. However, studies in Spain and China reported lower prevalence of 13.3% and 11.1% respectively [7,32]. This could be explained first by their larger sample size, the study population and the difference in treatment protocols: contrary to us they included only hypertensive patients with CKD stage 1 to 4 and it is known that RAH is most frequent in patients with CKD stage 5 [21,34].

In our study, the prevalence of RAH increased with the stage of CKD. It was 18.37%, for stage 3, 46.67%, for CKD stage 4 and 65.85% for stage 5. These results are similar to those found in the literature. In Switzerland in 2018, Viuzzi F, et al. found similar results, 37.3% for stage 3 and 62.7% for stages 4 and 5 [35]. Also, Ayisi-Boateng NK, et al. in Ghana in 2020 had prevalence of 15.8% for a GFR >60 ml/min/m², 24.9% for a GFR between 45-59 ml/min/m², and 33.4% for a GFR <45ml/min/m² [21]. Hypertension in CKD is caused either by an excess of intravascular volume or by excessive activation of the renin-angiotensin-aldosterone system in relation to the state of sodium/volume balance [36]. Among these are increased activity of the sympathetic nervous system, increased endothelin production, decreased availability of endothelium-derived vasodilators/endothelial dysfunction, structural changes of the arteries, renal ischemia [29,34]. All these mechanisms increase with the stage of CKD making HTN more severe and difficult to control with the severity of CKD [34,36].

Factors associated to RAH

In our study, associated factors to RAH were: Age >60 years, CKD stage 5, diabetes, dyslipidemia, obesity and smoking. Our findings are similar to reported studies [7,25,35,37]. Tanner RM, et al. in USA, and Viazzi F, et al. in Switzerland also reported older age as an associated factor to RAH [35,37]. This can be explained by the fact that older age increases arterial stiffness, baroreceptor and endothelial dysfunction, oxidative stress and therefore poorer BP control [2]. Regarding obesity, Viazzi F, et al. in Switzerland, and De Nicola L, et al. in Italy in 2011 found similar results [25,35]. Several hormones secreted by adipose tissue are involved in the synthesis of aldosterone (C1q/TNF, adiponectin, leptin) [29]. Aldosterone causes inflammation with vascular fibrosis, reduction of nitric oxide and therefore vasoconstriction; in addition, obese patients show an increase in sympathetic vegetative activity [29]. Verdalles U, et al. in Spain, Zheng Y, et al. in China also found diabetes, dyslipidemia and smoking as factors associated with RAH [7,32]. Patients with diabetes have increased arterial stiffness compared to non-diabetics [2]. Also diabetes and dyslipidemia are often associated with elevated aldosterone which contributes to poorer BP control [2,38]. Smoking promotes atherosclerosis and causes progressive arterial stenosis, it accelerates arterial aging, and leads to permanent sympathetic activity [7,32,37].

Limitations and Strength

We acknowledge some limitations to this study. The sample size is relatively small for the condition of arterial hypertension and we didn't look for etiologies of secondary HTN, however secondary HTN is largely responsible for RAH. The study group is relatively small for the condition of arterial hypertension.

Our strength: home BP self-measurement has allowed us to eliminate differential diagnoses such as white coat HTN. This study is to the best of our knowledge the only one that has studied the prevalence and associated factors of RAH in patients with CKD in Cameroon.

Conclusion

RAH affected 1 out of 4 patients with CKD in our setting and it was associated with cardiovascular risk factors and CKD stage 5. It is therefore important to screen these patients and reinforce measure to control BP and modifiable cardiovascular risk factors such as obesity dyslipidemia and smoking with the aim to reduce morbi mortality in affected patients.

Competing Interests

The authors declare that they have no competing interests.

Author's Contribution

HMP: Study conception and design, drafting of the manuscript, interpretation of data ; MMD: data collection and analysis, drafting of the manuscript; MAS: Study design, data analysis, critical revision of the manuscript; NVE: supervision of data collection, critical revision of the manuscript; NMS: Data interpretation and critical revision of the manuscript; FH: Data interpretation and critical revision of the manuscript; KF: critical revision of the manuscript; DTA: critical revision of the manuscript; KFF: critical revision of the manuscript; AEG: study conception and design, critical revision of the manuscript. All authors read and approved the final manuscript.

Availability of Data and Material

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

Ethics Approval and Consent to Participate

Ethical approval was obtained from University of Douala, ethical clearance number 2584, and consent for participated was obtained from each patient.

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