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Hematological Disorders during Chronic Kidney Disease Stages 3 to 5 Non-Dialysed in Cameroon

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Abstract

Introduction: Haematological disorders are common complications of chronic kidney disease (CKD) leading by anemia which increase with the severity of the disease. **Objective:** Assess the haematological profile of CKD patients stages 3 to 5 non-dialysed seen at the first nephrology consultation in Cameroon. **Patients and Methods:** A hospital-based cross-sectional study was conducted from February to July 2018 at the nephrology unit of the Yaounde University Teaching Hospital and Douala General Hospital. All adults' (≥18 years old) patients who provided a written informed consent and attended their first nephrology consultation with a nephrologist diagnosis of CKD stages 3 to 5 non-dialysed were included. Clinical and paraclinical data (serum creatinine, full blood count, reticulocytes count, iron status, vitamin B12 and folates count, and bleeding time) were collected. Parametric, non-parametric and correlations tests were used to compare variables. **Results:** We included 105 (59% males) participants with a mean age of 55.2 ± 13.6 years divided into 20 (19%), 36 (34.3%) and 49 (46.7%) respectively in stage G3, G4 and G5 of CKD. The profile of hematological abnormalities was anemia (86.7%), leucopenia (15.2%), hyperleucocytosis (6.7%), thrombopenia (23.8%), thrombocytosis (3.8%) and prolonged bleeding time (13.3%) without any association with the stage of CKD ($p > 0.05$). The pattern of anemia was mainly normocytic and normochromic (59.3%) and aregenerative (92.3%) with iron deficiency found in 23 (21.9%) participants. There was no case of vitamin B12 and folates deficiency. Prolonged bleeding time was observed in 14 (13.3%) participants with a weak correlation between platelets

count and bleeding time (r = 0.122). **Conclusion:** We observed that aregenerative normocytic normochromic anemia is the leading haematological abnormality during CKD in this setting. None of the full blood count parameters was associated with CKD stages and there was a week correlation between bleeding time and platelet count.

Keywords

Hematologic Disorders, Chronic Kidney Disease, Cameroon

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem with 8% to 10% prevalence in adult population [1]. CKD is highly prevalent in Africa affecting 15.8% of adults overall and 10% to 14.2% in Cameroon [2] [3] [4]. Haematological disorders are among complications of CKD which increase with the severity of the disease [5]. Anemia is the most common haematological complication of CKD with increasing prevalence associated to the progressive decline of glomerular filtration rate (GFR) [6] [7] [8]. It's a predictor of all cause and cardiovascular morbi-mortality as well as reduction of quality of life [9]. The occurrence of anemia during CKD is multifactorial involving uremic and context specific factors. Despite the reduction of endogenous production of erythropoietin as a main pathophysiological factor of anemia, other contributing factors include deficiency in iron, B12 vitamins and folates, shortened red blood cell lifespan, blood loss, "uremic environment", hyperparathyroidism, inflammation, aluminum toxicity and hypothyroidism [10] [11]. Moreover, Sub-Saharan Africa (SSA) specific factors like nutritional deficiencies, hemoglobinopathies and infectious diseases contribute to the burden of anemia and the pattern modification in this setting [6]. CKD is associated with malnutrition, inflammation and atherosclerosis which can explain the modification of the total and differential white blood cell count [12]; this modification leads to the suggested use of the ratio of neutrophil-to-lymphocyte count as an alternative to measure inflammation in CKD patients [13] [14]. The progression of CKD is associated with bleeding which is unrelated to platelet count; it is more linked to platelet reactivity which is best explored by bleeding time [15] [16].

A study in our setting in patients on maintenance hemodialysis revealed that 79% had anemia at baseline which was predominantly microcytic and hypochromic in 43% of them [17]. We therefore undertook this study aiming to assess the hematological profile of CKD patients seen at the first nephrology consultation in two referral hospitals of Cameroon.

2. Patients and Methods

2.1. Study Design and Setting

This was a hospital-based cross-sectional study of 6-month duration (February

to July 2018), conducted at the nephrology unit of the Yaounde University teaching hospital (YUTH) and the Douala General Hospital (DGH) which are two tertiary hospitals in the Cameroon. This study received administrative authorization from the YUTH and DGH, and was approved by the ethic committee of the Higher Institute of Health Sciences, Bangangté, Cameroon.

2.2. Data Collection

Final year undergraduate medical student collected consecutively data of all adults' (≥18 years old) patients who provided a written informed consent and attended their first nephrology consultation with a nephrologist diagnosis of CKD stage 3 to 5 non-dialysed. We excluded patients with active bleeding, history of blood transfusion within 3 months of enrolment, and on oral iron, erythropoietin stimulating agents, anticoagulant and antiplatelet therapy. We used data entry form to collect during face-to-face interview patient's information's. Socio-demographic characteristics include age, gender and employment status. Clinical data were baseline nephropathy, comorbidities, weight, height, blood pressure and capillary glucose measurements. Blood samples were collected for serum creatinine, full blood count, reticulocytes count, iron status, vitamin B12 and folates count, and bleeding time. Full blood count includes red blood cell, white blood cell, platelet, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and MCH concentration (MCHC) whereas iron status was assess with serum iron, serum ferritin and transferrin saturation (TSAT).

2.3. Definitions and Calculations

We calculated the body mass index (BMI, kg/m^2) as weight (kg)/height (m) * height (m), and ranked participants as normal weight for $20 \leq BMI < 25\ kg/m^2$, overweight for $25 \leq BMI < 30\ kg/m^2$ or obese for $BMI \geq 30\ kg/m^2$. Hypertension was diagnosed in the presence of systolic (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg on two consecutive occasions two weeks apart, or ongoing use of BP lowering medications. Diabetes mellitus was defined as repeated fasting glycemia ≥ 126 mg/dl or use of glucose control agents. Estimated glomerular filtration rate (eGFR, mL/min) was based on the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [18]. Serum creatinine from Jaffe reaction (SCr_{Jaffe}) was converted to standardized serum creatinine ($SCr_{Standardized}$) to be used in CKD-EPI formula, via the formula $SCr_{Standardized} = 0.95 * SCr_{Jaffe} - 0.10$ [19]. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were used to classified CKD into G3 (eGFR: 30 - 59); G4 (eGFR: 15 - 29) and G5 (eGFR < 15) [20]. For the purpose of the study, anemia was defined by haemoglobin level < 13.5 g/dL for men and <12 g/dL for women. Microcytosis and macrocytosis were defined respectively by MCV < 80 and >100 fl. Hypochromia and normochromia were defined by MCH < 27 and ≥27 pg respectively. Anemia was regenerative and aregenerative when reticulocytes count was respectively above and less than $120{,}000/mm^3$. Absolute iron deficiency was

defined as TSAT < 20% and serum ferritin < 100 ng/mL while functional iron deficiency was defined as TSAT < 20% and serum ferritin > 100 ng/mL. Vitamine B12 deficiency was defined by a serum level < 150 ng/L whereas hypervitaminose B12 was >950 ng/L. Folates deficiency was serum level < 5 µg/L and high when >15 µg/L. Hyperleucocytosis referred to WBC ≥ 10,000/mm^3 whereas leucopenia was WBC ≤ 4000/mm^3. Thrombocytosis was defined as platelet count ≥ 450,000/mm^3 while thrombopenia was platelet count ≤ 150,000/mm^3. Bleeding time was prolonged when >5 minutes.

2.4. Statistical Analysis

Statistical analysis was performed using the SPSS® version 18 software for Windows (SPSS, Chicago, IL, USA). Means and standard deviations and percentages were used to express results. Chi-square test and equivalents, and Student t-test and non-parametric equivalents were used to compare qualitative and quantitative variables. Correlation between variables was performed using the Pearson and Spearman's correlation tests. The level of significance was set at $p < 0.05$.

3. Results

Characteristics of study population

As presented in Table 1, we included 105 participants with a mean age of 55.2 ± 13.6 years, 62 (59%) men and 53 (50.5%) overweight/obese; they were divided into 20 (19%), 36 (34.3%) and 49 (46.7%) respectively in stage G3, G4 and G5 of CKD. Hypertension (47.6%) and Diabetes (31.4%) were the leading baseline nephropathy as shown in Figure 1. Asthenia (69.5%), dizziness (58.1%) and palor (42.8%) were the main clinical signs reported in participants, Figure 2.

Distribution of hematoligical parameters

The haematologic parameters of study population are presented in Table 2. As shown in Figure 3, anemia was the main haematological abnormality observed

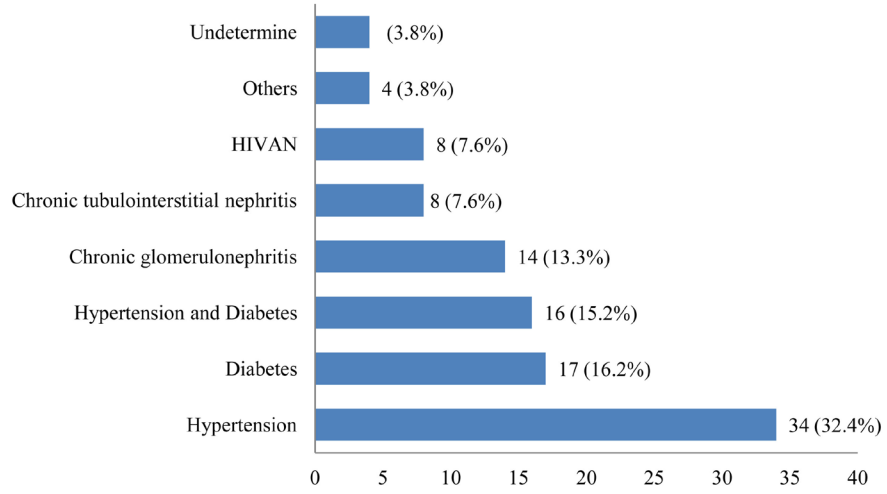

Figure 1. Distribution of baseline nephropathy.

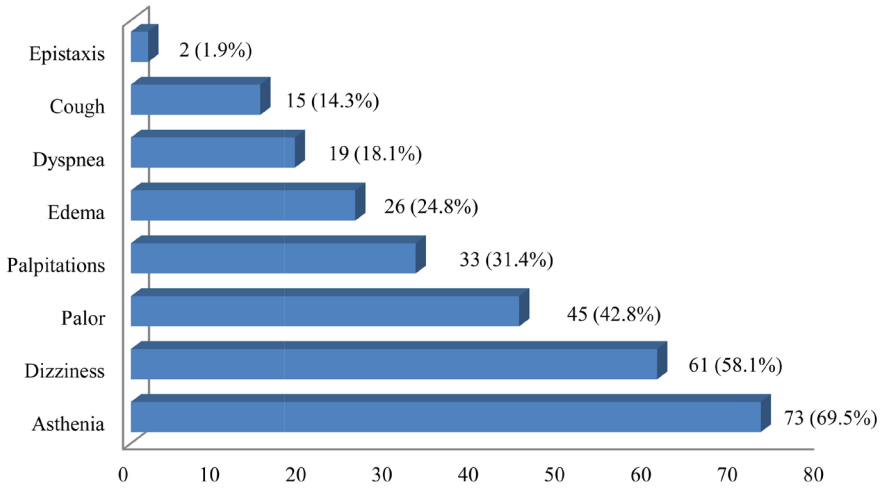

Figure 2. Frequency of clinical signs.

Table 1. Socio-demographic and clinical characteristics of study population.

Variables	N (%)
Total	105 (100)
Mean age ± SD (years)	55.2 ± 13.6
Sex	
Male	43 (41)
Female	62 (59)
Employment	
Yes	45 (42.9)
No	60 (57.1)
GFR categories	
G3	20 (19)
G4	36 (34.3)
G5	49 (46.7)
Comorbidities	
Hypertension	86 (81.9)
Diabetes	37 (35.2)
Gout	19 (18.1)
HCV infection	11 (10.5)
HBV infection	4 (3.8)
HIV infection	4 (3.8)
Mean BMI ± SD (kg/m^2)	25.9 ± 5.1
Overweight	34 (32.4)
Obese	20 (19)
Mean SBP ± SD (mmHg)	155.6 ± 25.9
Mean DBP ± SD (mmHg)	89.9 ± 15.1
Uncontrolled hypertension	74 (70.5)
Mean glycemia ± SD (mg/dl)	144 ± 23.5
Uncontrolled glycemia	21 (56.7)

BMI—body mass index; DBP—diastolic blood pressure; GFR—glomerular filtration rate; HBV—hepatitis B virus; HCV—hepatitis C virus; HIV—human immunodeficiency virus; SBP—systolic blood pressure; SD—standard deviation.

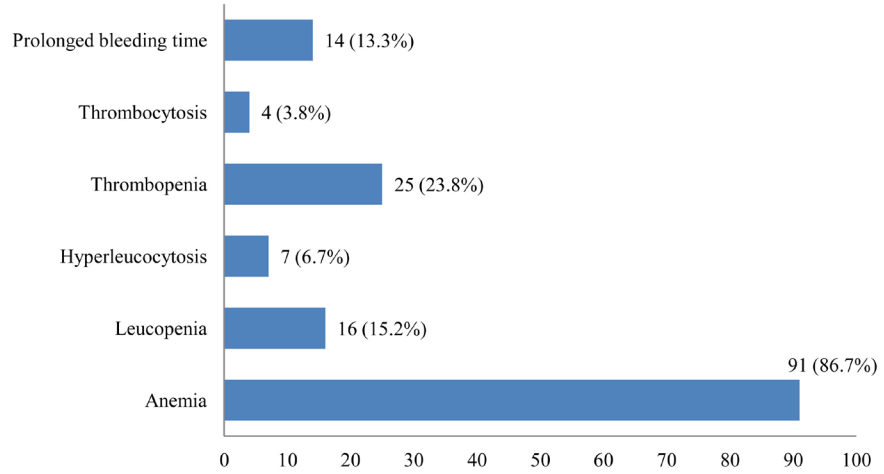

Figure 3. Prevalence of haematological abnormalities.

Table 2. Haematological parameters of study population.

Parameters	Mean (standard deviation)
RBC ($\times 10^{12}$/L)	3.5 (0.8)
Haematocrit (%)	28 (6)
Haemoglobin (g/dL)	9.4 (2.3)
MCV (fl)	82 (9)
MCH (pg)	26 (3)
MCHC (g/dL)	29 (4)
Reticulocytes (10^9/L)	53 (11)
Serum iron (mmol/L)	12.3 (4.3)
Serum ferritin (ng/L)	342.6 (98.1)
TSAT (%)	25.6 (6.5)
Vitamine B12 (ng/L)	769.2 (265.6)
Folates (µg/L)	11.1 (2.2)
WBC ($\times 10^9$/L)	5.9 (2.3)
Platelets ($\times 10^9$/L)	215.6 (61.2)
Bleeding time (minutes)	3.7 (1.1)

MCH—mean corpuscular haemoglobin; MCHC—mean corpuscular haemoglobin concentration; MCV—mean corpuscular volume; RBC—Red blood cell; TSAT—transferrin saturation coefficient; WBC—White blood cell.

in 91 (86.7%) participants. His prevalence increases with the progression of CKD with 75% in G3, 83.3% in G4 and 93.9% in G5 without statistical significance among GFR categories of CKD ($p > 0.05$). The patterns of anemia presented in Figure 4 revealed that it was mainly normocytic and normochromic in 54 (59.3%) patients and aregenerative in 84 (92.3%) of them. Only anemic participants had iron deficiency found in 23 (21.9%) participants. Absolute and functional iron deficiency was observed in 13 (56.5%) and 10 (43.5%) participants

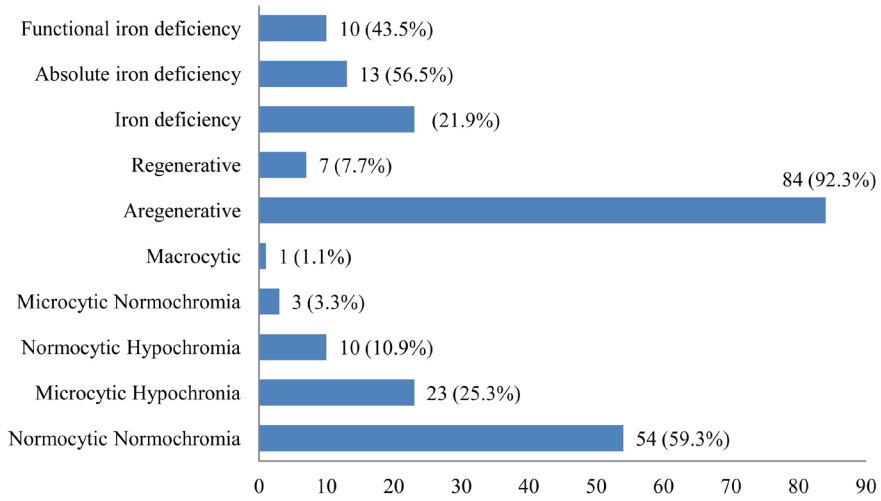

Figure 4. Anemia patterns in CKD participants.

respectively. None of the participants have vitamin B12 deficiency while 71 (67.6%) patients had hypervitamin B12. Folates levels were within normal limits.

Leucopenia was present in 16 (15.2%) participants while hyperleucocytosis was observed in 7 (6.7%), **Figure 4**. Leucopenia was observed 5 (31.2%), 6 (37.5%) and 5(31.2%) participants respectively in G3, G4 and G5 of CKD GFR categories without statistically significance difference ($p > 0.05$). Equivalents figures for hyperleucocytosis were 2 (28.6%), 3 (42.8%) and 2 (28.6%) participants respectively in G3, G4 and G5 of CKD GFR categories ($p > 0.05$).

There was thrombopenia and thrombocytosis in 25 (23.8%) and 4 (3.8%) participants respectively, **Figure 4**. The prevalence of thrombopenia increased with the severity of CKD in 6 (24%), 8 (32%) and 11(44%) participants respectively in CKD G3, G4 and G5 without statistical significance with CKD GFR categories ($p > 0.05$). Equivalents figures were 2 (50%), 1 (25%) and 1 (25%) for thrombocytosis ($p > 0.05$).

Prolonged bleeding time was observed in 14 (13.3%) participants divided into 4 (28.6%), 4 (28.6%) 6 (42.8%) respectively for G3, G4 and G5 of CKD GFR categories without any statistical significance with the category ($p > 0.05$). Among participants with prolonged bleeding time, 10 (71.4%) had thrombopenia. There was a weak correlation between platelets count and bleeding time ($r = 0.122$).

4. Discussion

This study revealed that anemia was the main hematological abnormality, mainly aregenerative, in nearly 9 out of 10 participants with increase prevalence associated to the CKD progression. Anemia was normocytic and normochronic in nearly 60% of cases with iron deficiency observed in more than one out of five participants. There was no case of vitamin B12 and folates deficiency. Leucopenia was present in 15% and thrombopenia in nearly 1 out of 4 patients. Prolonged bleeding time was observed in 13% with a weak correlation with platelets count and bleeding time.

The haematological profile observed in this study is closed to similar studies in this setting [8] [21]. There was a high prevalence of anemia increasing with the disease progression in our study similar to previous study in this setting compare to other study which can be explain by context specific factors, higher prevalence of unemployed participants and lack of social security program [8] [17]. The main pattern of anemia was normocytic and normochromic similar to the south African study [8]; this highlight the reduction of erythropoietin secretion as the main pathophysiological factors of anemia in CKD. Microcytic hypochromic pattern was the second most common anemia profile which can be explained by specific factors like nutritional deficiencies, hemoglobinopathies and infectious diseases in this setting [6]. There was a high prevalence of iron deficiency, predominantly absolute, close to previous results in similar setting which can be explain by the high prevalence of hemoglobinopathies and infectious disease in SSA [21] [22]. We did not report any deficiency in vitamin B12 and folates which correlate well with few case of macrocytic anemia; this suggest that complete blood count could be enough to indicate these parameters deficiency in our setting with no social insurance policy and higher prevalence of unemployment hence limitating exhaustive work up.

We reported a high prevalence of leucopenia compare to hyperleucocytosis without any correlation with CKD progression as reported elsewhere [8]. The hyperleucocytosis could be related to the inflammation which occurs during CKD in the context of malnutrition, inflammation and atherosclerosis syndrome [12]. However, we did not assess the neutrophil/lymphocytes ratio and C reactive protein (CRP) which can permit us to evaluate inflammation in such patients [12] [14]. The predominance of leucopenia could be related to the physiologic conditions in this high risk infectious environment [23].

Thrombopenia was more prevalent without any correlation with CKD categories as observed in previous studies [8] [21] [22]. There was a weak correlation between platelet count and bleeding time suggesting the platelet reactivity abnormality during CKD [15] [16].

5. Strength and Limitations

The main limitations of this study are the lack of CRP and assessment of neutrophil/lymphocytes ratio which could help to better assess inflammation status. However, this is on our knowledge the only published study in Central Africa assessing haematological profile of CKD patients. It therefore provides lacking data in non-dialysed CKD patients and completes the previous one in patients on maintenance haemodialysis [17].

6. Conclusion

We observed that aregenerative normocytic normochromic anemia is the leading haematological abnormality during CKD in this setting suggesting the role of nutritional deficiencies, hemoglobinopathies and infectious diseases. None of the

full blood count parameters was associated with CKD categories and there was a week correlation between bleeding time and platelet count.

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Ethics Approval and Consent to Participate

This study received administrative authorization from the Yaounde University Teaching Hospitals, and was approved by the ethic committee of the Higher Institute of Health Sciences, Bangangté, Cameroon and all participants provided a written informed consent before enrolment.

Consent for Publication

All authors gave their approval for publication.

Conflicts of Interest

The authors report no conflicts of interest.

Funding

The authors did not receive any fund for this study.

Authors' Contribution Statement

Study conception—FFK, INW, MPK.
Clinical data collection and supervision—FFK, INW, MM, MPK.
Acquisition and validation of the biological data—FFK, HDFME, INW, MM.
Data analysis—FFK, MPH.
Data interpretation—FFK, MPH.
Manuscript drafting—FFK, MPH.
Critical revision of the manuscript—HDFME, INW, MM, MPK.

Availability of Data and Materials

Data and materials are available with corresponding author which is the principal investigator. They can be consulted at anytime upon request. However, the ethical clearance and the inform consent form did mention that patient data could be shared to a third party.

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List of Abbreviations

BMI—Body Mass Index; CKD—Chronic Kidney Disease; CKD-EPI—Chronic Kidney Disease Epidemiology Collaboration; CRP—C Reactive Protein; DBP—Diastolic Blood Pressure; GFR—Glomerular Filtration Rate; HBV—Hepatitis B Virus; HCV—Hepatitis C Virus; HIV—Human Immunodeficiency Virus; KDIGO—Kidney Disease: Improving Global Outcomes; MCH—Mean Corpuscular Haemoglobin; MCHC—Mean Corpuscular Haemoglobin Concentration; MCV—Mean Corpuscular Volume; SBP—Systolic Blood Pressure; TSAT—Transferrin Saturation Coefficient; WBC—White Blood Cell.