

Anemia in patients on chronic hemodialysis in Cameroon: prevalence, characteristics and management in low resources setting

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Abstract

Background: Anemia is a common complication of chronic kidney disease. We investigated the prevalence, characteristics and management of anemia in patients on chronic hemodialysis and assessed the response to blood-transfusion based management in Cameroon.

Methods: This was a cohort study of five months' duration (August-December 2008) conducted at the Yaoundé General Hospital's hemodialysis center, involving 95 patients (67 men, 70.5%) on chronic hemodialysis by a native arterio-venous fistula. A monthly evaluation included full blood counts, number of pints of red cell concentrates transfused, and vital status.

Results: At baseline, 75 (79%) patients had anemia which was microcytic and hypochromic in 32 (43%). Anemia was corrected in 67 (70.5%) patients using blood transfusion only, while 28 (29.5%) patients were receiving erythropoietin (11 regularly, 39%). Only 77.2% of 342 pints (median 3.0, range 0-17 per patients) of red cell concentrates prescribed were effectively received during the follow-up at an unacceptably high cost to patients and families. Mean hemoglobin and mean corpuscular hemoglobin levels remained stable during follow-up, while mean corpuscular volume increased. Erythropoietin treatment was the main determinant of favorable trajectories of hematological markers.

Conclusions: Patients on chronic hemodialysis have predominantly microcytic hypochromic anemia, with limited capacity for correction using blood transfusion.

Key words: Anemia; Blood transfusion; End stage renal disease; Hemodialysis; Sub-Saharan Africa

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Introduction

Anemia is a common complication of chronic kidney disease (CKD) which is associated with increased morbidity and mortality. The prevalence of anemia correlates with the severity of kidney impairment, and ranges from about 1% in stage 2 of CKD to almost 100% in end stage renal disease (ESRD) or chronic hemodialysis

(CHD) patients²⁻⁵. Although diminishing erythropoietin production by the failing kidney is a major contributor, the etiology of anemia in CKD is multifactorial involving among other factors, deficiency in iron, B12 vitamins and folate, shortened red blood cell lifespan, blood loss, "uremic environment", hyperparathyroidism, inflammation, aluminum toxicity and hypothyroidism⁶. With the discovery of erythropoiesis stimulating agents (ESA) some 30 years ago, the prevention and management of renal anemia have significantly improved in developed countries. However, the prohibitive cost of these therapies and the lack of a third payer system in resource-poor settings implies most patients in developing countries cannot afford them^{2,3}. In addition, anemia in such settings like sub-saharan African (SSA) countries is likely more frequent in patients with

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CKD as a result of context specific factors like nutritional deficiencies, hemoglobinopathies, infectious and parasitic diseases^{7,8}. In this context, management of anemia heavily relies on blood transfusion, a paradox given the scarcity of safe blood in these settings with various endemic infectious diseases^{2,3}. In general however, little is known about the prevalence of anemia in patients on chronic hemodialysis in SSA and its evolution under blood transfusion-based management.

In Cameroon, a SSA country, the care of ESRD patients requiring dialysis has improved over the recent years following government subsidized access to hemodialysis⁹. This governmental support however, does not cover the care of comorbidities including anemia. Hence, the management of anemia in patients on dialysis in this setting is mainly based on blood transfusion, despite the absence of a coordinated national blood transfusion service. Thus, it seemed appropriate to examine the prevalence, characteristics and management of anemia in patients on chronic hemodialysis and assess their response to blood transfusion therapy in Cameroon.

Patients and Methods

Setting

This was a prospective cohort study of five months duration from 1st August to 31st December 2008 conducted at the Yaoundé General Hospital (YGH) hemodialysis center. The study center has been described in detail previously¹⁰. In brief, this center is one of the two government-funded dialysis centers that serve the needs of the entire country (population: 19 millions) at the time this study was conducted. The center is equipped with 12 hemodialysis generators that use the Fresenius® 4008S dialysis technology (Fresenius Medical Care, Homburg, Germany), synthetic polysulfone dialysis membrane, and bicarbonate. The center operated from Monday to Saturday and offered to registered patients two hemodialysis sessions of 4 hours duration each per week. This study was approved by the Cameroon National Ethics Committee, and participants or their next-of-kin provided written informed consent.

Data collection

During the study period, all consenting patients who had been on chronic dialysis for at least 3 months with the use of a native arterio-venous fistula were included

in the study. Patients who presented with an acute illness were excluded. Baseline demographic, clinical and laboratory data were collected at inclusion during the first week of participant's recruitment, including age, sex, dry weight, duration on dialysis and full blood count (FBC). Furthermore, the etiological factors of CKD and comorbidities were noted. Full blood counts were repeated monthly throughout the study period using blood collected from the arterial dialysis line at the beginning of the first dialysis session of the month. The full blood count exam was done free of charge to the participants for the purpose of the study.

The hemoglobin (Hb) level, the mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) levels were noted for analysis. According to the Kidney Disease Outcome Quality Initiative (K-DOQI) guidelines, anemia was defined by hemoglobin levels less than 11 g/dl¹¹. For the purpose of the study, anemia requiring blood transfusion was defined by hemoglobin levels less than 9.0 g/dl. Microcytosis and macrocytosis were defined respectively by MCV < 80 and > 100 fl. Hypochromia and normochromia were defined by MCH < 27 and ≥ 27 pg respectively. Dry weight was the theoretical weight of the patient necessary to perform well-tolerated dialysis sessions without cramps and hypotension. Patients receiving at least 50 IU per kilogram per week of erythropoietin were considered to be "regularly on erythropoietin", as opposed to "occasional intake" attributed to all who were on doses of less than 50 IU per kilograms per week.

The French Health Products Safety Agency (AFSSAPS) recommendations were applied to estimate the number of pints of red cell concentrates (RCC), to determine the rate of blood transfusion and to monitor blood transfusion¹². The formula applied was $N_p = (WBV/100)(tHb - iHb)/QHbpc$; where N_p is the number of pints of RCC; WBV (ml) is whole blood volume; tHb (g/dl) is the target hemoglobin (11.0 g/dl); iHb (g/dl) is the initial hemoglobin level; QHbpc (g) is the quantity of hemoglobin in each unit of RCC (it was estimated at 45 g per unit). The WBV was determined using the "5 rules of GILCHER"¹²: for a female subject:

Normal= 70 ml/kg, Underweight= 65 ml/kg, Obese= 60 ml/kg. WBV values for male subjects are those for female augmented with 5 ml/kg. Blood was obtained from the blood bank of the YGH. Transfusion was executed during dialysis session at a rate of 8 ml/min with

the vital parameters monitored according to the AFS-SAPS recommendations.

Statistical analysis

Statistical analysis used SPSS® version 17.0 for Windows. Means and standard deviations, medians, ranges and percentages were used to express results. Person χ^2 test and equivalents, and Student t-test and non-parametric equivalents were used to compare qualitative and quantitative variables. Mixed linear regression models were used to examine changes in hematological parameters during follow-up and relate baseline or follow-up levels of potential predictors of those changes. Effects of baseline variables on all-cause mortality during follow-up were investigated through logistic regression

models. A "p" value of < 0.05 was used to indicate statistically significant results.

Results

Baseline profile of patients

At the beginning of the study, 109 patients were on chronic hemodialysis in the centre among which 7 (6.4%) were dialyzed for less than 3 months, 4 (3.6%) were dialyzed by a catheter and 3 (2.7%) refused to participate in the study. A total of 95 patients (67 men, 70.5%) were recruited, including 93 (97.9%) with hypertension, 28 (29.5%) with diabetes and 6 (6.3%) with HIV infection, comparably among men and women (all $p \geq 0.27$), and irrespective of status for erythropoietin use (all $p \geq 0.22$), Table 1.

Table 1 - Baseline profile of participants overall and by gender

Characteristic	Overall	Men	Women	p-value	No EPO	On EPO	p-value
N	95	67	28		67	28	
Males sex, n	67	67	0		49	18	0.46
Mean age, years (SD)	47.6 (14.3)	48.5 (12.7)	45.2 (17.7)	0.38	47.9 (14.6)	46.8 (13.7)	0.74
Median duration in dialysis, months (min-max)	6.5 (4-64)	8 (4-64)	4 (4-54)	0.32	5.0 (4-11)	8.8 (4.5-22.7)	0.10
Mean weight, kg (SD)	61 (11.1)	62.9 (11.1)	56.8 (9.8)	0.008	59 (9)	66 (13)	0.007
Hypertension, n	93	65	28	>0.99	65	28	>0.99
Diabetes, n	28	17	11	0.27	17	11	0.22
HIV infection, n	6	5	1	0.67	4	2	>0.99
Tuberculosis, n	5	3	2	0.63	3	2	0.63
Mean hemoglobin level, g/dl (SD)	8.6 (1.9)	8.7 (1.7)	8.3 (2.4)	0.35	8.3 (1.9)	9.2 (1.7)	0.05
Hemoglobin level <11 g/dl, n	75	55	20	0.24	55	20	0.28
Mean corpuscular volume, fl (SD)	78.7 (7.7)	77.8 (7.7)	80.8 (7.4)	0.07	78.4 (8.5)	79.3 (5.4)	0.62
Microcytosis, n	56	40	16	0.82	39	17	>0.99
Mean corpuscular hemoglobin, pg (SD)	26.8 (2.5)	26.7 (2.5)	27.2 (2.3)	0.40	26.8 (2.7)	27.0 (2.0)	0.68
Hypochromia, n	37	26	11	0.96	34	15	0.83
Iron treatment, n	17	12	5	>0.99	2	15	<0.0001
Erythropoietin treatment, n				0.69			
None	67	49	18				
Occasionally	17	11	6				
Regularly	11	7	4				

EPO – Erythropoietin; HIV – Human Immunodeficiency Virus; SD – Standard Deviation.

The overall age of patients ranged from 18 to 75 years with a mean of 47.6±14.3 years. As presented in Table 1, patients had been on dialysis for a median duration of 6.5 months (range 4-64), with no significant differences observed either by sex or use of erythropoietin (both $p \geq 0.10$). The dry weight of the patients ranged

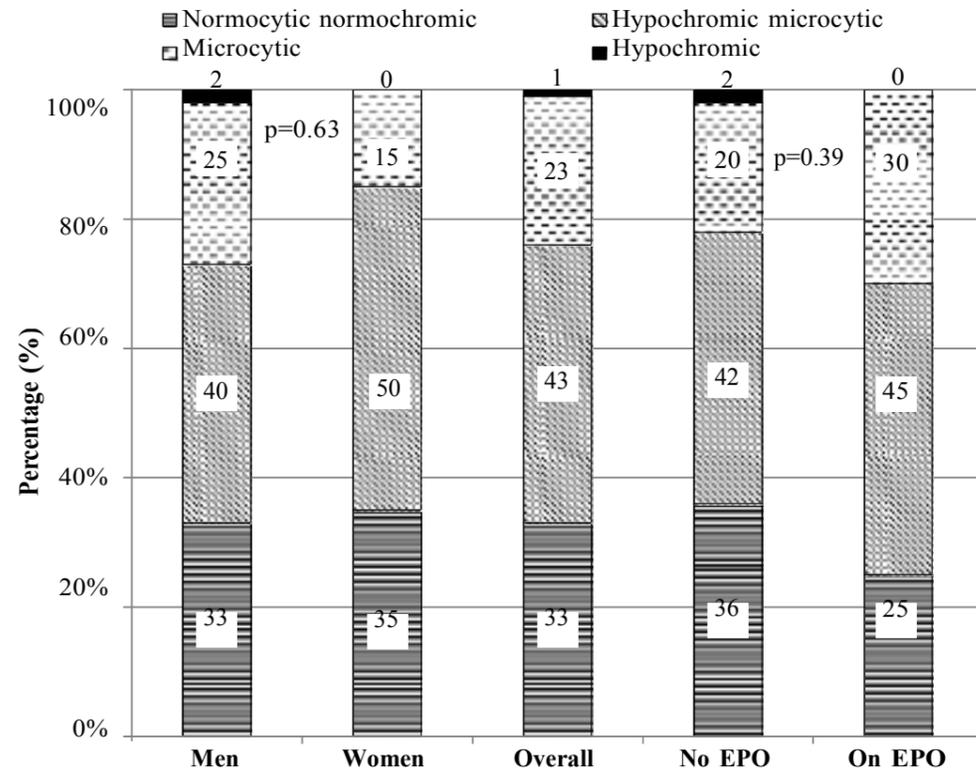
from 40 to 98 kg with a mean of 61.0±11.1 kg overall; it was 62.9±11.1 kg (range 45-98) in men and 56.8±9.8 kg (range 40-72) in women with a significant difference ($p=0.008$). In the erythropoietin-treated group, the mean dry weight was 66±13 kg (range 49-98), significantly higher than 59±9 kg (range 40-69) in those not receiving erythropoietin ($p=0.007$).

Hematological profile and prevalence of anemia

Baseline hematological parameters are described in Table 1. Mean values were 8.6 g/dl (range 3.3-14.0) for hemoglobin level, 78.7 fl (range 55-99) for mean glob-

ular volume and 26.8 pg (range 18-32) for mean corpuscular hemoglobin, with no significant difference observed either by sex or use of erythropoietin (both $p > 0.05$). At baseline, 75 (79%) participants had anemia with characteristic presented in Figure 1.

Figure 1 – Baseline characteristics of the anemia overall, and by sex and status for erythropoietin (EPO treatment)



For each subgroup, the proportional contribution of each type of anemia to the total population with anemia (100%) within that subgroup is indicated by a specific pattern on the vertical bar, each time with the accompanying percentage. The p-values comparing the distribution of type of anemia between men and women, and between participants on EPO vs. those not on EPO are also shown, always displayed between the vertical bars representing the subgroups been compared. Horizontal bars have been added at 20% intervals to assist visual interpretation.

Anemia correction at baseline and during follow-up

At baseline, 28/95 (29.5%) patients were initially on erythropoietin among which 11 (11.6%) on regular erythropoietin with 7 (7.4%) men and 15 (15.8%) receiving IV iron therapy. Therefore 67 patients (70.5%) were neither on erythropoietin, nor on IV

iron at baseline, Table 1.

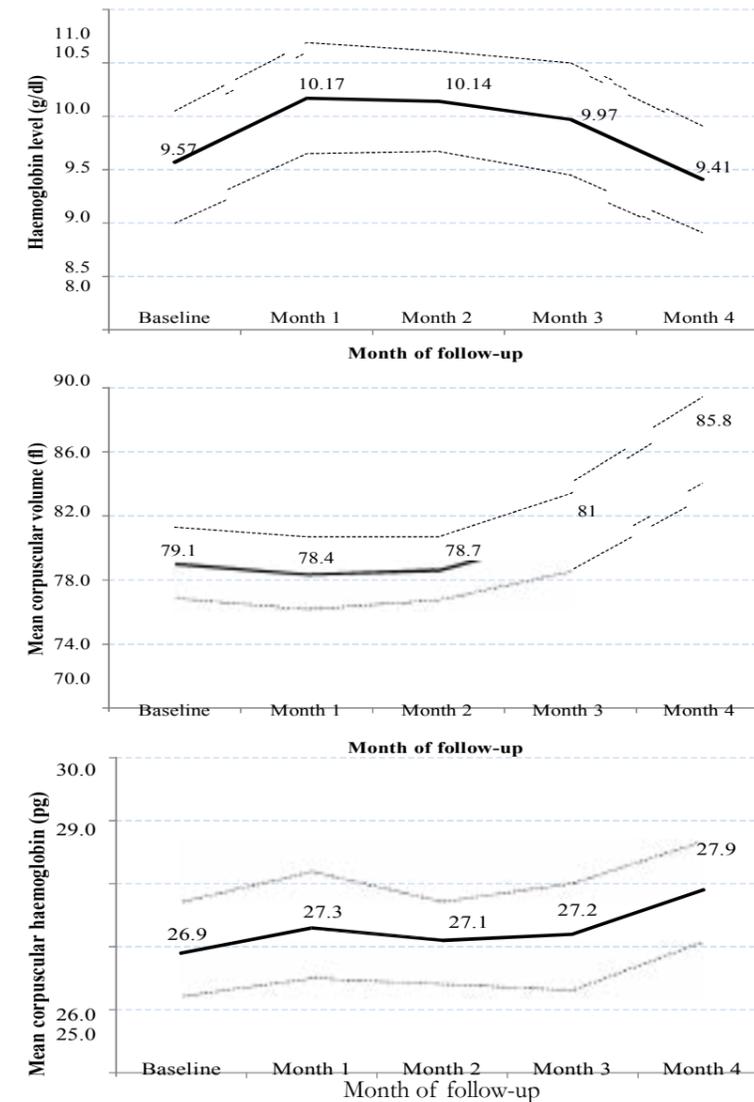
During follow-up, 22 (23%) patients were excluded for various reasons including death or transfer to another dialysis center (see the next section for more details) without any clinically significant difference of their profile compared to the remaining patients (Online Table 1). During the study period, a total of 342 pints of RCC (median 4.0 pints, range 0-18 per patients) were prescribed to the 73 patients with valid follow-up, but they effectively received only 264 (77.2%) pints of RCC (median 3.0 pints, range 0-17 per patients). The out-of-pocket payment for blood transfusion by patients, excluding staff charges, ranged from \approx US\$ 0 to 627.2 (median US\$ 141.6), based on a conversion rate of US\$ 1=XAF 500. The monthly variation in the number of blood units received and related cost is shown in the Online Table 2.

Trajectories of hematological parameters during follow-up

Hemoglobin levels increased between baseline and first month, and remained stable during the 2 subsequent

months, before dropping at the final month (Figure 2). After a drop between baseline and month 1, MCV levels steadily increased during follow-up. The trend was also towards increasing levels of MCH during follow-up (Figure 2).

Figure 2 – Trajectories of hematological parameters during follow-up



For each figure panel, the solid curve depicts the trajectory of the relevant parameters during follow-up, and the dotted line about are for the 95% confidence interval. The mean values of each parameter at baseline and during follow-up are also displayed. The superimposed dotted horizontal lines on each figure panel are to assist the visual interpretation.

In mixed linear regression analysis, being on erythropoietin was associated with 1.1 g/dl (range 0.6-1.6) higher levels of hemoglobin, 2.6 fl (range 0.4-4.9) high

er MCV level and 0.9 pg (range 0.1-1.6) higher levels of MCH (Table 2).

An inverse association was observed between blood transfusion and hemoglobin level (likely reflecting the reverse causality), whereby each unit of RCC was associated with 0.7 g/dl (range 0.6-0.9) lower hemoglobin levels. In addition, each 10-month duration on dialysis was associated with 0.3 g/dl (range 0.2-0.4) higher hemoglobin levels, and iron therapy with 0.5 g/dl (range 0.1-0.9) higher hemoglobin, while non-diabetic had 2.4 fl (range 0.6-4.2) higher MCV than diabetics (Table 2).

Table 2 - Determinants of changes in hematologic parameters during follow-up, based on mixed linear regression models

Variable	Hemoglobin (g/dl)	Mean corpuscular volume (fl)	Mean corpuscular hemoglobin (pg)
Intercept	9.4 (8.4 to 10.5)	83.6 (78.7 to 88.6)	26.9 (25.2 to 28.5)
Men vs. women	0.1 (-0.2 to 0.5)	-1.3 (-2.9 to 0.3)	-0.2 (-0.7 to 0.4)
Age (per 10 years)	0.07 (-0.04 to 0.2)	0.9 (0.4 to 1.5)	0.3 (0.2 to 0.5)
Duration in dialysis (per 10 months)	0.3 (0.2 to 0.4)	-0.4 (-0.9 to 0.1)	-0.2 (-2.5 to 1.4)
No diabetes vs. diabetes	-0.01 (-0.4 to 0.4)	2.4 (0.6 to 4.2)	0.8 (0.2 to 1.5)
No HIV vs. HIV infection	0.04 (-0.6 to 0.7)	-0.3 (-3.3 to 2.8)	-0.1 (-1.6 to 0.9)
No iron vs. iron therapy	-0.5 (-0.9 to -0.1)	-1.7 (-3.5 to 0.2)	-0.4 (-1.1 to 0.2)
No EPO vs. EPO therapy	-1.1 (-1.6 to -0.6)	-2.6 (-4.9 to -0.4)	-0.9 (-1.6 to -0.1)
Blood transfusion (per pint)	-0.7 (-0.9 to -0.6)	-0.1 (-0.7 to 0.5)	-0.1 (-0.2 to 0.1)

EPO – Erythropoietin ; HIV – Human Immunodeficiency Virus.

Fatal outcomes

According to the vital status of the 95 participants, 18 (19%) patients (12 men, 63.1%) died and 4 (4%) moved to a different dialysis center, with no difference observed either in sex ($p=0.60$), or by status for erythropoietin treatment ($p=0.29$ for erythropoietin treatment vs. none and $p=0.36$ for regular erythropoietin treatment vs. irregular or none). In age and sex adjusted logistic regression analysis, baseline dry weight [odd ratio per kg higher level: 0.88 (95% confidence interval 0.81-0.96)] was significantly associated with lower mortality risk. Hematological parameters including anemia and its characteristics were not associated with mortality.

Discussion

In this study based on a convenient sample of patients on chronic hemodialysis, receiving care in one of the main hemodialysis centers in Cameroon, 79% had anemia which was mainly microcytic hypochromic, and blood transfusion was the dominant strategy for correcting anemia. Only about 77% of the estimated blood requirements were effectively received during the observation period, at a very high cost in the study context. As a result, improvements in the trajectories

of hematological parameters during follow-up was modest, and mostly observed among those who were receiving erythropoietin or IV iron, non-diabetics or had been on dialysis for a longer duration. Death rate was very high during follow-up, but unrelated to baseline hematological profile.

The higher prevalence of anemia in our study was within the range of figures reported in similar groups of patients elsewhere^{2,3,13-15}. However, the predominantly microcytic and hypochromic patterns could be explained either by the inflammatory state associated with chronic infection or by the presence of context specific factors (not investigated) such as nutritional deficiencies, hemoglobinopathies and parasitic diseases^{7,8}. In our setting, chronic hemodialyzed patients were younger, likely including more individuals in their productive years, mainly unemployed and facing financial constraints for their care as previously reported in similar settings. This could affect their capacity for coping with ESRD management, including caring for complications such as anemia^{1,10,16}.

Just about three quarters of the estimated blood amount required by patients was effectively received during fol-

low-up. This result constitutes one of the relevant information provided by this study which was difficult to obtain before the study period regarding the delay between blood prescription and effective transfusion to patient. This non-optimal achievement of the estimated blood transfusion likely explained the dropping hemoglobin level after two months of follow-up. This non-optimal rate of RCC received by patients could be related to the scarcity of safe blood in this setting where various infectious diseases including HIV/AIDS, viral hepatitis and syphilis, and hemoglobinopathies are highly endemic¹⁷.

Moreover, inadequate hemodialysis related to the practice of only 2 weekly hemodialysis sessions could be an additional factor. The difficulties of patients to receive the amount of RCC required could also be due to the unacceptably higher cost of transfusion to patients and their families in the absence of social security programs. With the absence of national blood transfusion centre in Cameroon, the blood bank in the study hospital and many others operate on a compensation mode whereby, a patient in need of blood provides two donors for each pint of RCC. More so, he must pay for the different screening tests carried out on the blood (about US \$40 per pint), and cover the blood donors fees. This does not include staff charges. These issues and the complexity of financing mechanisms for blood transfusion in resources-limited settings have been nicely clarified in a study by Hensher & Jefferys¹⁷.

However, chronic hemodialyzed patients have chronic anemia due to the lack of erythropoietin production related to ESRD, achieving effective anemia correction in these patients in such settings by blood transfusion can be very challenging due to the scarcity of safe blood as already mentioned and the absence of a coordinated national blood transfusion service. In order to reduce the risk of blood transmitted diseases in our setting, improved access to ESA and IV iron should be the best way for correcting ESRD related anemia as recommended elsewhere^{11,13-15}. As of now, erythropoietin and IV iron accessibility is limited by the prohibitive cost which was about US\$ 30 for 2000 IU of erythropoietin and US\$ 25 for 100 mg of IV iron at the time this study was conducted. Moreover, in spite of government's subsidies, patients on chronic hemodialysis must pay the equivalent of US\$ 12 per dialysis session [US\$ 1248 per annum, which is higher than the

gross national income (GNI) per capita of US\$ 1210 in 2011¹⁸ excluding fees of others comorbidities.

Our study has some limitations. These include the relatively small and non-random sample, the recruitment of participants from a single center and the short duration of follow-up. Comorbidities were mainly based on prevalent (diagnosed comorbidity) which may underestimate the true prevalence of those conditions in our sample and accordingly bias estimates of their association with anemia in CKD. We were also unable to investigate the full spectrum of etiology of anemia in our population related to the high cost of exams and the absence of study funding. For instance, we could have learned more by investigating the iron status, B12 vitamin and folate, reticulocyte counts, G6PD status, hemoglobin electrophoresis status, inflammatory markers and stool test for occult blood or parasites.

There are however some concerns about the yield of such investigations. An investigation of iron status in Tunisian chronic hemodialyzed patients revealed a 22% iron deficiency, with only 2% of the patients presenting with microcytic hypochromic anemia¹⁴. Our study also has some strengths in the sense that it provides a unique picture, which, in this setting can potentially contribute to raise more attention on anemia, a leading condition in people with CKD. It revealed the positive correlation between hematological profile and erythropoietin and IV iron therapy in a few patients receiving these therapies, even in non-optimal dose, due to financial constraints as reported in similar setting^{14,15}. Our efforts in tracking a large number of our participants during follow-up provides some indicators of the burden of anemia in chronic hemodialysis patients and the outcome of anemia correction approaches in the context of limited access to ESA and intravenous iron therapies. This study provides also some answers to the government queries and the counseling of patients to be admitted in chronic hemodialysis.

Conclusion

There is a high prevalence of anemia in CKD patients and failure or limited capacity for correction via blood transfusion-based treatment in this setting where blood transfusion could be unsafe, where the pool of blood donor is very restricted, and where the cost of transfusion or alternative correction approaches such as ESA or IV iron use remain very prohibitive. Strategies to

improve anemia management in CKD patients could include and are not limited to: 1) the establishment of coordinated national blood transfusion service; 2) the implementation of cost-recovery policies by blood transfusion service; 3) the subsidized access of ESA and IV iron therapy and 4) the CKD prevention program to reduce the growing population of people in need of renal replacement therapy.

Declaration of interest

The authors report no conflicts of interest.

Authors' contributions

Study conception: FFK and GA Data collection: FFK and ATM

Data analysis and interpretation: FFK and APK Manuscript drafting: FFK and APK

Manuscript revision: DM, GA, ATM and MPH. Approval of the submission to the Journal: All authors

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