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Prevalence, Risk Factors and Management of Anaemia In Non-Dialysis Chronic Kidney Disease Patients: Findings from A Single Centre Study in Pakistan

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Abstract: *Background: Anaemia is associated with adverse outcomes in patients withchronic kidney diseases (CKD). There is scarcity of published literature regarding prevalence, risk factors and management of anaemia in CKD patients from Pakistan. Objective: To evaluate the prevalence, risk factors and management of anaemia in non-dialysis CKD (CKD-ND) patients. Methodology: This was a cross-sectional study conducted at Balochistan Institute of Nephrology-Urology Quetta (BINUQ), Pakistan. Eligible CKD-ND patients who were visiting the outpatient department of BINUQ and gave consent to participate in the study were included. A purpose developed data collection form was used to collect patients' socio-demographic, clinical and laboratory data. Anaemia was defined as haemoglobin level of <13 g/dl in males and <12g/dl in females. Data was analysed by SPSS 20. Multivariate binary logistic regression analysis was used to identify factors associated with the presence of anaemia. A p-value <0.05 was considered statistically significant. Results: A total of 220 patients were included in the final analysis. Mean age of the patients was 46.78 +18 years. Majority of them were males (62.3%), belonged to the age group 46-65 years (30.5%) and suffered from CKD stage-5 (75.9%). A total of 177 (80.5%) patients suffered from anaemia. In multivariate analysis, only CKD stage-5 had statistically significant association with the presence of anaemia (OR=4.521, p-value=0.001). Among 177 anaemic patients, only 75.7%received anti-anaemic treatment. Among them, 98.5% received blood transfusion, 6.7% folic acid, 2.9% iron and 2.2% received vitamin B_{12}. Conclusion: Despite its high prevalence, a notable proportion (24.3%) of anaemic patients was not managed for anaemia. Guidelines preferred iron supplements and erythropoietin stimulating agents (ESAs) were extremely underutilized. Almost all(98.5%)anaemic patients received guidelines discouraged blood transfusion for anaemia management.*

Keywords: *Chronic kidney disease, anaemia, iron, erythropoietin stimulating agent, blood transfusion*

INTRODUCTION

Kidney, in addition to blood filtration, wastes removal and maintenance of electrolytes' balance, also produces erythropoietin, a signalling molecule that stimulates the production of red blood cells (RBCs) in hypoxic conditions (Babitt and Lin, 2012). A reduction in the glomerular filtration rate (GFR) to <60 mL/min/1.73 m^2 due to structural or functional abnormalities indicates chronic kidney disease (CKD) (Inker, et al., 2014).

Disturbance of erythropoietin synthesis, secondary to functional abnormality due toCKD has the potential to decrease RBCs' production and cause anaemia (Babitt and Lin, 2012). In addition to disruption of erythropoietin synthesis, other possible causes of anaemia in CKD patients are iron deficiency, accumulation of uremic toxins and inflammation (Babitt and Lin, 2012; van Nooten, et al., 2010; AHEMIÏ, 2012). Anaemia in renal patients is reported to be associated withthe adverse outcomes of higher mortality, cardiovascular and cerebrovascular diseases, CKD progression, and cognitive impairment, sleep disturbances and deteriorated quality of life (Farag, et al., 2011; Iseki and Kohagura, 2007; Tamura, et al., 2016; Sarnak, et al., 2002; Abramson, et al., 2003).

As the early diagnosis and timely management of anaemia in CKD patients can decrease the rate of CKD progression, incidence of cardiovascular and cerebrovascular comorbidities and cognitive impairment, improve patients' quality of life and reduce mortality (Abramson, et al., 2003; Ma, et al., 1999; Moreno, et al., 2000; Marsh, et al., 1991), a supplement of theKidney Disease: Improving Global Outcomes (KDIGO) guidelines specifically addresses the diagnosis and management of anaemia in this population (AHEMIÏ, 2012). The guidelines recommend that any patient with glomerular filtration rate (GFR) of <60 ml/min should be evaluated for anaemia by measuring haemoglobin (Hb) level and treated for anaemia if present (Hb<13.0 g/dl in males and <12.0 g/dl in females of age >15 years) (AHEMIÏ, 2012). As anaemia is usually asymptomatic in the early stages of CKD, despite its high prevalence and complications in CKD patients, it is often clinically detected, usually sub-optimally treated and poorly controlled. Although, Pakistan has an estimated CKD burden of 15-20% in adult population, but unfortunately, there is a scarcity of published information regarding the prevalence and management of anaemia in CKD patients from Pakistan. Therefore, the current study was conducted with the aim to evaluate the prevalence, factors associated and management of anaemia in non-dialysis CKD (CKD-ND) patients.

Materials and Methods

This was a cross-sectional study conducted at Balochsitan Institute of Nephrology-Urology Quetta (BINUQ), Pakistan. The study site is the only public sector tertiary care hospital for renal patients in Balochistan (the largest province of Pakistan by area), where the patients from all over the province and nearby Afghanistan are referred for treatment. All new and established non-dialysis CKD patients of age $\geq$18 years, who were visiting the outpatient department of the study site and gave the consent to participate in the study were included in it. A standardized data collection form was used to collect the patients' socio-demographic, clinical and laboratory data. Estimated GFR (eGFR) was calculated by using CKD-Epidemiology Collaboration (CKD-EPI) equation by using an online calculator. Patients were categorized into different CKD stages in line with KDIGO guidelines (Inker, L.A., et al., 2014). Patient was consider anaemic if the Hb level was <13.0 g/dl in male and <12.0 g/dl in female or was taking an anti-anaemic preparation irrespective of Hb level.Mild anaemia was defined as Hb>11 g/dL, whereas moderate and severe anaemia was defined as Hb 9-11 g/dL and < 9 g/dL, respectively. Diagnosis of comorbidities was based on documentation in the medical record. Multiple comorbidities were noted and reported as different disease entities, for example, the number of patients with hypertension, diabetes mellitus, heart disease, and others was reported individually.

Statistical analysis

Data was analysed by using Statistical Package for Social Sciences (SPSS) version 20. Continuous variables were presented as mean $\pm$ standard deviation, whereas, categorical variables were presented as frequencies and percentages. One-way analysis of variance (ANOVA) was used to evaluate difference between different laboratory parameters on the basis CKD stages.Multivariate binary logistic regression analysis was used to find ultimate factors associated with the presence of anaemia. Independent variables which had p-value <0.2 in chi-square test were included in multivariate analysis. A p-value <0.05 was taken statistically significant.

This study was approved by the Research and Ethics committee of Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta.

Results

A total of 220 CKD patients were included in the final analysis. Table 1 presents the socio-demographic and clinical characteristics of the patients. Mean age of the study particpants was 46.78±18 years. Majority of them were males (62.3%), belonged to the age group 46-65 years (30.5%), suffered from CKD stage-5 (75.9%), and had ≥ 1 comorbidity (78.6%). The most common comorbidity was hypertension (65%) followed by diabetes mellitus (33.6%).

Table 1: Patients' socio-demographic and clinical characteristic

Variables	Mean ± SD	No. (%)
Gender		
Female		83 (37.7)
Male		137 (62.3)
Age (years)		
18-30		54 (24.5)
31-45		51 (23.2)
46-65	46.78 ±18.55	67 (30.5)
>65		48 (21.8)
Residence		
Rural		137 (62.3)
Urban		83 (37.7)
Nationality		
Pakistan		203 (92.3)
Afghan		17 (7.7)
Body mass index		
Underweight(<18.5)	19.33 ±2.96	88 (40.0)
Overweight(>25)		12 (5.5)
Normal(18.5-25)		120 (54.5)
Smoking		
Never		169 (76.8)
Current and active		8 (3.7)
Ex-smoker		43 (19.5)
CKD stages		
3		37 (12.3)
4		26 (11.8)
5		167 (75.9)
Duration of disease (years)		
≤ 1		50 (22.7)
> 1		170 (77.3)
FamilyHistory of CKD		
No		161 (73.2)
Yes		59 (26.8)
Comorbidity		
No		47 (21.4)
Yes		173 (78.6)
Type of comorbidity		
Hypertension		143(65)
Diabetes mellitus		74 (33.6)
Cardiovascular disease (other than hypertension)		25 (11.4)
Others		48 (21.8)

CKD, chronic kidney disease; SD, standard deviation

Patients' mean haemoglobin level was 9.3 ± 2.6 g/dl. A total of 177 (80.5%) patients suffered from anaemia. Among them,48.6% suffered from severe anaemia, followed by moderate (30.9%) and mild anaemia (0.9%). A significant increase in prevalence of anaemia was observed with decline in kidney function. The percentage of patients with severe anaemia was significantly higher in CKD stage-5 patients. Similarly, significantly lower Hb, haematocrit, RBCs, MCH and MCHC values were observed in patients with CKD stage-5 as compared to CKD stage-3 and 4 (Table 2).

Table 2: Prevalence and severity of anaemia, its parameters and relationship with different stages of chronic kidney disease

Variable	Total (n=220)	CKD stage-3	CKD stage-4	CKD satge-5	p-value
Anemia(n, %)	177 (80.5)	15 (55.6)	20 (76.9)	142 (85.0)	0.001*
Severity (n, %)					0.003¶
Mild	2 (0.9)	1 (3.7)	-	1 (0.6)	
Moderate	68 (30.9)	8 (29.6)	10 (38.5)	50 (29.9)	
Severe	107 (48.6)	6 (22.2)	10 (38.5)	91 (54.5)	
Hemoglobin(g/dl, mean±SD)	9.3±2.6	10.9±2.5	9.7±2.6	8.9±2.5	0.001#
Hematocrit (%, mean±SD)	27.1±7.9	31.6±9.6	26.7±8.4	26.4±7.3	0.006#
RBC(million cells/l, mean±SD)	3.3±1.0	4.3±0.8	3.6±0.9	3.1±0.9	<0.001#
MCV (fL/red cell, mean±SD)	75.0±8.3	76.1±6.3	74.5±5.1	74.9±9.0	0.720#
MCH (pg/cel, mean±SD)	24.6±3.1	26.6±2.8	24.4±3.3	24.3±3.1	0.002#
MCHC(g/dl, mean±SD)	33.1±3.7	35.1±2.5	33.2±2.6	32.7±4.0	0.009#

CKD: chronic kidney disease; HCT: hematocrit; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RBC: red blood cells; SD: standard deviation.

*Chi-square; ¶Fisher exact; #One-way ANOVA

In univariate analysis, CKD stage-5 (OR=4.544, p-value=0.001) and DM mellitus (OR=2.192, p-value=0.048) were associated with the presence of anaemia. However in multivariate analysis, CKD stage 5 was the only factor which emerged as a significant risk factor for the presence of anemia(OR=4.521, p-value=0.001) (Table 3). This model fit was based on non-sinificantHosmerlemeshow test (p-value=0.129) and overall percentage of 80.5% from classification table.

Table 3: Multivariate analysis of factors associated with anaemia

Variable	Anaemia n (%)	Univariate analysis OR (95%CI)	p-value	Multivariate analysis OR (95%CI)	p-value
Gender					
Female	69 (83.1)	Referent			
Male	108 (78.8)	0.756 (0.373-1.530)	0.436		
Age (years)					
18-30	44 (78.6)	Referent			
31-45	43 (82.3)	1.303 (0.498-3.407)	0.589		
46-60	45 (80.4)	1.116 (0.446-2.793)	0.815		
>60	45 (80.4)	1.116 (0.446-2.793)	0.815		
Residence					
Rural	109 (79.6)	Referent			
Urban	68 (81.9)	1.165 (0.580-2.337)	0.668		
Nationality					
Pakistani	165 (81.3)	Referent			
Afghan	12 (70.6)	0.553 (0.184-1.663)	0.291		
BMI					
Normal	96 (80.0)	Referent			

Underweight	71 (89.7)	1.197 (0.240-5.976)	0.826		
Overweight	10 (83.3)	0.958 (0.479-1.915)	0.903		
Smoking					
Never	137 (81.1)	Referent			
Current and active	6 (85.7)	1.401(0.163-12.052)	0.759		
Ex-smoker	34 (77.3)	0.794(0.356-1.773)	0.574		
CKD stage					
3	15 (55.6)	Referent		Referent	
4	20 (76.9)	2.667 (0.814-8.738)	0.105	2.547 (0.753-8.623)	0.133
5	142 (85.0)	4.544(1.904-10.846)	0.001	4.521(1.818-11.241)	0.001
Duration of disease (years)					
≤ 1	43 (86)	Referent			
> 1	134 (78.8)	1.650 (0.685-3.977)	0.264		
Comorbidity					
No	35 (74.5)	Referent			
Yes	142 (82.1)	1.571 (0.733-3.365)	0.246		
Number of comorbidities					
No	35 (74.5)	Referent		Referent	
Single	66 (77.6)	1.191 (0.519-2.734)	0.680	0.548 (0.165-1.820)	0.326
Multiple	76 (86.4)	2.171(0.888-5.313)	0.089	0.671 (0.135-3.327)	0.625
Hypertension					
No	58 (75.3)	Referent		Referent	
Yes	119 (83.2)	1.624 (0.824-3.202)	0.161	1.826 (0.619-5.389)	0.275
Diabetes mellitus					
No	112 (76.7)	Referent		Referent	
Yes	65 (87.8)	2.192 (1.212-4.859)	0.048	1.883 (0.698- 5.083)	0.211
CVD					
No	157 (80.5)	Referent			
Yes	20 (80.0)	0.968 (0.341-2.745)	0.951		
Other comorbidities					
No	136 (79.1)	Referent			
Yes	41 (85.4)	1.550 (0.642-3.744)	0.330		

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; OR, odds ratio; SD, standard deviation

Out of 177 anaemic patients, only 134 (75.7%) were managed for anaemia. Among the 134 treated anaemic patients, 132 (98.5%) received blood transfusion, nine (6.7%) folic acid, four (2.9%) iron and three (2.2%) received vitamin B-12. None of the patients received ESA therapy.

Discussion

The present study evaluated the prevalence, factors associated and management of anaemia in CKD patients at a tertiary care hospital in Quetta, Pakistan. High proportion of male patients (62.3%) in the studied cohort is in line with the findings of studies conducted elsewhere (Salman, et al., 2016). Majority of our study participants (75.1%) suffered from advanced renal disease (CKD stage-5). Similar high proportion of advanced renal disease has been reported by studies conducted in India (Sathyan et al., 2017) and Malaysia (Salman, et al., 2016). This advocates the grossly inadequate early screening and diagnosis of CKD in the health care settings of developing countries like Pakistan (Jafar, 2006). The delayed diagnosis of CKD and other asymptomatic conditions like hypertension may be partly attributed to the fact that the health care system in

developing countries is directed towards providing symptomatic treatment (Jafar, 2006). It has been reported that an average Pakistani adult visits a primary care physician 4-5 times each year, but 64% of adults have never had their blood pressure measured, and 70% of patients with hypertension and 50% with DM are unaware of their condition (Ahmad and Jafar, 2005).

The prevalence of anaemia observed in the current study (80.5%) was comparatively high than that reported by studies conducted in United States of America (15.4%) (Stauffer and Fan, 2014), Nepal (47.8%) (Poudel, et al., 2013) and Spain (58.5%) (Cases-Amenós, et al., 2014). However, almost similar prevalence of anaemia in CKD patients (75.8%) has been reported by a study conducted at a tertiary care hospital in Malaysia (Salman et al., 2016). The comparatively high prevalence of anaemiain the present study could be attributed to the high proportion of patients (75.1%) with advanced renal disease (CKD stage-5) which also emerged as the only significant risk factor for the presence of anaemia in the studied patients. We observed a statistically significant increase in the severity of anaemia and decrease in the levels of hemglobin, haematocrit, MCH and MCHC along with the advancement of renal disease. In current study, the prevalence of severe anaemia increased from 22.2% in stage-3 to 54.4% in stage-5. High prevalence and severe anemia in advanced renal disease patients could be due to erythropoietin insufficiency, iron and vitamin deficiency, malnutrition, inflammation, platelet dysfunction and hemolysis (Nurko, 2006). Likewise increase in the prevalence and severity of anaemia with decline in GFR have been reported by various studies conducted elsewhere (Salman, et al., 2016; Stauffer and Fan, 2014; Clase et al., 2007). A study conducted at a tertiary care hospital in Malaysia has reported an increased prevalenceof anaemia with advancement of renal disease. The proportion of anaemic patients increased from 41.9% in CKD stage-1 to 97.4% in CKD stage-5 (Salman, et al., 2016). Similar increase in prevalence of anaemia from 8.4% in CKD stage-1 to 53.4% in CKD stage-5 has been revealed by National Health and Nutritional Health Surveyreport in USA (Stauffer and Fan, 2014).

In the present study, despite high prevalence of anemia, a noteworthy proportion of anemic patients (24.3%) were not managed for it.This finding was in compliance with the previously reported suboptimal management of anemia in CKD-ND patients (Salman, et al., 2016; Cases-Amenós, et al., 2014; Stauffer and Fan, 2014). According to KDIGO guidelines recommendations, the state of CKD and the severity of anaemia usually determine the choice of intervention from iron supplements, ESA therapy or blood transfusion (AHEMIÏ, 2012). Guidelinesprefer iron supplements and ESA therapyfor the management of chronic anaemia in CKD patients. Blood transfusion is recommended only where urgent correction of the anaemia is needed, ESA and iron therapy have failed to produce the response, Hb level is very low (<7 g/dl) or the patient has malignancy or history of stroke (AHEMIÏ, 2012). Otherwise, due to the general risks associated with blood transfusion like infections, volume overload, hyperkalimia, citrate toxicity, coagulopathy, fever, allergic reactions, transfusion related lung injury etc. it should be avoided as much as possible (AHEMIÏ, 2012). However, in contrast to guidelines recommendations, blood transfusion was the major treatment used for the correction of anaemia at the study site. In the present study, among 134 patients who were treated for anaemia, 132 (98.5%) received blood transfusion, nine (6.7%) folic acid, four (2.9%) iron and three (2.2%) received vitamin B-12. None of the patients received ESA therapy. The suboptimal use of iron and ESAs at the study site was in compliance with the previous findings reported by studies conducted elsewhere (Salman, et al., 2016; Cases-Amenós, et al., 2014). However, in contrast to 2.9% anaemic patients who received iron supplements in the current study, a relatively higher proportion of anaemic patients (38%)were on iron therapy in Malaysian study (Salman, et al., 2016). Similarly, comparatively higher proportion of anaemic CKD-ND patients received iron replacement therapy in studies conducted in Catalonia (66%) (Cases-Amenós, et al., 2014) and Saudi Arabia (81.6%) (Al-Ageel, et al., 2012). As information about ferritin and transferrin saturation values (TSAT) are necessary for assessing the iron status and guiding the iron replacement therapy in anaemic CKD patients, no information or underreporting of these values at the study site might be one of the possible reasons for underutilization of iron supplements. In the present study, none of the patient was treated with ESA. This was in line with a Malaysian study in which none of the anaemic CKD patients received ESAs

(Salman et al., 2016). However, despite its underutilization, still a comparatively high proportion of anaemic patients received ESAs in the Catalonian study (68%) (Cases-Amenós et al., 2014). The cost associated with the use of ESAs and the guidelines divergent practices of anaemia management at the study site could be the possible reasons for not utilizing ESAs.

Conclusion

Anaemia was highly prevalent in the current study. The prevalence and severity of anaemia increased with declining renal function. Advanced renal disease (CKD stage-5) emerged as the only risk factor for the presence of anaemia. Information about ferritin and TSAT at the study site will help in assessing the patients' iron status and may improve the severe underutilization of guidelines recommended iron supplements and ESAs. In order to avoid the general risks associated with the blood transfusion, the doctors at the study site should avoid the unnecessary blood transfusion to the maximum possible extent. In order to get an insight about the underutilization of iron supplements and ESAs at the study site, doctors' knowledge and attitudes on guidelines' recommendations for management of anaemia should be evaluated through a questionnaire.

Although this study provides valuable information about the prevalence, risk factors and management of anaemia in CKD-ND patients at a tertiary care hospital in Pakistan, but being a cross-sectional study from a single centre its results cannot be generalized. A large, multicentre, prospective cohort study is recommended to confirm these findings.

Conflict of interest

The authors declare no conflict of interest.

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