

Prevalence and management of anemia in pre-dialysis Malaysian patients: A hospital-based study

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SUMMARY

Objective: Anemia, a common complication of chronic kidney diseases (CKD), is involved in significant cardiovascular morbidity. Therefore, the objective of our study was to investigate the prevalence and severity of anemia in pre-dialysis patients, as well as to determine the predictors of anti-anemic therapy.

Method: A retrospective, observational study was conducted on adult pre-dialysis patients receiving treatment at the Hospital Universiti Sains Malaysia from January 2009 to December 2013.

Results: A total of 615 eligible cases were included. The mean age of patients was 64.1±12.0 years. The prevalence of anemia was 75.8%, and the severity of anemia was mild in 47.7% of the patients, moderate in 32.2%, and severe in 20%. Based on morphological classification of anemia, 76.9% of our patients had normochromic-normocytic anemia whereas 21.8 and 1.3% had hypochromic-microcytic anemia and macrocytic anemia, respectively. Oral iron supplements were prescribed to 38.0% of the patients and none of the patients was given erythropoietin stabilizing agents (ESA) or intravenous iron preparations. In logistic regression, significant predictors of anti-anemic preparation use were decreased hemoglobin and hematocrit, and advanced stages of CKD.

Conclusion: The results of the present study suggest that the prevalence of anemia in pre-dialysis patients is higher than currently accepted and it is found to be correlated with renal function; prevalence increases with declined renal function. An earlier identification as well as appropriate management of anemia will not only have a positive impact on quality of life but also reduce hospitalizations of CKD patients due to cardiovascular events.

Keywords: anemia, antianemic therapy, chronic kidney disease, physician inertia.

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INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem across the world and end-stage renal disease (ESRD) is conventionally considered the most serious outcome of CKD.¹ Other outcomes include complications of declined renal function, e.g. high risk of cardiovascular diseases (CVD), acute renal injury, cognitive impairment, infections, and impaired physical function.²⁻⁶

Anemia is a very common complication of CKD and is the result of interference of erythropoietin production. However, iron and vitamin deficiencies, blood loss, reduced erythrocyte life span, chronic inflammation, and uremic milieu are also the contributing factors for anemia in CKD patients.⁷ Published data suggest that anemia is an independent risk factor for cardiovascular morbidity and mortality,⁸ and the combination of anemia and CKD is associ-

ated with a significantly higher stroke risk.⁹ CVD is the foremost cause of mortality in the CKD population, accounting for nearly half of the overall mortality.¹⁰ Even mild renal insufficiency is linked to a higher risk of cardiovascular events. Cardiovascular mortality in CKD population is 10 to 20 times greater than in normotensive populations.¹¹ Untreated anemia contributes to the increased CVD burden in CKD populations.⁷

Timely treatment of anemia with an emphasis on raising hematocrit to at least 36% can improve patient's quality of life,¹² decrease the need of blood transfusions,^{13,14} improve cognitive function¹⁵ and muscle strength,¹⁶ and decrease hospitalizations and mortality.^{17,18} This study aimed at estimating the prevalence and severity of anemia in adult pre-dialysis patients. The secondary objective was to determine the predictors of anti-anemic therapy.

METHOD

This retrospective, observational study was conducted at Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, Kelantan, Malaysia. All adult (≥ 18 years of age) pre-dialysis patients receiving treatment at CKD Resource Centre, HUSM, from January 2009 to December 2013 were included in the study. Patients with acute renal impairment, severe hemorrhage, age < 18 years, and dialysis patients were excluded. Data regarding demographics, laboratory investigations and medications for the treatment of anemia were gathered using a data collection form. Permission to conduct this study was obtained from Human Research Ethics Committee, Universiti Sains Malaysia, prior to data collection.

Anemia was defined as per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [hemoglobin (Hb) < 13.0 g/dL in males and < 12 g/dL in females] or patient utilizing anti-anemic preparations at any Hb level.¹⁹ Mild anemia was defined as Hb > 11 g/dL, whereas moderate and severe anemia were defined as Hb 9-11 g/dL and < 9 g/dL, respectively.²⁰ Glomerular filtration rate was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) Equation²¹ and patients were classified into the stages of CKD as per KDIGO guidelines.²²

Continuous variables were presented as mean \pm standard deviation, whereas categorical variables were presented as number and percentage. Comparison of continuous variables was made by t-test and one-way ANOVA, whereas categorical variables were analyzed using chi-square test. Binary logistic regression analysis was performed with use of anti-anemic preparations as a dependent variable, controlling covariates. Covariates used for the regression model to predict use of anti-anemic preparations were age,

gender, diabetes, cardiovascular disease, Hb, serum albumin, hematocrit (HCT), and CKD stage. Data analysis was carried out using SPSS version 20.0 for Windows. A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 615 cases were included in the study. Patient's demographic data are shown in Table 1. The mean age was 64.1 ± 12.0 years, with a preponderance of male subjects and Malay ethnic group. The most common etiology of CKD was diabetes followed by hypertension.

TABLE 1 Demographic data of the study population.

Characteristics	
Age (years; mean \pm SD)	
Total (n=615)	64.1 \pm 12.0
CKD stage 3a (n=74)	60.9 \pm 11.3
CKD stage 3b (n=186)	64.9 \pm 12.0
CKD stage 4 (n=240)	66.2 \pm 10.5
CKD stage 5 (n=115)	60.5 \pm 14.0
Gender	
Male	394 (64.1%)
Female	221 (35.9%)
Ethnicity	
Malay	583 (94.8%)
Chinese	26 (4.2%)
Indian	3 (0.5%)
Other	3 (0.5%)
Etiology	
Diabetes	264 (42.9%)
Hypertension	177 (28.8%)
Glomerular disease	24 (3.9%)
Other	147 (23.9%)
Serum urea (mmol/L; mean\pmSD)	14.4 \pm 8.1
Serum creatinine (μmol/L; mean\pmSD)	256.8 \pm 179.0
eGFR (mL/min/1.73 m²; mean\pmSD)	27.8 \pm 13.5

CKD: chronic kidney disease; SD: standard deviation; eGFR: estimated glomerular filtration rate.

As presented in Table 2, the prevalence of anemia was 75.8%, with significant increase in percentage of anemic patients by declining kidney function ($p < 0.001$). The percentage of patients with mild, moderate and severe anemia was around 47.7, 32.2 and 20.0%, respectively, with a higher percentage of patients with moderate and severe anemia by decreasing renal function. The morphological classes of anemia in our patients were hypochromic-microcytic anemia (21.8%), normochromic-normocytic anemia (76.9%) and macrocytic anemia (1.3%).

TABLE 2 Anemia and its parameters with different stages of chronic kidney disease.

Characteristics	Total (n=615)	CKD stage 3a (n=74)	CKD stage 3b (n=186)	CKD stage 4 (n=240)	CKD stage 5 (n=115)	p-value
Anemia (%)	75.8	41.9	63.4	85.4	97.4	<0.001
Severity of anemia (%)						
Mild	47.7	75.7	65.4	42.5	12.2	<0.001
Moderate	32.2	20.3	26.5	37.5	38.3	
Severe	20.0	4.1	8.1	20.0	49.6	
Morphological types (%)						
Microcytic anemia	21.8	18.9	22.7	21.7	22.6	0.78
Normocytic anemia	76.9	78.4	75.7	77.1	77.4	
Macrocytic anemia	1.3	2.7	1.6	1.3	-	
Hb (g/dL; mean±SD)	10.9±2.4	12.8±2.1	11.8±2.3	10.6±2.0	8.9±1.8	<0.001
HCT (%; mean±SD)	32.8±6.8	37.9±5.7	35.4±6.3	31.9±5.9	27.1±5.4	<0.001
RBC (x 10¹²/L; mean±SD)	3.87±0.80	4.43±0.67	4.19±0.74	3.76±0.70	3.22±0.65	<0.001
MCV (fL; mean±SD)	84.9±7.4	86.2±7.2	84.5±7.3	85.1±7.5	84.4±7.3	0.33
MCH (Pg; mean±SD)	28.3±2.7	28.9±2.5	28.3±2.7	28.3±2.7	27.8±2.6	0.047
MCHC (g/dL; mean±SD)	33.2±1.6	33.6±1.3	33.3±1.8	33.2±1.7	33.0±1.3	0.046

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

The prevalence of mild, moderate, and severe anemia by gender is presented in Table 3. There were significantly greater anemic female CKD patients as compared to male patients ($p=0.001$). Moreover, prevalence of mild anemia was significantly greater in male than in female patients. But the prevalence of female CKD patients suffering from moderate and severe anemia was significantly higher as compared to male subjects. There was a significantly lower level of Hb, HCT and erythrocytes in females as compared to male patients.

TABLE 3 Gender-based comparison of anemia parameters.

Parameters	Male (n=394)	Female (n=221)	p-value
Anemia (%)	71.6	83.3	0.001
Severity of anemia (%)			
Mild	53.9	36.7	<0.001
Moderate	31.0	34.4	
Severe	15.0	29.0	
HCT (%; mean±SD)	34.0±6.8	30.7±6.3	<0.001
RBC (x 10¹²/L; mean±SD)	4.01±0.78	3.63±0.79	<0.001
MCV (fL; mean±SD)	85.0±7.0	84.8±8.0	0.053
MCH (Pg; mean±SD)	28.4±2.6	28.2±2.8	0.28
MCHC (g/dL; mean±SD)	33.3±1.6	33.2±1.7	0.95

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

Anti-anemic preparations were prescribed for only 38.0% of the patients. Underutilization of erythropoietin stabilizing agents was apparent as none of the patients received these agents for the management of anemia. The predictors of oral anti-anemic therapy use are shown in Table 4. The logistic regression model was statistically significant, $\chi^2(10) = 196.086$, $p < 0.001$. The model explained 37.1% (Nagelkerke R^2) of the variance in use of anti-anemic preparations and correctly classified 75.6% of cases. Result of Hosmer and Lemeshow test for goodness-of-fit indicated that our model predicts values not significantly different than what we observed, $\chi^2(8) = 7.320$, $p = 0.50$. Patients with Hb 9-11 g/dL were 2.14 times more likely to be prescribed anti-anemic preparations, holding all other independent variables constant. Moreover, patients with Hb < 9 g/dL were 2.90 times more likely to be given anti-anemic therapy. Decreased HCT level was associated with 2.65 times odds of anti-anemic therapy use. Moreover, the deteriorating kidney function (increased severity of CKD) was also a positive predictor of oral anti-anemic preparations use.

DISCUSSION

Our main findings in this study showed that prevalence of anemia increased significantly with deteriorating renal function. Furthermore, decreased Hb and HCT, as well as advanced stages of CKD were the significant predictors of anti-anemic agents use in pre-dialysis patients at a Malaysian tertiary care hospital.

TABLE 4 Predictors of use of oral anti-anemic preparations.

Variables	Univariate		Multivariate	
	OR (95CI)	p-value	OR (95CI)	p-value
Age	0.99 (0.98-1.00)	0.17		
Gender				
Male	1.00 (Reference)	-		
Female	1.65 (1.18-2.31)	0.004		
Diabetes	0.97 (0.68-1.37)	0.85		
CVD	0.636 (0.45-0.90)	0.010		
Hb (g/dl)				
>11	1.00 (Reference)	-	1.00 (Reference)	-
9-11	4.61 (3.04-7.00)	<0.001	2.14 (1.28-3.61)	0.013
<9	15.15 (9.09-25.26)	<0.001	2.90 (1.25-6.73)	0.004
Albumin (g/L)				
>44	1.00 (Reference)	-		
38-44	0.86 (0.43-1.70)	0.66		
≤37	2.14 (1.09-4.19)	0.027		
Hematocrit (%)				
>30	1.00 (Reference)	-	1.00 (Reference)	-
<30	7.93 (5.44-11.56)	<0.001	2.65 (1.43-4.92)	0.002
CKD severity				
Stage 3a	1.00 (Reference)	-	1.00 (Reference)	-
Stage 3b	1.67 (0.76-3.68)	0.20	1.36 (0.60-1.37)	0.47
Stage 4	6.11 (2.91-12.83)	<0.001	4.08 (1.86-8.98)	<0.001
Stage 5	16.51 (7.40-36.82)	<0.001	6.07 (2.54-14.52)	<0.001

CKD: chronic kidney disease; CVD: cardiovascular disease; OR: odds ratio; CI: confidence interval; Hb: hemoglobin.

The mean age of the patients in this study was similar to that reported in a previous study.²³ There was a predominance of male subjects, which was similar to the results of previous reports.^{20,23} The study population included mostly Malays, since our setting was the northeastern peninsular Malaysia, more specifically the States of Kelantan, Terengganu and Pahang. There is a wide variation in the prevalence of anemia and its severity in CKD patients. In the present study, the prevalence of anemia was 75.8%. By contrast, Martinez-Castellao et al. reported a 51.3% prevalence of anemia in their Spanish cohort of CKD stage 3 and 4 patients.²⁰ Likewise, a study conducted by Poudel et al.²⁴ reported that the prevalence of anemia was 47.85% in Nepali CKD patients. In both of these studies, the findings were lower than our results because most of our CKD cohort had advanced stages of CKD. We found that prevalence of anemia increased with progressively deteriorating renal function. Regarding the severity of anemia, majority of the patients in our study had mild anemia followed by moderate anemia. Conversely, most of the patients in a previous study had moderate anemia followed by mild anemia.²⁵ We also observed that the percentage of CKD

stage 5 patients with mild anemia was significantly lower than in the early stages, whereas the percentage of patients with CKD stage 5 having moderate and severe anemia were significantly higher as compared to other CKD stages. These findings reflect that severity of anemia increases with declining renal function, which can be attributable to various factors associated with the development of anemia in CKD, such as erythropoietin insufficiency, iron and vitamin deficiency, malnutrition, inflammation, platelet dysfunction, reduced red blood cell survival, and hemolysis.⁷ Similar to the findings of a previous study,²⁴ we also found that mean level of Hb, red blood cells, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were significantly decreased by deteriorating renal function. This considerable decrease could be another cause of a higher prevalence of anemia by deteriorating kidney function. Levels of Hb, HCT, and red blood cells were significantly lower in female CKD patients than in male patients. Findings from a previous study conducted on ESRD patients also revealed that Hb-level was significantly lower in females as compared to male patients.²⁶ Most of the patients in the current study had

normochromic-normocytic anemia followed by hypochromic-microcytic anemia, which was comparable to the findings of an earlier study.²⁵

We observed a mismatch between the number of patients with anemia and the number of patients treated for anemia. Nearly half of the patients with anemia (37.8%) were not being treated with an anti-anemic agent according to their medical charts. Probable explanations for this finding are clinical inertia or a higher frequency of patients with mild anemia using vitamins (vitamin B complex). Nonetheless, the use of oral iron therapy in this study was greater than previously reported.²³ Ferrous fumarate (325 mg once daily) and folic acid (5 mg once daily) were the predominantly prescribed oral iron supplement combination for the treatment of anemia in our cohort. Underutilization of erythropoietin stabilizing agents in the current study might also be attributable to physician inertia or its prohibitive cost. Our study proposes that there is room for substantial improvement in terms of anemia control. Bailie et al.²³ reported that the positive predictors of iron use in pre-dialysis patients were Caucasians [odds ratio (OR) = 2.6] and diabetics (OR = 2.1). Contrary to these findings, we found that the significant predictors of anti-anemic therapy prescribed were decreased HCT and Hb level, and increased severity of CKD.

This study was carried out in a single Malaysian tertiary care hospital and the vast majority of the patients were Bumiputera (Malay ethnicity) from the northeastern peninsular region. Therefore, the findings may not be representative of the multiethnic Malaysian population. This study indicates the need to conduct a brief survey among physicians, enquiring reasons for prescribing or not prescribing erythropoietin stabilizing agents. Nevertheless, this study offers valuable information regarding the prevalence, severity and treatment of anemia in Malaysian pre-dialysis patients.

CONCLUSION

Prevalence of anemia is high among pre-dialysis Malaysian patients at this tertiary care hospital, and is correlated with declining renal function. Earlier identification as well as proper management of anemia may not only have a positive impact on the patient's quality of life but also reduce hospitalization of CKD patients due to CVD.

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RESUMO

Anemia em pacientes pré-diálise: prevalência, gravidade, manejo

Objetivo: anemia é uma complicação comum de doenças renais crônicas (DRC) e está significativamente envolvida na morbidade cardiovascular. O objetivo de nosso estudo foi investigar a prevalência e a gravidade da anemia em pacientes adultos pré-diálise, bem como determinar fatores preditores da terapia antianêmica.

Método: estudo retrospectivo observacional foi realizado em pacientes pré-diálise adultos que recebiam tratamento no Hospital Universiti Sains Malaysia de janeiro de 2009 a dezembro de 2013.

Resultados: ao todo, 615 casos elegíveis foram incluídos. A idade média dos pacientes foi de 64,1±12,0 anos. A prevalência de anemia foi de 75,8%, e a gravidade da anemia foi considerada leve em 47,7%, moderada em 32,2% e grave em 20% dos pacientes. Com base nas características morfológicas da anemia, os pacientes foram classificados em anemia normocrômica normocítica (76,9%), anemia hipocrômica microcítica (21,8%) e anemia macrocítica (1,3%). Suplementos de ferro oral foram prescritos para 38% dos pacientes e a nenhum dos pacientes foram dados eritropoietina, agentes estabilizadores (ESA) e preparações de ferro por via intravenosa. Na regressão logística, os preditores significativos de utilização da preparação antianêmica foram diminuição da hemoglobina e do hematócrito e estágios avançados da DRC.

Conclusão: os resultados do presente estudo sugerem que a prevalência de anemia em pacientes pré-diálise é maior do que o atualmente aceito e está associado com a função renal; a prevalência aumenta com a diminuição da função renal. A identificação precoce e o manejo adequado da anemia não só terão um impacto positivo na qualidade de vida, mas também reduzirão internações de pacientes com DRC decorrentes de eventos cardiovasculares.

Palavras-chave: anemia, terapia antianêmica, doença renal crônica, inércia do médico.

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