Original Article

Anemia in Sudanese Patients with Chronic Renal Failure (CRF) and in Patients undergoing Chronic Hemodialysis

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Abstract

Background: The term of anemia of chronic renal failure (CRF) in sufficiency refers to that anemia resulting directly from failure of the endocrine and excretory functions of the kidney and decreased production of erythropoietin by damaged kidneys. The serum erythropoietin level in patients with renal failure does not increase in response to the developing anemia, which is the primary cause of inadequate erythropoiesis.
Aim: The purpose of our study was to examine, among patients with CRF, the combined association of CRF and anemia on adverse outcomes. ***Settings and Design:*** A hospitalized study using administrative data, we identified all patients hospitalized with CRF in IBN-Sena hospital and Khartoum teaching hospitals, Khartoum, Sudan. ***Materials and Methods:*** This was a retrospective cohort study of 500 patients having a diagnosis of chronic renal failure hospitalized and discharged between October 2007 to February 2010 from two Sudanese Teaching hospitals (Khartoum and IBN-Sena). All adult patients with chronic renal failure hospitalized for hemodialysis. ***Results:*** Hemoglobin level was recorded for 500 members (100%) of the cohort. The mean (SD) hemoglobin was 13.0 g/dL (2.2) range from 11.8 g/dL to 14.6 g/dL. On admission, an hemoglobin of = 14 g/dL was found in 36.2% of the patients, 36.2% had an hemoglobin between 12 g/dL and 14 g/dL, 19.6% between 10 g/dL and 12 g/dL, and 8% = 10 g/dL. The proportion of patients with CRF was associated with increasing anemia ***Conclusion:*** The results obtained indicated the further evidence that the concomitant presence of either CRF or anemia increased the risk of dying in the hospital or of being readmitted within 30 days among patients hospitalized. The association persisted after controlling for other factors associated with adverse outcomes in these patients.

Key words: Anemia, Chronic Renal Failure.

Introduction

Anemia is an almost constant complication of chronic renal failure that significantly contributes to the symptoms and complications of the disease. The anemia of chronic renal disease is caused by failure of renal excretory and endocrine function. The anemia of chronic renal disease is normocytic and normochromic. It occurs primarily because of lower production of erythropoietin by the decreased mass of functioning renal tubular cells[1].

Anemia results in fatigue, reduced exercise capacity, decreased cognition, and impaired immunity. Thus, it decreases quality of life. In addition, increased workload on the heart as a result of anemia can lead to left ventricular hypertrophy and maladaptive cardiomyopathy. These conditions increase the risk of death from heart failure or ischemic heart disease.[2]

Study results[3,4] have shown that correction of anemia can limit the progression of chronic kidney disease and possibly decrease mortality. The NKF K/DOQI guidelines[5] recommend a target hemoglobin concentration of 11 to 12 g per dL (110 to 120 g per L) in patients with chronic kidney disease. Patients with plasma ferritin concentrations below 100 ng per mL (100 mcg per L) should be given iron supplements.

Erythropoietin should be administered to predialysis patients who have anemia-dependent angina or severe anemia with a hemoglobin concentration below 10 g per dL (100 g per L).[6] Hypertension and an increased risk for thrombotic events are potential adverse effects of treatment. Therefore, patients receiving erythropoietin must be monitored closely. Independent associations between both CRF and anemia with increased risk of one-year mortality were found. In both studies, a 1% decrease in hema-

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tocrit was associated with a 2.5% increase in the 12 month risk of death.

The purpose of our study was to examine, among patients with CRF, the combined association of CRF and anemia on adverse outcomes. To our knowledge, this is the first study using in hospital mortality and early readmission for this purpose.

Methods

Study design

This was a retrospective cohort study of patients having a diagnosis of chronic renal failure hospitalized and discharged between October 2007 to February 2010 from two Sudanese Teaching hospitals(Khartoum and IBN-Sena). All adult patients with chronic renal failure hospitalized for hemodialysis. Outcome measures of interest were in hospital. Follow-up for each patient began on the date of discharge from the hospital and continued for 30 days.

Population

Using administrative data, we identified all patients hospitalized with CRF. We then selected a random sample of 500 patients hospitalized in both hospitals undergo hemodialysis. Patients were excluded from the sample if the initial hospitalization was terminated against medical advice, or if they were transferred to another acute care hospital or if no information on the creatinine level was available.

Data

Data were abstracted from medical charts by medical record specialists. The entire medical chart was available in one hospital and the scanned medical record was used in the other. Variables abstracted from the chart included age and sex. Hemoglobin levels were distributed in four groups: <10 g/dL, 10 g/dL to 12 g/dL, 12 g/dL to 14 g/dL, and = 14 g/dL. The final serum creatinine values recorded during the hospitalization were also considered. Chronic kidney disease (CRF) was defined as a serum creatinine = 124 μmol/L for women and = 133 μmol/L for men. We choose these ranges because they were used previously in an US study, in order to be able to do comparisons of CRF prevalence between countries[7]. We did not calculate creatinine clearance because, in many patients, the information available in our data set did not allow us to calculate it. A random replicate sample of 100 charts was abstracted to assess inter-rater reliability. The Kappa estimate was 1.0 for the determination of in hospital mortality.

Information on in hospital mortality and readmission within 30 days was gathered using administrative data provided by the hospitals. We assessed all cause readmission and included only patients from the index hospital. Because these hospitals are university referral centers, each for a different area, we assumed that only few patients could have been readmitted to a different hospital. Indeed, for one provider, we could assess that none of the patients were readmitted to another Sudan hospital.

The determination of the renal function was based on the chart by the presence of a value for a previously measured creatinine, urea and electrolytes a narrative statement in the chart. Patients with renal dysfunction were identified by looking in medical charts for a current (from the index hospitalization) or laboratory analysis equal or less than 40%. The Charlson co-morbidity index, a weighted average of selected co-morbidities, was computed at index hospitalization for each patient as a measure of severity of illness measure using the Deyo modification [8].

Statistical analysis

Bivariate analyses of the dependent and the primary exposure variables were conducted. We also calculated the crude risk ratio and 95% confidence intervals for in hospital mortality and 30-day readmission. We used chi-square tests, Fisher's exact tests, Student T-tests or ANOVA methods when appropriate. Dichotomous outcome variables were in hospital mortality and readmission within 30 days. Primary exposure variables were hemoglobin and creatinine levels. Other variables, potential confounding factors, included in the bivariate analysis were: hospital, age findings at admission. We then performed multivariate analyses using logistic regression to adjust for potential confounding factors. Logistic regression was used to calculate adjusted odds ratio with associated 95% confidence intervals. Covariates were initially selected using a priori considerations as well as strength of association and statistical significance in bivariate analyses. We first looked if interaction between hemoglobin and creatinine was significant. After defining the starting model as above, we assessed, by backward elimination, which confounding factors should remain in the model. We first looked to see if the

least significant variable was a confounding factor by dropping it and refitting the model. We then assessed if the odds ratio changed by more than 10% compared to odds ratio of the starting model. If the odds ratios changed by more than 10%, the variable was considered as a potential confounding factor and remained in what became the final model. If a variable did not meet these criteria, it was removed from the model and the same procedures were reapplied until the best final model was found. For all models, we checked for any potential co linearity problems between the variables. All analyses were implemented with the SPSS software, version 15.0.

Baseline characteristics

Our sample included 500 eligible patients with CRF

Table I: Patients Characteristics at Admission in Patients with Chronic Renal Failure*, N = 500

Characteristics	N (%)	Mean (SD) serum creatinine µmol/l*
N (%)	500(100.0)	113.9 (100.0)
Hospital A	215 (43.0)	116.4 (43.0)
Hospital B	285 (57.0)	112.0 (57.0)
Age (N = 500)		
16 – 60 years	60 (12.0)	111.4 (12.0)
61 – 70 years	90 (18.0)	110.2 (18.0)
71 – 80 years	145 (29.0)	113.2 (29.0)
> 80 years	205 (41.0)	116.7 (41.0)
Sex (N = 500)		
Male	272 (54.4)	120.1 (54.4)
Female	228 (54.6)	120.1 (45.6)**

* Chronic Renal Failure (CRF) was defined as a serum creatinine > = 124 µmol/L for women and > = 133 µmol/L for men ** p value < 0.05

available for analysis. Among those 215 (43.0%) were admitted to hospital A(IBN-Sena) and 285 (57.0%) in hospital B(Khartoum State Teaching). The mean (SD) age was 75.4 years (12.8) and 45.6% were female.

Prevalence of CRF

The mean (SD) value of the last serum creatinine value reported during the hospitalization was 113.9 (100.0) µmol/L, with a range from 32 to 545 µmol/L and a 25th to 75th intraquartile range from 84 to 126 µmol/L. Chronic Renal Failure was defined as a serum creatinine = 124 µmol/L in women and = 133 µmol/L in men. Men (54.4%) were more likely than women (45.6%) to have CRF. In total, 500 (100.0%) patients of the entire cohort had CRF. The mean serum creatinine value was statistically significantly higher (Table II). Higher creatinine values were also observed in patients in hospital mortality and staying for 0-6 days (Table II).

Prevalence of anemia

Table II: Hospital Characteristics in Patients with Chronic Renal Failure*, N = 955

Characteristics	N (%)	Mean (SD) serum creatinine µmol/l
N (%)	500 (100.0)	113.9 (100.0)
In hospital mortality (N = 500)	89 (17.8)	159.3 (106.1)**
30 days readmissions (N = 411)	116 (23.2)	107.7 (38.7)
Length of stay (days) (N = 500)		
0–6	129 (25.8)	118.3 (25.8)
7–12	167 (33.4)	112.6 (33.4)
>12	204 (40.8)	112.0 (40.8)

** p value < 0.05

Hemoglobin level was recorded for 500 members (100%) of the cohort. The mean (SD) hemoglobin was 13.0 g/dL (2.2) range from 11.8 g/dL to 14.6 g/dL. On admission, an hemoglobin of = 14 g/dL was found in 36.2% of the patients, 36.2% had an hemoglobin between 12 g/dL and 14 g/dL, 19.6% between 10 g/dL and 12 g/dL, and 8% = 10 g/dL. The proportion of patients with CRF was associated with increasing anemia (Table III). The mean serum creatinine was increasing with severity of anemia (Table 3) from 102.0 µmol/L among patients with no anemia, up to 141.0 µmol/L for severe anemia (p < 0.0001). Patients with severe anemia. (Table III).

Mortality and readmission

Eighty-nine (17.8%) patients died during their hospitalization, 20% among those with CRF and 6.1% among those without CRF (p < 0.0001). Among patients who died in the hospital, and their mean (SD) serum creatinine value was 159.3 µmol/L (106.1) (p < 0.0001).

Anemia on admission to the hospital was associated

with increased risk of death. In-hospital mortality was 24.7% for patients with a hemoglobin of = 14 g/dL, 9.3% for a hemoglobin between 12 g/dL and 14 g/dL, 24.7% for a hemoglobin between 10 g/dL and 12 g/dL, and 15.7% for a hemoglobin < 10 g/dL (p = 0.002) (Table 3). 17.8% in-hospital mortality rates and116 (23.2%) were readmitted within 30 day (Table IV).

Multivariate analysis

Both hemoglobin and serum creatinine were independently associated with poor outcomes after controlling for confounding factors (Table V). For in hospital mortality, the model controlled for length of stay. For each g/dL increase in hemoglobin, the in hospital mortality rate declined by 39% (p = 0.0008). For each one µmol/L increase in serum creatinine, in hospital mortality rate decreased by 1% (p = 0.166). Further, the interaction term between hemoglobin and serum creatinine was statistically significant (p = 0.008). At the mean creatinine level, increasing hemoglobin levels were associated with lower mortality (RR = 0.86, for each unit increase in hemoglobin). Effect modification, suggested a weaker association of hemoglobin with mortality as creatinine levels increased. Further, at the mean level hemoglobin, increasing creatinine levels were associated with higher mortality (RR = 1.015, for each unit increase in creatinine).

In the multivariate analysis using 30 days readmission as dependent variable, we controlled for age. The interaction term between hemoglobin and serum creatinine was not statistically significant. Results showed that for each one g/dL increase in hemoglobin, readmission rate declined by 13% (p = 0.009). Further, for each one µmol/L increase in serum creatinine, readmission rate increased by 0.08% (p = 0.744).

After controlling for all other risk factors, the odds ratio related to in hospital mortality associated with the presence of anemia defined as hemoglobin less than 12 g/dL, was 1.47 (95% CI 0.89 to 2.42) in all CRF patients 4.04 (95% CI 2.46 to 6.66) and in patients with additional CRF compared with patients who had a hemoglobin level = 12 g/dL and no CRF. Similarly, the odds ratio for early readmissions were 1.60 (95% CI 1.00 to 2.58) for anemia and 1.14 (95% CI 0.67 to 1.93) for CRF. In these models, the interaction terms between anemia and CRF lacked statistical significance.

Table III: Hospital Characteristics in Patients with Chronic Renal Failure According to Hemoglobin Level, N = 500 Hemoglobin in g/dL

	<10 N (%) or Mean (SD)	**10–12 N (%) or Mean (SD)**	**12–14 N (%) or Mean (SD)**	**≥14 N (%) or Mean (SD)**
N (%) (N = 500)	40 (8.0)	98 (19.6)	181 (36.2)	181 (36.2)
CRF (N = 500)*	180 (36.0)	160 (32.0)	107 (21.4)	53 (10.6)
Mean (SD) serum creatinine (N = 500)* (µmol/L)	141.0(40.0)	131.6 (33.8)	110.3(14.6)	102.0 (11.6)
Hospital A (N = 215)	14 (6.5)	35 (16.3)	80 (37.2)	86 (40.0)
Hospital B (N = 285)	25 (8.8)	54 (19.0)	90 (31.5)	116 (40.7)
In hospital mortality (N = 89)*	14 (15.7)	22 (24.7)	31 (34.9)	22 (24.7)
30 days readmissions (N = 116)	8 (6.9)	34 (29.3)	38 (32.8)	36 (31.0)
Mean (SD) length of stay (days) (N = 500)*	33 (6.6)	114 (22.8)	140 (28.2)	207 (42.4)

*p value < 0.05

Table IV: Patients Characteristics at Admission in Patients Hospitalized with Chronic Renal Failure, N = 500

	In hospital mortality N = 89		30 day readmission N = 116	
Patients Characteristics	**N**	**N dead (%) 89 (17.8%)**	**N**	**N Readmitted (%) 116 (23.2%)**
Hospital A	50	41 (10.0)	66	43 (11.6)
Hospital B	39	48 (8.8)	50	73 (14.7)
Age (N = 500)				
16 – 60 years	60	7 (6.1)	60	18 (16.8)
61 – 70 years	90	12 (7.0)	90	20 (12.5)
71 – 80 years	145	23 (8.2)	145	43 (16.6)
> 80 years	205	47 (12.1)	205	35 (10.3)
Sex (N = 500)				
Male	272	49 (9.5)	272	64 (13.7)
Female	228	40 (9.2)	228	52 (13.1)

Table V: Results of the Logistic Regression Models, N = 910

	Parameter	Standard Error	P Value
Risk Factors			
Model for Inhospital Mortality, N = 500			
Hemoglobin in g/dL	-0.3898	0.1159	0.0008
Serum creatinine in µmol/L	-0.0122	0.0088	0.166
Hemoglobin in g/dL × Serum creatinine in	0.0021	0.0008	0.008
Length of stay	0.0063	0.0060	0.296
Model for 30 Day Readmission, N = 500			
Hemoglobin in g/dL	-0.1300	0.0499	0.009
Serum creatinine in µmol/L	-0.0008	0.0026	0.744
Hemoglobin in g/dL × Serum creatinine in	NA	NA	NA

Discussion

In this study, both anemia and chronic renal failure were highly prevalent among patients discharged from two university hospitals and independently associated with an increased risk of dying in the hospital or of being readmitted within 30 days. The association between CRF, anemia and these outcomes (in hospital mortality and readmission) in CRF patients has not been reported previously. Most studies have focused only on survival after hospital discharge as an outcome.

The risk of increased mortality associated with a 1% reduction in hematocrit was 2.7% [9]. These results were comparable to another study conducted among Medicare beneficiaries in community hospitals in the US. In this latest study, patients with CRF. The risk of death associated with a 1% reduction in hematocrit was 2% [7]. In a new large recent study, among CRF patients and anemia were found independently to confer a twofold increased risk of death [10]. Silverberg et al. recently reported that, in a randomized trial of 32 ambulatory CRF patients with NYHA class III and IV and an hemoglobin < 12 g/dL, the correction of anemia was associated with an improved functional status and decreased hospitalization. However, the major limitation of this study was its small sample size and the fact that the randomization was not blinded[11]. These observations suggest that anemia is a clinically important risk factor for death and readmission among CRF patients. The clinical implication of these findings for patients with CRF is that failure to correct severe anemia among patients confers a preventable burden of reduced quality of life, while clinical trials have demonstrated that correction of anemia improved these measures. CRF patients should be carefully examined for presence of anemia and, if present, treated according to current evidence[12]. Treating ane-

mia among inpatients with CRF may then reduce in hospital mortality and early readmission. However, currently no large clinical trials have been conducted to evaluate the effect of erythropoietin therapy on survival or readmission among patients suffering from CRF.

In our study we found that, the prevalence of CRF was 54.4% among males and 45.6% among females respectively. However, by using this cut-point of a serum creatinine of = 124 μmol/L for women and = 133 μmol/L for men for defining CRF, we underestimated the true prevalence of CRF especially among elderly people. We choose these cut-points based on previous studies implemented in the USA [7]. Reduced kidney function occurred frequently in patients with CRF. In another study, which included Medicare beneficiaries with CRF hospitalized in community hospitals, 38% had CRF. In this cohort, the prevalence of CRF was 33% in females and 46% in males[7].

Interest in the relationship between CRF and anemia is growing. Anemia commonly complicates CRF (14-28% of patients depending on the cut off used) [13] and is a potential exacerbating factor [14]. In our study the prevalence of anemia (hemoglobin < 12 g/dL) among CRF patients was 28.6%. In another study performed in one Swiss university hospital, the prevalence of anemia was 15%[15]. Silverberg et al. showed that the prevalence of anemia increased with the severity of CRF[10]. Anemia observed among individuals with CRF is highly multi-factorial.

Anemic patients with chronic renal failure should receive treatment with recombinant human erythropoietin (r-HuEPO, Eéoetin) to maintain hemoglobin levels over 11 g/dL with an acceptable target of 12 to 12.5 g/dL, according to recommendations from the European practice guideline for management of anemia in patients with chronic renal failure [16] and the National Kidney Foundation K/DOQI clinical practice guidelines for anemia of chronic kidney disease [11]. Benefits of adequate hemoglobin levels had been established in patients undergoing dialysis, and are supposed to be relevant also in CKD patients. In addition, anemic patients should receive iron supplementation in order to maintain serum ferritin levels above 100 μg/L and transferrin saturation above 20%.

This study had a number of limitations. It is an observational study based on information available in medical records. The chart abstraction process was implemented in each hospital by different persons with different education and backgrounds, although with similar training. Then, in one hospital the entire medical chart was available to the abstractors, whereas in the other only the laboratory findings and reports testing were available. In addition, the quality of medical records and completeness of information may also vary between the two hospitals. Incorrect information may have led to some misclassification bias. Further this study was conducted on an opportunity sample of two hospitals, making the generalisibility of results uncertain. Then, we excluded patients with heart disease and acute myocardial infarction, because it was our intent to focus on a homogenous group of individuals with established CRF. However, we agree that the issue of anemia and outcomes in both of these patient groups is important. Further, we were not able to exclude other causes of anemia, including the presence of iron, folate and vitamin B12 deficiencies, dilutional anemia, and the anemia of chronic diseases different from CRF, as explanations for anemia observed in this population and perhaps, to account for some potential confounders. Then, given the relative high number of elderly patients in the study population and that these patients may have CRF even with normal creatinine value; we underestimated the true prevalence of CRF. Finally, we acknowledge that we were not able to measure others risk factors associated with epo-resistance such as immune activation. We will consider measuring it in future studies. In conclusion, we found further evidence that the concomitant presence of either CRF or anemia increased the risk of dying in the hospital or of being readmitted within 30 days among patients hospitalized. The association persisted after controlling for other factors associated with adverse outcomes in these patients.

References

1. Erslev AJ, Besarab A: Erythropoietin in Pathogenesis and Treatment of Anemia of Chronic Renal Failure. Kid Intern 1997, 51:622-130. http://dx.doi.org/10.1038/ki.1997.91 PMid:9067892

2. European Best Practice Guidelines for the Management of Anemia in Patients with chronic Renal Failure Nephrol Dial Transplant 1999, 14(suppl 5):1-50.

3. Revicki DA, Brown RE, Feeny DH, Henry D, Teehan BP, Rudnick MR, et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal diseasepatients. Am J Kidney Dis. 1995;25:548-54. http://dx.doi.org/10.1016/0272-6386(95)90122-1

4. Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. Am J Kidney Dis. 1997;29:541-8. http://dx.doi.org/10.1016/S0272-6386(97)90335-8

5. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 suppl 1):S1-266. http://dx.doi.org/10.1016/S0272-6386(02)70081-4

6. Fink J, Blahut S, Reddy M, Light P. Use of erythropoietin before the initiation of dialysis and its impact on mortality. Am J Kidney Dis. 2001;37:348-55. http://dx.doi.org/10.1053/ajkd.2001.21305 PMid:11157377

7. McClellan WM, Flanders WD, Langston RD, Jurkovitz EC, Presley R: Anemia in Renal Insufficiency are Independent in Risk Factors for Death among Patients with Congestive Heart Failure admitted to Community Hospitals: A Population-based Study. J Am Soc Nephrol 2002, 13:1928-1936. http://dx.doi.org/10.1097/01.ASN.0000018409.45834.FA PMid:12089390

8. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbity index for use with ICD-9 CM administrative databases. J Clin Epidemiol 1992, 45:613-619. http://dx.doi.org/10.1016/0895-4356(92)90133-8

9. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ: Reduced Kidney Function and Anemia as Risk Factors for Mortality in Patients with Left Ventricular Dysfunction. J Am Coll Cardiol 2001, 38:955-962. http://dx.doi.org/10.1016/S0735-1097(01)01470-X

10. Herzog CA, Li S, Collins AJ: The impact of congestive heart failure (CHF), chronic kidney disease (CKD), and anemia on survival in the Medicare population. Circulation 2002, 106(suppl):471-2.

11. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A: The Use of Subcutaneous Erythropoietin and Intravenous Iron for the Treatment of Anemia of Severe, Resistant Congestive Heart Failure Improved Cardiac and Renal Function and Functional Cardiac Class, And Markedly Reduces Hospitalization. J Am Coll Cardiol 2000, 35:1737-1744. http://dx.doi.org/10.1016/S0735-1097(00)00613-6

12. National Kidney Foundation K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000 Am J Kidney Dis 2001, 37(suppl 1):S182-S238. http://dx.doi.org/10.1016/S0272-6386(01)70008-X

13. Crommie N, Lee C, Struthers AD: Anemia in Chronic Heart Failure: What is its frequency in the UK and its underlining causes? Heart 2002, 87:377-378. http://dx.doi.org/10.1136/heart.87.4.377 PMid:11907017 PMCid:1767058

14. Coletta AP, Niktin N, Clarc AL, Cleland IJGF: Clinical Trials Updates from the American Heart Association Meeting: PROSPER, DIAL, Home Care Monitoring Trials, Immuno-Modulation Therapy, COMPANION and Anemia in Heart Failure. European Journal of Heart Failure 2003, 5:95-99. http://dx.doi.org/10.1016/S1388-9842(02)00249-0

15. Tanner H, Moschovitis G, Kuster GM, Hullin R, Pfiffner D, Hess OM, Mohacsi P: The prevalence of anemia in chronic heart failure. International Journal of Cardiology 2002, 86:115-121. http://dx.doi.org/10.1016/S0167-5273(02)00273-5

16. European Best Practice Guidelines for the Management of Anemia in Patients with chronic Renal Failure. Nephrol Dial Transplant 1999, 14(suppl 5):1-50.