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Prevalence of Anemia in Patients with Stages 3 and 4 Chronic Kidney Disease in Portugal: The NEFROPOR Study

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ABSTRACT

Introduction: Anemia is highly prevalent in chronic kidney disease (CKD). The NEFROPOR study aimed to estimate anemia prevalence and characterize anemia treatment in patients with CKD stages 3 and 4 in Portugal.

Methods: NEFROPOR was a retrospective study in 10 Portuguese centers. Patients with CKD stages 3 and 4 CKD admitted to a first Nephrology consultation over three months were invited to participate, and data for up to 24 months after admission were analyzed. Three assessments of anemia prevalence were performed: at the time of the first visit (presentation), at first analytical results after the first visit, and in the overall study cohort (overall prevalence).

Results: A total of 176 patients were included, mostly (61.9%) male, with a median of 76 years (range, 26-97) and a mean body mass index of 28.2. CKD stage 3b prevailed (43.2%), followed by stages 4 (32.4%) and 3a (24.4%). The most frequent CKD etiologies were diabetes (39.8%), hypertension (27.8%), and unknown (25.6%). Hypertension was largely the most frequent comorbidity (90.3%), followed by diabetes (54.0%). Anemia at presentation was found in 44.9% of patients and was significantly more prevalent in CKD stage 4, diabetic kidney disease, and patients with comorbid peripheral vascular disease, myocardial infarction, and diabetes, and significantly less prevalent in those with unknown CKD etiology. The overall prevalence of anemia was 61.9%, which was significantly more prevalent in patients with comorbid diabetes and peripheral vascular disease and with diabetic kidney disease and significantly less prevalent in patients with glomerular CKD etiology. The prevalence of anemia on first analytical results was 49.4%, and was significantly more prevalent in CKD stage 4, diabetic kidney disease, patients with non-skin cancer active for >2 years, and those with comorbid peripheral vascular disease, myocardial infarction, and diabetes. Anemia was mainly treated with oral iron.

Conclusion: The three anemia prevalence estimates were consistent with each other, particularly those for the first visit and first analytical results. The latter was also consistent with the literature, which reports an anemia prevalence in CKD stages 3 and 4 of 40%-60%. These data support the need for optimized and individualized treatment strategies for these patients.

Keywords: Anemia/etiology; Portugal; Renal Insufficiency, Chronic/complications; Renal Insufficiency, Chronic /epidemiology

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INTRODUCTION

Anemia, defined by the World Health Organization (WHO) as hemoglobin (Hb) levels <12 g/dL for females and <13 g/dL for males,[1] is a highly prevalent comorbidity in patients with chronic kidney disease (CKD) that tends to aggravate as the disease progresses.[2–6] In a large-scale, cross-sectional, US multicenter survey from 2004, anemia was present in 47.7% of 5222 predialysis CKD patients, with its prevalence increasing with kidney function decline (41.5% of stage 3, 53.6% of stage 4, and 75.5% of CKD stage 5 patients had Hb ≤12 g/dL).[4] Two more recent large US analyses in non-dialysis-dependent CKD patients corroborated these findings.[5,6] One, derived from the National Health and Nutrition Examination Survey (NHANES) 2007–2008 and 2009–2010 datasets, showed that 15.4% of CKD patients (stages 1–5, including dialysis) had anemia, with a prevalence of 17.4%, 50.3%, and 53.4% in stage 3, 4, and 5, respectively.[6] The other, derived from Medicare and commercially insured beneficiaries data, found an anemia prevalence similar to NHANES in younger (≤63 years) patients (22.4%, 41.3%, and 53.9% in CKD stages 3, 4, and 5 [not including dialysis patients], respectively) and higher in the older population (46.2%, 65.8%, and 73.8% in CKD stages 3, 4, and 5 [not including dialysis patients], respectively).[5] In Europe, the prevalence rates of CKD-associated anemia range from 12.8% to 61.5%, with higher prevalence in older individuals (>60 years) and later CKD stages.[7]

Overall, the prevalence of anemia in CKD populations has been reported to be higher among older people, women, black people, and people with comorbid conditions, such as diabetes, cardiovascular disease, and hypertension.[5,8,9]

Anemia in CKD has been mainly attributed to functional or absolute iron deficiency[9–11] and inadequate production of endogenous erythropoietin, but also to inflammation and uremic toxin accumulation.[11–13] In addition, certain factors, such as diabetic nephropathy, CKD stages, body mass index (BMI), smoking status, leukocyte count, and serum albumin, have been associated with the development of anemia in CKD patients.[14]

Anemia has long been established as an independent prognostic factor in CKD, namely by increasing cardiovascular risk, progression to kidney failure, hospitalization and/or hospital days, and death.[15–20] This is associated with a high economic burden due to increased use of healthcare resources.[7,21–24] As shown by health insurance US data from 2018, anemic non-dialysis-dependent CKD patients are more likely to use healthcare resources – including hospitalizations and emergency department, hematologist, nephrologist, and outpatient visits – than non-anemic counterparts.[5] In addition, these patients commonly face a relevant impairment in quality of life (e.g., fatigue, reduced physical capacity and energy levels, reduced work productivity).[7,21,25–27]

Despite being a common complication in CKD, anemia is also a highly modifiable comorbidity, with the use of iron therapies and erythropoiesis-stimulating agents (ESAs) having improved the outcomes of this population.[9,28] In a study from 2018 including a comprehensive sample of non-dialysis-dependent CKD patients, red blood cell (RBC) transfusions, followed by ESAs and intravenous (IV) iron, were the most common anemia-related treatments.[5]

In Portugal, the 2011 population-based PREVADIAB study reported a prevalence of CKD stages 3–5 of 6.1%, but ten years later the RENA study reported a prevalence of 20.9% in the Portuguese population followed at the primary care.[29] The authors attributed this difference to the possibly poorer health condition of primary care users, to the inclusion of a wider population, with no upper age limit, in the RENA study, and to the growing prevalence of CKD over a 10-year period.[29] Other European studies have reported marked variations in the prevalence of CKD, from 3.3% in Norway to 15.1% in Spain and 17.3% in Germany.[30–32]

Regarding anemia and iron deficiency in these patients, a recent Delphi Panel with Nephrology and Transfusion Medicine experts showed heterogeneity in the national clinical practice regarding the choice of laboratory parameters to assess patient status and base therapeutic decisions and in cut-off values for defining anemia and/or iron deficiency, highlighting a general lack of consensus in the diagnosis, management, and treatment of anemia in CKD in Portugal.[33]

Data on the prevalence and treatment of anemia in CKD stages 3 and 4 in Portugal are lacking. However, these data are crucial to define optimal treatment strategies for this patient population, enable individualized management, and optimize the use of healthcare resources. The NEFROPOR study was designed to tackle this unmet need. The study's primary objective was to estimate the prevalence of anemia in patients with CKD stages 3 and 4 in Portugal, and its secondary objective was to characterize anemia treatment patterns in this patient population.

METHODS

NEFROPOR was a national, retrospective, multicentric study carried out in 10 Portuguese centers. All patients aged ≥18 years, with CKD stages 3 and 4 based on the estimated glomerular filtration rate (eGFR) according to Kidney Disease: Improving Global Outcomes (KDIGO) classification,[34] admitted for a first Nephrology consultation between January 1 and March 31, 2017, and capable of understanding and signing informed consent were invited to participate. Exclusion criteria included active malignancy for less than two years, chronic (e.g., autoimmune diseases, chronic infections) or acute (e.g., acute infections) inflammatory conditions, hematologic disease of unknown etiology, gastrointestinal bleeding or occult blood loss, prior gastrectomy, anticoagulant therapy during the study period, anemia due to etiologies other than CKD, and pregnancy during the study period.

Data for up to 24 months after admission were collected from patients' clinical files. Retrieved data included age, BMI, CKD stage at diagnosis, comorbidities, CKD etiology, anemia status according to the World Health Organization (WHO) diagnostic criteria,[1] and type and duration of anemia treatment. Three assessments of the prevalence of anemia were performed: anemia at the time of the first Nephrology visit (i.e., at presentation), anemia in the first analytical results, and overall prevalence of anemia in the study cohort.

Statistical analysis was performed in SPSS Statistics (v26), adopting a 0.05 significance level. Mean and standard deviation (SD) or median and interquartile range (IQR) were reported for continuous variables, and absolute and relative frequencies for categorical variables. 95% confidence interval (CI) was estimated when relevant. Fisher exact

test or χ2, as appropriate, were used to compare categorical variables among groups, and student's t-test or Mann-Whitney U test were used for continuous variables.

RESULTS

Characteristics of the study population

A total of 176 patients with CKD stages 3 and 4 were included in this study, mostly (61.9%) male, with a median age of 76 years (range, 26-97; Table 1). The cohort had a mean BMI indicative of pre-obesity as per WHO definition (28.2; SD, 4.2),[1] with only four patients (2.3%) in class II or III obesity and none below normal weight. CKD stage 3b was predominant (43.2%), followed by stage 4 (32.4%) and stage 3a (24.4%). The most frequent CKD etiologies were diabetes (n=70; 39.8%), followed by hypertension (n=49; 27.8%), and unknown etiology (n=45; 25.6%), with four cases (2.3%) attributed to primary glomerulonephritis. Other CKD etiologies identified included solitary kidney (n=3; 1.7%), polycystic kidney disease, cardiorenal syndrome, overuse of non-steroidal anti-inflammatory drugs, chronic interstitial nephritis, and ischemic kidney disease (n=2; 1.1% each). Left renal agenesis, ischemic heart failure, and lithiasis were only identified in one patient (0.6%) each.

Hypertension was the most frequent comorbidity in this CKD population, present in 159 patients (90.3%), followed by diabetes (n=95; 54.0%). Although less prevalent, coronary artery disease (n=32; 18.2%), congestive heart failure (n=26; 14.8%), and cerebrovascular disease (n=20; 11.4%) were also present.

Clinical assessment

A total of 44.9% of patients (95% CI, 37.7%-52.3%) had anemia at clinical presentation, which was significantly more prevalent in patients with CKD stage 4 (59.6%; *p*=0.002), diabetes as CKD etiology (60.9%; *p*=0.001), and peripheral vascular disease (70.6%; *p*=0.038), myocardial infarction (75.0%; *p*=0.016), and diabetes (54.3%; *p*=0.010) as comorbid conditions. Conversely, most patients with unknown CKD etiology (73.3%; *p*=0.005) did not have anemia at presentation.

The overall prevalence of anemia in this CKD cohort was 61.9% (95% CI, 54.6%-68.9%), with anemia significantly more present in patients with diabetes (73.7%; *p*=0.001) and peripheral vascular disease (88.2%; *p*=0.019), and in those with diabetes as CKD etiology (77.1%; *p*=0.001). On the other hand, no patients with primary glomerulonephritis as CKD etiology presented with anemia (*p*=0.020).

Laboratory assessment

The prevalence of anemia in the first analytical results was 49.4% (95% CI, 42.1%-56.8%), subsequently declining in the following assessments, associated with therapeutic interventions and mainly due to a decrease in the number of patients in study over time, which were lost to follow-up (Fig. 1).

Table 1

Demographic and main clinical and laboratory characteristics of the study population

	CKD study population (N=176)
Gender, n (%)	
Male	109 (61.9)
Female	67 (38.1)
Age (years)	
Median (range)	76 (26–97)
BMI (kg/m^2)	
Mean (standard deviation)	28.2 (4.2)
WHO BMI classification, n (%)	
Underweight	0 (0)
Normal weight	22 (12.5)
Overweight	39 (22.2)
Obesity class I	26 (14.8)
Obesity class II	3 (1.7)
Obesity class III	1 (0.6)
Unknown	85 (48.3)
CKD stage at diagnosis, n (%)	
CKD stage 3a	43 (24.4)
CKD stage 3b	76 (43.2)
CKD stage 4	57 (32.4)
Comorbidities, n (%)	
Hypertension	159 (90.3)
Diabetes	95 (54.0)
Coronary artery disease	32 (18.2)
Congestive heart failure	26 (14.8)
Dyslipidemia	25 (14.2)
Cerebrovascular disease	20 (11.4)
Peripheral vascular disease	17 (9.7)
Myocardial infarction	16 (9.1)
Non-skin cancer	11 (6.3)
Obesity	11 (6.3)
Neurological disease	10 (5.7)
CKD etiology, n (%)	
Diabetes	70 (39.8)
Hypertension	49 (27.8)
Unknown	45 (25.6)
Primary glomerulonephritis	4 (2.3)
Solitary kidney	3 (1.7)
Polycystic kidney disease	2 (1.1)
Cardiorenal syndrome	2 (1.1)
NSAID overuse	2 (1.1)
Chronic interstitial nephritis	2 (1.1)
Ischemic kidney disease	2 (1.1)
Left renal agenesis	1 (0.6)
Ischemic heart failure	1 (0.6)
Lithiasis	1 (0.6)
Anemia at clinical presentation	
n (%)	79 (44.9)
95% confidence interval (%)	37.7–52.3
Total anemia	
n (%)	109 (61.9)
95% confidence interval (%)	54.6–68.9
Anemia at first analytical results	
n (%)	87 (49.4)
95% confidence interval (%)	42.1–56.8

BMI, body mass index; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; WHO, World Health Organization

Significant differences were found in the prevalence of anemia in the first analytical results according to CKD stage, etiology, and comorbidities, with anemia being significantly more prevalent in patients with CKD stage 4 (66.7%; *p*=0.002), diabetes as CKD etiology (65.7%; *p*=0.001), and non-skin cancer active for more than two years (90.9%; *p*=0.005), and also in the presence of diabetes (57.9%; *p*=0.016), peripheral vascular disease (76.5%; *p*=0.022), and myocardial infarction (75.0%; *p*=0.038) comorbidities.

eGFR showed a decreasing trend over time, from a maximum of 35.6 mL/min in the first laboratory assessment to a minimum of 8.2 mL/min in the 15th. A similar trend was observed in hematocrit values, from a mean of 38.3% in the first evaluation to 26.9% in the last evaluation. The mean corpuscular volume remained steady over time (around 88 fl), only peaking (108.9 fl) at laboratory assessment 6. Ferritin showed pronounced variations over time, ranging from a maximum mean of 384.0 ng/mL at assessment 8 to a minimum of 149.7 ng/mL at assessment 12, as well as transferrin saturation (TSAT) values, which ranged between 33% at assessment 8 and 12% at assessment 16. Albumin levels slightly increased in the first three laboratory assessments, fluctuating over time from there until a mean value of 3.5 g/dL, and heterogeneously declined henceforth. C-reactive protein (CRP) slightly but steadily decreased from presentation until assessment 8, showing a sharp increase from a mean of 0.1 mg/dL to 36 mg/dL from then on. No data was available after that point in time.

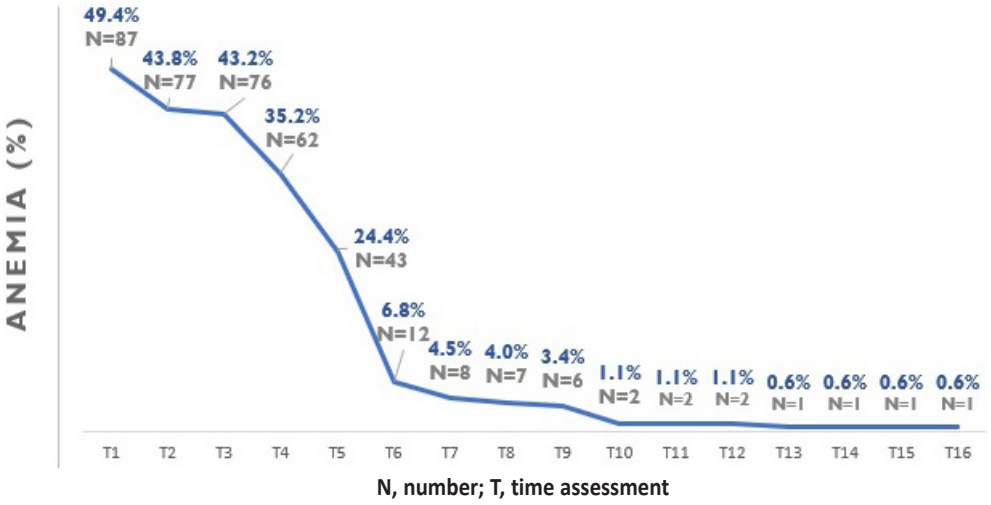

Figure 1

Prevalence of anemia in the first analytical results of patients with CKD stages 3 and 4, with indication of the number of patients assessed at each time point

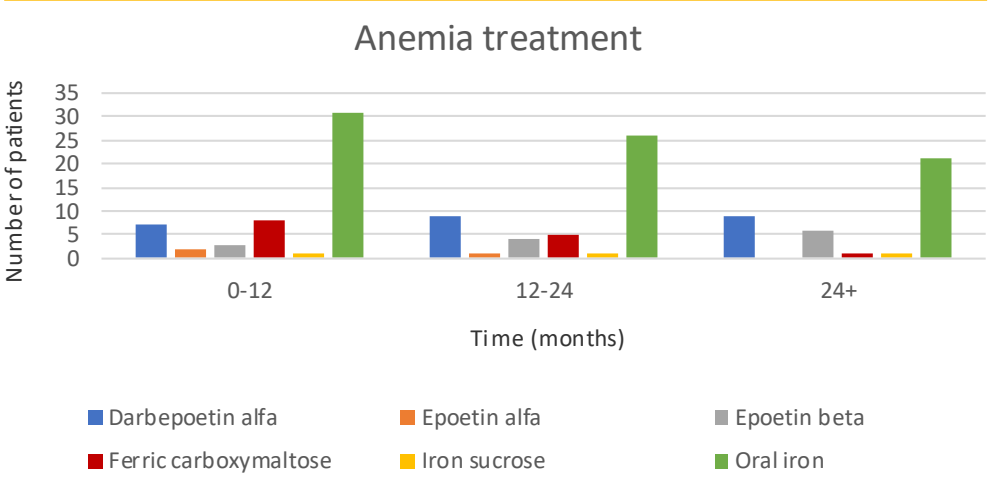

Figure 2

Treatment of anemia in the cohort of patients with CKD stages 3 and 4 over 24+ months

Anemia treatment pattern

Over 24+ months, patients with CKD stages 3 and 4 were mostly treated for anemia with oral iron (17.6% in the 0-12-month period, 14.8% in the 12-24-month period, and 11.9% in the 24+-month period; Fig. 2.

DISCUSSION

The NEFROPOR study showed a prevalence of anemia in CKD patients at clinical presentation of 44.9%, which was significantly associated with CKD stage (23.8% in stage 3a; 46.1% in stage 3b; 59.6% in stage 4), diabetes (54.3% *vs* 34.6% in diabetic versus non-diabetic patients), peripheral vascular disease (70.6% *vs* 42.4% in patients with versus without the comorbidity), myocardial infarction (75.0% *vs* 42.1% in patients with versus without the comorbidity), diabetes as CKD etiology (60.9% *vs* 34.9% in patients with versus without this etiology), and unknown CKD etiology (26.7% *vs* 51.5% in patients with versus without this etiology).

This study also showed an overall prevalence of anemia of 61.9% in this CKD population and that anemia was associated with diabetes (73.7% *vs* 48.1% in diabetic versus non-diabetic patients), peripheral vascular disease (88.2% *vs* 59.1% in patients with versus without this comorbidity), diabetes as CKD etiology (77.1% *vs* 51.9% in patients with versus without this etiology), and primary glomerulonephritis as CKD etiology (0.0% *vs* 63.4% in patients with versus without this etiology).

In addition, an anemia prevalence of 49.4% was identified at the time of the first analytical results in this patient cohort, with the condition significantly associated with CKD stage (32.6% in stage 3a; 46.1% in stage 3b; 66.7% in stage 4), diabetes (57.9% in diabetic *vs* 39.5% in non-diabetic), non-skin cancer (90.9% in patients with *vs* 46.9% in patients without the disease), peripheral vascular disease (76.5% in patients with *vs* 46.5% in patients without the disease), myocardial infarction (75.0% in patients with *vs* 46.6% in patients without the disease), and diabetes as CKD etiology (65.7% in patients with *vs* 38.7% in patients without this etiology).

The estimates of the prevalence of anemia in this study were consistent with each other, particularly those concerning the first visit and the first analytical results (44.9% and 49.4%, respectively). These estimates are also consistent with the evidence in the literature reporting a prevalence of anemia in the population of patients with CKD stages 3 and 4 between 40% and 60%.[4,5] The overall prevalence of anemia found was 12%-15% higher than the estimated at the first visit and first analytical results, in agreement with the fact that this refers to a cumulative prevalence.

In the three definitions of anemia assessed, this study had the power to show a significant association with CKD stage, diabetes, peripheral vascular disease, myocardial infarction, and diabetes as CKD etiology. A larger study may potentially uncover additional associations.

Regarding anemia treatment, it was surprising that such a high proportion of patients in this study were treated for anemia (and for such an extended period in time) with oral iron instead of intravenous iron, as recommended in most international guidelines and review articles and by several expert working groups.[11,35–38] This finding highlights the need to raise awareness of health professionals to the recommendations in the guidelines, improving the outcomes of these patients.

Overall, this study shows that there is a high prevalence of anemia in the Portuguese population of patients with CKD stages 4 and 5 (≈50%), which overlaps with that documented in the literature, and that the condition is treated rather heterogeneously among national centers. Although the study shows a marked reduction in the prevalence of anemia from the beginning of follow-up (49.4%) until six months later (6.8%), longer prospective studies with larger patient numbers are necessary to draw conclusions regarding which is the most effective therapy for the treatment of anemia in this population.

Study limitations

This study's retrospective nature represents a limitation that should be acknowledged. On the other hand, although study sampling sought to include the main geographic areas of Portugal and all national Nephrology hospital departments were invited to participate, only 10 actually did and included patients. This may also represent a limitation for the reproducibility of study conclusions and their applicability in certain country regions. The fact that this study was conducted in a specific population of patients referred to a Nephrology consultation may also pose a limitation to the study's external validity and to the possibility of extrapolating its results to the whole of CKD stages 3 and 4 patients in Portugal.

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