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Original Article

ORIGINAL ARTICLE

Post-transplant renal anemia: a call to action from a national study in routine clinical practice

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ABSTRACT

Background. Post-transplant anemia is a prevalent yet often overlooked condition that poses significant risks. Current guidelines consider the same treatment recommendations and goals for these patients as for chronic kidney disease patients not on dialysis. Previous reports demonstrated a lack of awareness and suboptimal management, indicating a pressing need for improvement. We therefore wanted to update the information on post-transplant anemia. We aimed to describe the present state of anemia management, goals and adherence to guidelines within a representative sample of the kidney transplant (KTx) population.

Methods. We designed a retrospective nationwide multicenter study including outpatients from eight KTx hospitals. Nephrologists gathered data from electronic medical records encompassing demographics, comorbidities, KTx characteristics and immunosuppressive therapy, and information pertaining to anemia management (laboratory values, previously prescribed treatments and subsequent adjustments). The European statement on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines was the reference for definitions, drug prescriptions and targets. Anemia occurring within the initial 6 months post-transplantation was classified as early onset.

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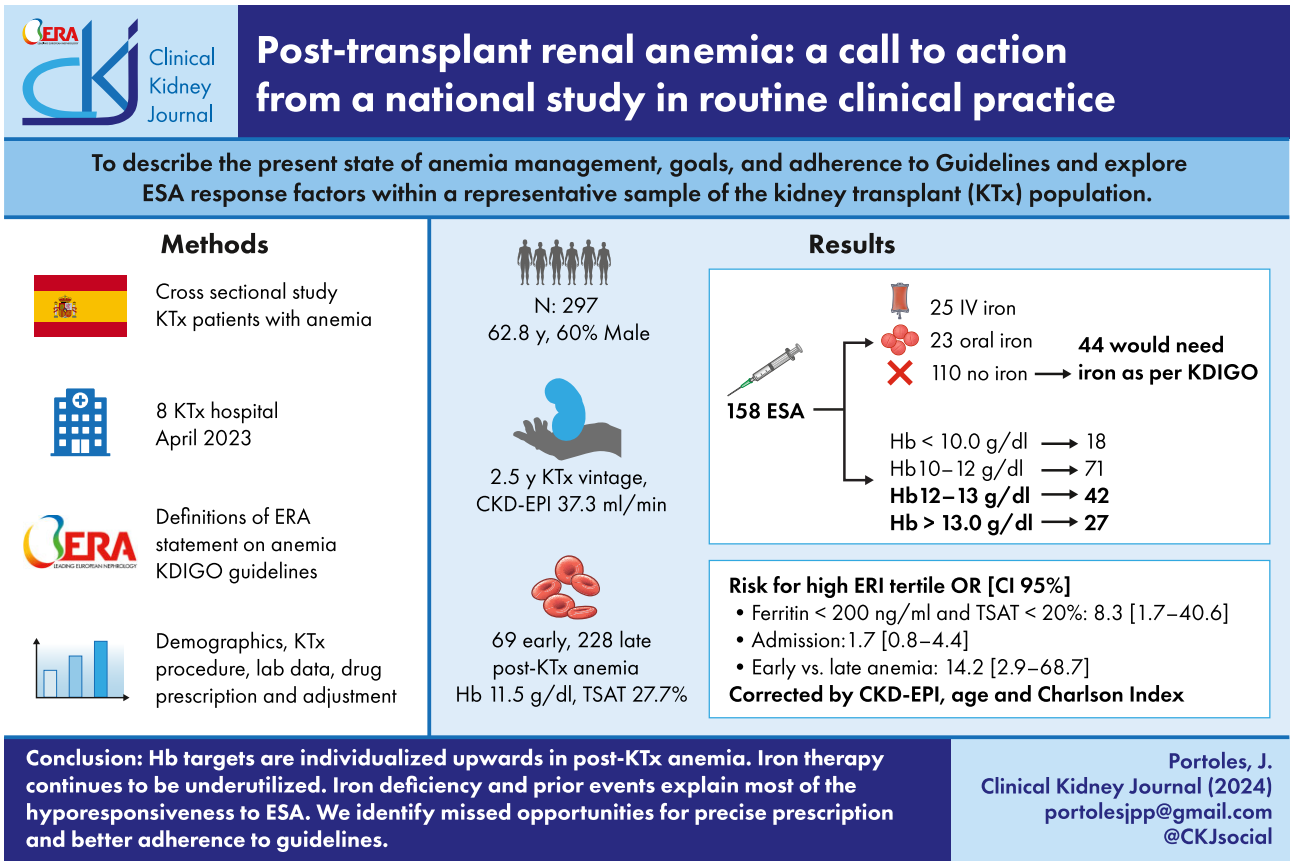
Results. We included 297 patients with post-transplant anemia aged 62.8 years (standard deviation 13.6), 60% of whom were male. They had received a graft from cardiac death or brain death donors (61.6% and 31.1%, respectively) a median of 2.5 years (0.5–8.7) before. Among them 77% ($n = 228$) were classified as having late post-transplant anemia, characterized by a higher prevalence of microcytic and iron deficiency anemia. A total of 158 patients were on erythropoietic-stimulating agents (ESAs) treatment, yet surprisingly 110 of them lacked iron supplementation. Notably, 44 patients had an indication for iron supplementation and among them, 30 exhibited absolute iron deficiency. Out of the 158 patients receiving ESAs, only 39 surpassed the limit for the ESA resistance index, indicating poor response. This resistance was more frequent among patients with early post-transplant anemia (26.1% vs 9.2%). We have identified iron profile, early post-transplant anemia and estimated glomerular filtration rate as factors associated with the highest risk of resistance

Conclusion. We found that hemoglobin targets are individualized upwards in post-transplant anemia. In this setting, iron therapy continues to be underutilized, especially intravenous, and iron deficiency and prior events (blood transfusion or hospital admission) explain most of the hyporesponsiveness to ESA. This highlights missed opportunities for precise prescription targeting and adherence to established guidelines, suggesting a need for improved management strategies in post-transplant anemia patients.

GRAPHICAL ABSTRACT



Keywords: anemia, erythropoiesis-stimulating agents, hemoglobin target, kidney transplant

KEY LEARNING POINTS

What was known:

- Post-transplant anemia is a relevant clinical problem that receives less attention than graft survival, rejection or other clinical problems.
- We do not have specific post-transplant anemia guidelines, but global anemia guidelines refer to anemia of chronic kidney disease non-dialysis-dependent (CKD-NDD) patients; however, post-transplant anemia incidence is higher at the same renal function and presents some differences in associated factors such as immunosuppression or inflammation with high hepcidin levels.
- Our objective is to comprehensively describe the current management strategies for post-transplant anemia, assess adherence to existing guidelines and identify opportunities for improvement.

This study adds:

- Our study provides insights into the current management of both early and late post-transplant anemia and compliance with guidelines: erythropoietic-stimulating agent (ESA) prescriptions meet guidelines; hemoglobin targets are personalized to fall between 12 and 13 g/dL; iron supplements remain underused; and iron deficiency emerges as the primary cause of hyporesponsiveness to ESAs.
- The findings underscore the need for improvement strategies such as structured dissemination of anemia guidelines; clinical pathways for intravenous (IV) iron administration in outpatient transplant clinics; assisted-prescription tools; and early identification of resistance to ESAs or inflammation.

Potential impact:

- This study promotes improvement strategies such as structured dissemination of CKD guidelines, clinical routes for in-center IV iron administration for outpatient transplant clinics, assisted-prescription tools and early identification of ESA resistance.
- Studies on anemia in KTx patients are needed to generate reliable evidence to individualize prescriptions and objectives.
- We need guidelines on post-transplantation anemia, different from the guideline on CKD-NDD, especially in terms of evaluation and treatment in early post–kidney transplant anemia.

INTRODUCTION

Post-transplant anemia is a relevant clinical problem that probably receives less attention from transplant nephrologists than graft survival, rejection, infections or other clinical problems. We do not have specific post-transplant anemia guidelines, but global anemia guidelines refer to post-transplant anemia as being like anemia of chronic kidney disease (CKD) non-dialysis dependant (NDD) patients, regardless of relying on native kidneys or a graft. However, post-transplant anemia incidence is higher than anemia in patients with native CKD patients not on dialysis (CKD-NDD) at the same estimated glomerular filtration rate (eGFR), and presents some differences in associated factors [1]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines use World Health Organization definitions for anemia, as does the European Renal Association (ERA) position statement [European Renal Best Practice (EBPG)] [2, 3]. European nephrologists usually refer to the ERA European statement for definitions, diagnosis, treatment recommendations and hemoglobin (Hb) targets [4]. The incidence of anemia depends on definitions and the time after transplantation. Taken together, prospective studies and retrospective multicenter surveys found that approximately 50% of kidney transplant (KTx) remain anaemic at 6 months, 40% at the first year and 30% after 5 years from transplantation, and between 12%–15% have severe post-transplant anemia (Hb <11 g/dL) [5].

Post-transplant anemia is driven by common CKD factors such as inadequate erythropoietin (EPO) production, iron deficiency, inflammation with high hepcidin levels (which impairs the absorption of dietary iron and mobilization from iron stores) and a shortened lifespan of red blood cell, among other things [6]. Post-transplant anemia is usually divided into early anemia (first 6 months) and late anemia (later) [7]. While the pathophysiology of post-transplant anemia is similar to CKD-associated anemia, specific additional factors related to surgery, induction therapy and infections are more relevant in early anemia, and immunosuppressive (IS) toxicity, viral infection and rejection influence throughout the life of the graft [8, 9].

CKD-NDD anemia has been associated with an increased risk of CKD progression, cardiovascular and overall mortality, as summarized in a recent metanalysis [10]. Similar findings have been reported for post-transplant anemia in a pooled analysis of 17 studies reporting an increased risk ratio of mortality [RR 1.7 (1.39–2.13)] and graft-loss [pooled risk ratio 2.28 (1.77–2.93)] [10, 11].

The Dialysis Outcomes and Practice Patterns Study (DOPPS) in hemodialysis (HD) [12] and CKD-DOPPS in NDD patients [13] are global initiatives that include analysis of anemia management and its clinical impact. Unfortunately, we do not have similar strategies for patients with post-transplant anemia. TRESAM (The TRansplant European Survey on Anemia Management) was the latest European global study on post-transplant anemia that included 4263 KTx patients from 16 countries reporting an overall post-transplant anemia incidence of 38.6% in a wide range of transplant recipients at different follow-up timepoints [14]. Five years later, a new analysis reported a post-transplant anemia prevalence of 42%, with 76% of patients with an Hb <11 g/dL without erythropoietic-stimulating agents (ESAs) treatment [15].

Therefore, post-transplant anemia is a common problem with important clinical implications. It should be noted that there are no specific guidelines for the diagnosis and treatment of post-transplant anemia, and that the KDIGO and EBPG guidelines recommend the same criteria as for CKD in the native kidney, ignoring the differences between both situations. Furthermore, there is a lack of recent evidence on actual management by nephrologists. Recognizing these gaps, the transplant-working group (SENTRA) and the anemia-working group (GAS

by its Spanish initials) of the Spanish Society of Nephrology promoted a shared nationwide study within real clinical settings.

The primary objective is to comprehensively describe the current management strategies for post-transplant anemia, assess adherence to existing guidelines and identify opportunities for improvement.

MATERIALS AND METHODS

The TRANSNEMIA study is a joint initiative of SENTRA and GAS working group of the Spanish Society of Nephrology designed as a cross-sectional, retrospective, non-interventional, nationwide study in real life that includes eight university transplant hospitals in Spain. Our objective was to describe the treatment patterns of post-transplant anemia and the objectives achieved in transplant patients, as well as the degree of compliance with current clinical guidelines in a real clinical practice scenario without intervention. We did not aim to estimate anemia prevalence. Based on this, we selected consecutive patients with post-transplant anemia in our outpatient clinics from 1 April 2023, until reaching the equally assigned number of cases to minimize center effect. We included adult patients with a functioning graft and anemia and classified as early post-transplant anemia those patients in the first 6 months after surgery as reported by others [7]. We stratified at the center level into two subgroups: early anemia and late anemia with a ratio of 1 to 3, to include a representative sample. Every center was allowed to include 38 patients, and the period from first to last patient was 19 days in our outpatient transplant clinics.

The study protocol was approved by Hospital Puerta de Hierro Ethics Committee (PI141/23) and was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization guidelines for Good Clinical Practice, and any other applicable local health and regulatory requirements.

At baseline, patient-caring nephrologists retrieved from electronic medical records data on demographics, cause of CKD, comorbidities (cancer, cardiovascular events, diabetes mellitus and Charlson Index), primary data on KTx (i.e. donor type, IS drugs, actual serum creatinine and eGFR), anemia treatments and laboratory values. We did not recover the reasons for not prescribing ESA or iron in those cases where patients were not receiving it. Data on transfusion, hospital admission and prescriptions (ESAs and iron) during the previous 4 months, and their adjustments on visits after knowing lab values, were collected. We include an open question for any reason for an Hb out-of-target not defined by structured data. All values were included in a shared dedicated database for analysis. We calculated the ESA resistance index (ERI) as a dose–response score defined as epoetin dose (IU per kg per week) per g/dL of Hb. The darbepoietin dose in µg/kg/week was converted to epoetin using a conversion factor of 1 to 200 [16, 17]. ESA hyporesponsiveness was defined as a subcutaneous ESA dose >300 IU/kg/week or an ERI ≥12.7 IU/kg/week/Hb g/dL (or equivalent darbepoietin dose) as previously proposed [17].

Anemia was defined as Hb <13 g/dL in men and Hb <12 g/dL in women, or any Hb with ESAs treatment according to 2012 KDIGO guidelines [18]. The EBPG position statement adapted the KDIGO recommendation for ESA treatment to the European population [4], suggesting that Hb levels between 10 and 12 g/dL be achieved and maintained, but individualizing the target according to the comorbidities. However, Hb values >13 g/dL should not be intentionally aimed for during ESA therapy.

The definition of absolute iron deficiency was a transferrin saturation index (TSAT) <20% and a serum ferritin concentration ≤100 ng/mL [4]. Functional iron deficiency was defined by a TSAT <20% and normal or elevated ferritin levels [4].

The correct indication for iron therapy defined according to the EBPG position statement for patients with NDD was evaluated, regardless of whether they were transplant recipients or not [4]. Among patients with CKD and anemia not receiving iron or ESA therapy, they recommend a trial of intravenous (IV) iron or a 3-month oral iron trial, with a switch to the IV route if oral iron was unsuccessful or not tolerated. Iron supplementation is also recommended in case of an absolute iron deficiency or if an increase in Hb concentration is desired without starting ESA treatment, or if TSAT is <25% and ferritin <200 ng/mL in CKD-NDD patients. In patients treated with ESA, iron supplementation is indicated where there is an increase in Hb or a decrease in ESA dose is desired and TSAT is <30% and ferritin <300 ng/mL. The TSAT limit of 30% and the serum ferritin limits of 500 ng/mL should not be intentionally exceeded [4].

Statistical analysis

We have calculated a sample size of 284 to estimate the percentage of patients with Hb on target, considering a prevalence of 50% of patients on ESAs and 75% of them on target [18, 19] with a precision of 5% in a two-tailed test. Continuous variables were presented as mean and standard deviations (SD) or median and interquartile range, and categorical variables as valid percentages. Comparisons between groups were performed using the Chi-Square or Fisher's test for qualitative variables and the Student's *t*-test/analysis of variance or Mann–Whitney/Kruskal–Wallis test for quantitative variables. The Kolmogorov–Smirnov test was used to determine whether the data were normally distributed. To describe the profile of patients with hyporesponse, we used resistance definition based on ERI ≥12.7 U/kg/week/Hb g/dL as previously described and to further explore factors associated to hyporesponse to ESAs, ERI was considered as an outcome event and it was analysed the risk factors associated to be in the highest ERI tertile [data shown as odd ratio (OR) and 95% confidence interval]. A *P*-value <.05 was considered statistically significant.

The statistical package STATA 16.0 (Stata Statistical Software: Release 16, Stata Corp. LP, College Station, TX, USA) was used for the statistical analysis.

This study has been reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (ref PMID: 17938396).

RESULTS

Baseline characteristics

We included 297 patients (Fig. 1) with anemia and a functioning graft with a mean age of 62.8 (SD 13.6) years, 60.0% of whom were male. They had received a graft primarily from cardiac death or brain death donors (31.1% and 61.6%, respectively) a median time of 2.5 years (0.5–8.7) before; eGFR was 37.3 mL/min/1.73 m^2 (SD 18.1). We divided them into two groups: 69 (23%) patients with early anemia and the remaining 228 (77%) with late anemia [4.9 (1.2–11.3) years since transplantation]. The main patient characteristics, kidney disease, prior renal replacement therapy (RRT), comorbidity and transplant data, are summarized in Table 1 for the entire sample and for the early and late anemia subgroups.

The early anemia group had a numerically lower mean Hb (11.3 vs 11.6 g/dL), the same percentage of patients with Hb on target (10–12 g/dL) and more patients with severe anemia

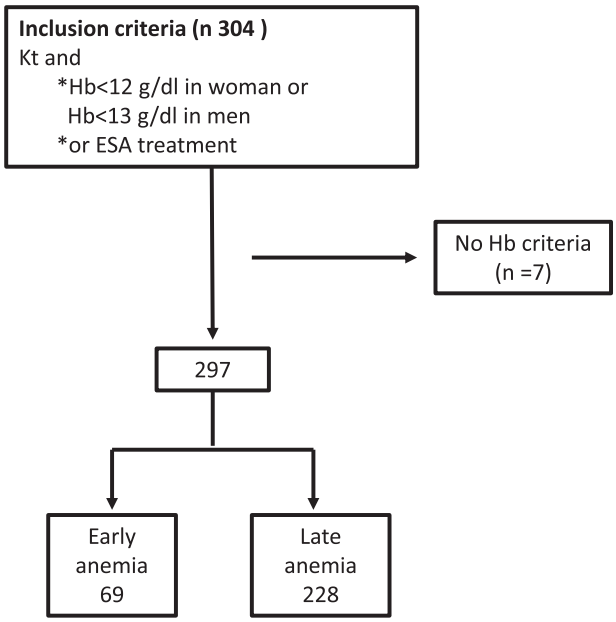


Figure 1: Flowchart. Kt: kidney transplant.

(15.9% versus 8.8% Hb <10 g/dL). They had received more blood transfusions in the previous 4 months (27.5% vs 4.8%), probably related to surgical procedures or as a complication of transplantation performed a median of 4 months before. They presented a higher eGFR, ferritin and TSAT but the same distribution of absolute or relative iron deficiency (Table 2).

ESA and iron treatment patterns

Among the 297 patients included, 53.2% were being treated with ESAs. The type of ESA was unique for each KTx center and the majority of the patients received darbepoetin [79.7%, median dose 1.0 (0.6–1.7) µg/kg/month] followed by epoetin α [19.6%, median dose 133.3 (85.1–290.2) IU/kg/month] (Table 2). Only 13 patients among those not receiving ESA had an Hb <10 g/dL and 6 of them were prescribed ESAs after knowing this lab result. The starting dose [80 µg/month (20–120)] was according to guideline recommendations.

Of the 297 patients, 10.4% had functional iron deficiency and 8.1% had absolute iron deficiency, with similar distribution for early and late anemia. Patients on ESA treatment showed a higher prevalence of absolute iron deficiency and higher prevalence of functional iron deficiency (Fig. 2); patients with early anemia presented more iron deficiency than those with late anemia (15.0% vs 8.5%).

Approximately three-quarters of the patients (72.4%) were not receiving any iron supplements. IV iron was prescribed more frequently than the oral route (15.5% vs 12.1%). Ferric carboxymaltose was the first choice (87.0%, median dose 1000 mg/6 months), followed by iron sucrose (13.0%, median dose of 100 mg/month). Patients with early anemia had received IV iron more frequently (27.5 vs 11.8) but less oral iron (4.3% vs 14.5%) (Table 3). Patients treated with ESA received oral iron more frequently (14.6% vs 9.4%) than those without ESAs ($P = .2$).

Table 1: Main characteristics on patient demography, kidney disease and RRT, morbidity and transplantation for patients with early and late anemia of CKD-NDD.

	All	Late anemia	Early anemia	*P*-value
N	297	228	69	
Demography				
Age (years)	62.8 (13.6)	63.0 (13.9)	62.3 (12.7)	.7
Male (%)	60	56.9	69.1	.07
Renal etiology (%)				.8
DM/Glom/NAE	14.5/25.6/8.4	13.2/26.8/7.9	18.8/21.7/10.1	
Interstitial/APKD/others	9.4/12.5/12.8	9.2/13.2/13.2	10.1/10.1/11.6	
Unknown	16.8	16.7	17.4	
Morbidity: Charlson index	5.2 (2.2)	5.2 (2.2)	5.3 (1.9)	.7
DM (%)	33.3	33.3	33.3	.9
Previous CV events (%)	20.5	21.5	17.4	.5
Cancer (%)	11.5	11.4	11.6	.9
Previous RRT (%)				.001
PD/HD	14.8/72.4	11.4/77.6	26.4/55.1	
Pre-emptive KTx/CKD due to previous failed graft	10.4/2.4	8.3/2.6	17.4/1.5	
Donor type (%)				
DCD/DBD/living donor	31.3/61.6/7.1	28.0/64.9/7.0	42/50.7/7.3	.04
Time since KTx (years)	2.5 (0.5–8.7)	4.9 (1.2–11.3)	0.3 (0.2–0.4)	<.001
Re-transplantation (%)	15.2	17.1	8.7	.09
IS induction therapy (%)				
Basiliximab/thymoglobuline/other	41.4/45.5/13.1	38.6/44.3/17.1	50.7/49.3/0.0	<.001
Current immunosuppression (%)				
Steroid	85.1	80.5	100	<.001
Tacrolimus	93.2	91.6	98.6	.04
Mycophenolate	72.5	70.4	79.7	.1
mTORi	16.0	17.3	11.6	.3
Cyclosporin	3.4	4	1.5	.3

Data are shown as mean (SD), median (interquartile range) or percentage (%).
DM: diabetes mellitus; Glom: glomerulonephritis; NAE: nephroangioesclerosis; APKD; autosomic polycystic kidney disease; CV: cardiovascular disease, PD: peritoneal dialysis; DBD: donation after brain death; DCD: donation after cardiac death; mTORi: mammalian target of rapamycin inhibitors.

Table 2: Laboratory values and anemia targets for early and late post-transplant anemia patients.

	All	Late anemia	Early anemia	P-value
N	297	228	69	
eGFR (mL/min/1.73 m^2)	37.3 (18.1)	36.1 (18.1)	41.3 (17.8)	.04
Weight (kg)	71.9 (15.0)	71.7 (15.3)	72.2 (13.9)	.8
Hb (g/dL)	11.5 (1.2)	11.6 (1.2)	11.3 (1.4)	.1
MCV (fL)	89.9 (7.7)	88.9 (7.9)	93.3 (5.7)	<.001
MCHC (g/dL)	32.8 (3.8)	32.6 (1.4)	33.6 (7.5)	.05
MCH (pg)	29.7 (4.6)	29.0 (2.65)	31.7 (8.1)	<.001
Patients according to Hb (%)				.3
Hb <10 g/dL	10.4	8.8	15.9	
Hb 10–12 g/dL	53.9	53.9	53.6	
Hb 12–13 g/dL	26.6	28.1	21.7	
Hb >13 g/dL	9.1	9.2	8.7	
Ferrokinetic lab values				
Ferritin (ng/mL)	347.4 (127–640)	306 (121.5–575.5)	526 (146.8–834.2)	.01
TSAT (%)	27.7 (15.0)	26.4 (13.5)	31.6 (18.4)	.02
Absolute/relative iron deficiency (%)	8.1/10.4	7.9/10.5	8.7/10.1	.9
CRP (mg/L)	1.2 (0.2–3.8)	1.4 (0.3–4.0)	0.6 (0.2–3.0)	.08
Albumin (g/dL)	4.1 (0.4)	4.1 (0.4)	4.2 (0.4)	.5
EPO alfa dose (IU/month)	16 000 (8000–32 000)	8000 (6000–18 000)	24 000 (18 000–72 000)	.004
Darbepoietin dose (µg/month)	110 (40–200)	80 (40–160)	160 (120–240)	.001
ERI (IU/kg by g/dL)	5.9 (2.8–12.7)	5.2 (2.3–9.1)	10.1 (5.5–18.6)	<.002
ERI >12.7 IU/kg/(g/dL) (%)	13.1	9.2	26.1	<.001
Previous clinical events potentially related to Tx anemia				
Blood transfusion (%)	10.1	4.8	27.5	<.001
Hospital admission (%)[a]	26.9	27.2	26.1	.09

[a]Admission for receiving graft excluded.
ERI: erythropoietin resistance index after converting to IU of EPO (1 µg darbepoietin = 200 IU EPO).
MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; MCH: mean corpuscular hemoglobin; Tx: transplant.

Patients on ESA	Absolute iron deficiency	Functional iron deficiency	No iron deficiency	All
Hb <10 g/dl	1 (0.6)	1 (0.6)	16 (10.1)	18 (11.4)
Hb 10-12 g/dl	7 (4.4)	13 (8.2)	51 (32.3)	71 (44.9)
Hb 12-13 g/dl	6 (3.8)	14 (8.9)	22 (13.9)	42 (26.6)
Hb > 13 g/dl	2 (1.3)	3 (1.9)	22 (13.9)	27 (17.1)
All	16 (10.1)	31 (19.6)	111 (70.3)	158 (100)

Figure 2: Patients on ESA treatment classified according to Hb and iron target. *n* (percentage over entire group of ESAs treated patients).

Among the 110 patients on ESA treatment but without iron prescription, 44 had an indication to receive iron according to guidelines (i.e. iron use if TSAT <30% and ferritin <500 ng/mL for ESA-treated patients), with 30 of them having absolute iron deficiency. Indeed, in 29 patients (26.4%) from six centers iron treatment was not prescribed after knowing the TSAT and ferritin results. The situation was worse for patients with late anemia treated with ESAs, since 28.0% of them had absolute iron deficiency and 43.9% of them had an indication for iron prescription, and none of them received it.

One in four patients with absolute iron deficiency and oral iron treatment were switched to IV iron after knowing the new lab results. None of the three patients with more than a 3-month oral iron prescription and with an indication for a change in regimen were switched to IV, as suggested by European position over KDIGO guidelines to improve efficacy.

Compliance with prescription and objectives of the guideline

According to EBPG recommendation, the majority of ESA-treated patients (71/158) had optimal Hb control within the range of 10–12 g/dL. Hb increased to the range of 12–12.9 g/dL in 42 of the 158 patients and was above the limit of 13 g/dL in 27/158 (Fig. 2).

The nephrologist did not withdraw ESA in 23 of the 27 patients with Hb >13 g/dL, despite guideline recommendations, nor was the ESA dose reduced in 28 of the 42 patients with Hb between 12 and 12.9 g/dL. In 1 of the 18 patients with Hb <10 g/dL, treatment with ESA was not started (Fig. 2).

We analysed the subgroup of patients who were receiving ESAs and the combined distribution by Hb and ferrokinetic targets is summarized in Fig. 2. We found no statistical differences in Hb targets among those receiving different ESAs (darbepoetin or short-action rHuEPO).

Table 3: Anemia treatments (ESA, oral and/or IV iron).

	No iron	Oral iron	IV iron	All
All anemic patients				
No ESA	105 (35.4)	13 (4.4)	21 (7.1)	139 (46.8)
ESA	110 (37.0)	23 (7.7)	25 (8.4)	158 (53.2)
Total	215 (72.4)	36 (12.1)	46 (15.5)	297 (100)
Late anemia				
No ESA	86 (37.7)	13 (5.7)	11 (4.8)	110 (48.2)
ESA	82 (36.0)	20 (8.8)	16 (7.0)	118 (51.8)
Total	168 (73.7)	33 (14.5)	27 (11.8)	228 (100)
Early anemia				
No ESA	19 (27.5)	0 (0)	10 (14.5)	29 (42)
ESA	28 (40.6)	3 (4.3)	9 (13.0)	40 (58)
Total	47 (68.1)	3 (4.3)	19 (27.5)	69 (100)

Data are presented as number (percentage over reference subgroup) for all patients, early and late subgroups.

Erythropoietin response and associated factors

Only 39/158 patients exceeded the pre-specified limit of 12.7 IU/kg/week/g/dL dose, which was more frequent in early anemia patients (18/40 vs 21/118; P: .001). A few patients (18/158) exceeded the criteria for resistance to ESAs (>300 IU/kg/week).

Resistance to ESA was more frequent during the early period (46.2% vs 18.5%; $P < .001$) and was associated with a higher prevalence of absolute or functional iron deficiency (25.6% vs 5.0%; P-value <.001). We found no differences in inflammation [C-reactive protein 1.4 (0.3–4.0) vs 0.6 (0.2–3.0) mg/dL, P: .08] and renal function by Chronic Kidney Disease Epidemiology Collaboration eGFR [36.4 (SD 17.8) vs 41.4 mL/min (SD 17.6); P: .05] or serum albumin [4.1 (SD 0.4) vs 4.2 (SD 0.4) g/dL; P: .5] between resistant and non-resistant patients. We have found only 34 patients with a previous diagnosis of cancer, probably resolved. This factor was not associated with a lower ESA response.

Patients with resistance to ESA also had more events during the previous 4-month period. They had received more red blood cells transfusions (20.5 vs 6.7%; P: .01) and numerically higher hospital admissions (35.9 vs 26.3%; P: .2). Despite a higher prescription of IV iron (23.1 vs 13.5%, P: .2), resistant patients showed a similar TSAT (27.9 vs 27.1%; P: .9) and higher ferritin levels [375 (74–839) vs 317 (144.5–603.9) ng/mL; P: .6].

The ERI was considered as a dependent factor, and the independent variables associated with the highest tertiles of the ERI (hyporesponsiveness) were analysed using univariate and multivariate logistic regression models. We have identified iron profile, early post-transplant anemia and eGFR as factors associated with risk for the highest ERI tertile. Those patients with iron overload (ferritin >800 mg/dL and TSAT >20%) or iron deficiency (TSAT <20% and ferritin <200 mg/dL) presented an OR of 6.0 (1.43–25.23) and 3.9 (1.23–12.4), respectively, for hyporesponsiveness in a univariant logistic regression analysis (Table 4).

DISCUSSION

ESA prescription

Our study provides updated information on the current management of post-transplant anemia in KTx centers in Spain. We generally prescribe ESAs in accordance with drug-prescribing recommendations and guidelines, and only a few patients do not receive ESAs when indicated. The EBPG statement on KDIGO guidelines considers KTx recipients in the same group as NDD patients with a native kidney [4]. Our data greatly improve those collected >10 years ago in the European study with 4263 patients from 10 countries, which reported that 76% of the patients with Hb <11 g/dL did not receive ESAs [15], and also from the previous TRESAM study on 2003, when only 17.8% of patients with severe anemia received epoietin [14]. In our study, <4.4% of patients presented Hb <10 g/dL and did not receive ESAs. Much progress has been made in raising awareness about the relevance of anemia in KTx recipients and the convenience of considering it as a relevant clinical problem.

Although the Hb targets achieved are generally within the range recommended by the guidelines, it seems that transplant nephrologists tend to raise the upper limit of Hb targets, maintaining ESAs at Hb between 12 and 13 g/dL. Guidelines strictly advise against maintaining ESAs when Hb reaches 13 g/dL based on the results from TREAT (Trial to Reduce cardiovascular Events with Aranesp® Therapy), CHOIR (Correction of Hemoglobin Outcomes in Renal Insufficiency) and CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) randomized controlled trials (RCT) and summarized in a recent meta-analysis [11]. The CAPRIT RCT in transplanted patients is smaller than all of these CKD-NDD trials and it is also limited by its short duration of 2 years [20]; however, this is the only RCT that addresses this question in the KTx population. The CAPRIT study included 125 KTx recipients with post-transplant anemia randomized to two Hb targets (10.5–11.5 g/dL and 13.0 to 15.0 g/dL). They found a slower decline in renal function, better death-censored graft survival and a significant improvement in quality of life (QoL). The results of this study as well as those of the large observational study by Heinze *et al.* [21] suggest that the optimal Hb target in KTx recipients with post-transplant anemia would be higher than the target suggested in NDD-CKD, and would probably be up to 12–13 g/dL. A larger RCT, designed like the CAPRIT study, Correction of Anemia and Progression of Renal Insufficiency in Transplant patients with a longer follow-up may help to define the optimum Hb level target in KTx recipients.

The EBPG statement of the KDIGO guidelines recommends individualizing the target between 12 and 13 g/dL according to patient's functional status, comorbidity, dialysis technique and cardiovascular risk. We have not asked for the reasons for prescription or targets, but we assume that treating nephrologists considered it safe enough and were aiming for a better physical function and QoL in patients without relevant comorbidities, who had an active life and who do not suffer the typical hemoconcentration of the HD session. A recent meta-analysis aimed at assessing the achievement of higher target Hb (11.5–13 g/dL) demonstrates an improvement in fatigue especially in younger and non-diabetic patients [22], as CAPRIT study did [20].

Patients with early anemia had a worse achievement of Hb target and, as we discuss later on, a worse response to ESAs.

Iron prescription

The situation is somewhat different with iron supplements. We found a clear underuse of iron (IV or oral) among patients receiving ESAs, who could benefit from a reduction in ESA doses. High doses of ESA are not only costly, but have also been shown to be a risk factor for hypertension thrombosis and infections [23]. Previous observational studies on post-transplant anemia did not report data on iron prescription [14]. *Post hoc* analysis of Hb targets in randomized trials in NDD-CKD (CREATE, TREAT and CHOIR [16, 24, 25]) have shown that the highest risk arises in the case of lower Hb level and higher ESA doses [23, 26]. Furthermore, iron deficiency is associated with thrombocytosis, which

Table 4: Factors associated with being in the highest ERI tertile.

		N	Univariate hyporesponsiveness (3rd tertile ERI)	P-value	Multivariate hyporesponsiveness (3rd tertile ERI)	P-value
Iron status	Ferritin <800 ng/mL and TSAT >20%	42	1.0		1.0	
	Ferritin <200 ng/mL and TSAT <20%	19	3.9 (1.2–12.4)	.02	8.3 (1.7–40.6)	.01
	Ferritin >200 ng/mL and TSAT <20%	16	2.3 (0.7–7.5)	.16	4.8 (0.9–24.7)	.06
	Ferritin >800 ng/mL and TSAT >20%	13	6.0 (1.4–25.2)	.01	9.0 (1.5–54.0)	.02
Early anemia		102	6.4 (2.2–18.9)	.001	14.2 (2.9–68.7)	.001
Charlson index with age		102	0.9 (0.7–1.1)	.30	0.7 (0.5–1.02)	.07
CKD-EPI (mL/min/1.73 m^2)	1st tertile (<27)	42	1.0		1.0	
	2nd tertile (27–42)	30	0.7 (0.3–1.7)	.40	0.6 (0.2–2.2)	.44
	3rd tertile (<42)	29	0.4 (0.2–1.1)	.08	0.2 (0.05–0.7)	.02
Hospital admission (3 months previous)		102	4.1 (1.5–11.4)	.007	3.5 (0.9–12.9)	.06

ERI: erythropoietin resistance index after converting to IU of EPO (1 µg darbepoietin = 200 IU EPO).
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration. Data shown OR and 95% confidence interval.

may further increase the thrombotic risk in patients treated with ESA, as suggested by Streja *et al*. [27]. In fact, in a classical editorial by Hung *et al*. the role of iron treatment concomitant with ESA therapy was highlighted [28].

We have not asked for the reasons for prescribing iron or not, but we tried to exclude formal reasons for it. A majority of patients on ESAs without an iron prescription did not have levels of TSAT or ferritin that would contraindicate their use according to the guidelines. On the other hand, comorbidity due to cancer and/or inflammation (elevated CRP) was not associated with the lack of iron supplementation in those patients for whom it was indicated. Although we do not have a direct answer as to the reason for this therapeutic nihilism, we suggest that it is due more to a lack of awareness than to a formal contraindication.

Some of these missed opportunities for accurate prescriptions guidance can be addressed with decision support tools. Previous experiences with artificial intelligence (AI) models in HD have shown that the integration of therapies and laboratory results (target ranges and trends in Hb changes) with events and comorbidities can improve the efficiency in anemia treatment and reduce the burden of work [29].

We have found several differences between early and late anemia. Patients with early anemia show lower Hb level, higher ferritin levels, higher incidence of absolute iron deficiency, received double the dose of ESA but less iron (oral or IV) supplements, and have worse response to ESAs. These divergences may reflect the greater complexity and healthcare requirements of this newly transplanted population.

ESA resistance

Few patients (18/158) meet the strict EBPG dose criteria for ESA resistance, but in our experience, ERI is the best way to define the response to ESA treatment [30]. One in four patients receiving ESAs presented an ERI over the threshold defining underresponsiveness as previously described [31]. These numbers are located at the top of the range of resistance incidence previously reported for NDD or peritoneal dialysis [31, 32]. We have found no previous reports on ESAs resistance in KTx patients. Patients with post-transplant anemia suffer from inflammatory conditions, viral infections and IS toxicity which could explain their worse response to ESAs. In fact, the incidence of resistance is higher in early anemia when the blood losses, iron deficiency, inflammation, induction therapy, pre-emptive therapy and early infection are more prevalent [33]. If we combine the data obtained on underuse of iron therapy with these results, the key message is that we have a clearly identified area for improvement. However, an intervention study would be necessary to confirm the potential protective effect of an adequate prescription of iron therapy.

We are unable to demonstrate a significant association between elevated ERI and induction therapy, IS prescription, inflammation (measured by CRP) or comorbidity. Only iron deficiency seems to be associated with resistance to ESAs in our study. Resistance to ESAs is associated with a higher risk of death in NDD and HD as well as a higher healthcare cost [31]. We have not found specific studies on the association between the response to ESAs and outcomes in transplant patients.

The association between post-transplant anemia and clinical outcomes is far from the aim and design of our study, but we want to highlight previous evidence that places post-transplant anemia as a relevant issue. Post-transplant anemia has been associated with a worse patient and graft survival. A recent meta-analysis including 16 463 KTx patients from 17 observational studies reported that it was associated with an increased overall mortality, cardiovascular death and cardiovascular events [10]. Early anemia associated a higher risk of overall mortality and graft loss than late anemia. Distinguishing whether post-transplant anemia is solely a marker of associated health issues or if it poses an independent risk remains challenging. To elucidate this distinction, a prospective intervention study design would be essential.

Our study was not aimed at estimating prevalence of anemia among KTx patients or investigating factors contributing to the development of post-transplant anemia. Rather, our goal was to describe how anemia is managed in the KTx population. Therefore, we designed a study that included only anemic patients and collected retrospective data to avoid observer bias induced by the study itself. We have external validity limitation and our data do not necessary represent the situation in other health systems or countries. However, we consider that our sample is representative, and we employed an adequate design to describe

the current reality in our national health system, since 20% of national transplant centers are included and the EHRs allow us to collect all the data without missing values.

CONCLUSIONS

In summary, our study provides insights into the current management of both early and late post-transplant anemia, and compliance with guidelines in a representative sample of KTx recipients. Key findings include: a majority of ESA prescriptions meet guidelines; Hb targets are personalized to fall between 12 and 13 g/dL; iron supplements remain underutilized; and iron deficiency emerges as the primary cause of hyporesponsiveness to ESAs.

These findings highlight the need for improvement strategies, such as: structured dissemination of anemia guidelines; development of clinical pathways for IV iron administration in outpatient transplant clinics; assisted prescription tools and early identification of resistance to ESAs or inflammation.

There is a pressing need for dedicated studies focused on anemia in KTx patients. These studies are essential for generating reliable evidence that can inform personalized prescriptions and treatment objectives as specific post-transplant anemia guidelines.

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AUTHORS' CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

DATA AVAILABILITY STATEMENT

Researchers may request access to anonymized participant level data, clinical level data and protocols previous requested to SENEFRO Foundation. senefro@senefro.org.

CONFLICT OF INTEREST STATEMENT

J.Portoles has received support for travel and consultancy, and speaker fees from CSL Vifor, Astellas and GSK. E.R.C. has received speaker fees from Astellas. J.Pascual and N.M. received a consultancy fee from GSK. A.G.-D. has received support for travel and consultancy, and speaker fees from Astellas and GSK. The rest of the authors do not declare any conflict of interest.

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