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Prevalence and Management of Anaemia in Renal Transplant Recipients: Data from Ten European Centres

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Key Words
Anaemia · Chronic renal disease · Erythropoiesis-stimulating agent therapy · Kidney transplantation

Abstract
Background: Although it is a known predictor of mortality, there is a relative lack of recent information about anaemia in kidney transplant recipients. Thus, we now report data about the prevalence and management of post-transplant anaemia (PTA) in Europe 5 years after the TRansplant European Survey on Anemia Management (TRESAM) study. ***Methods:*** In a cross-sectional study enrolling the largest number of patients to date, data were obtained from 5,834 patients followed at 10 outpatient transplant clinics in four European countries using the American Society of Transplantation anaemia guideline. ***Results:*** More than one third (42%) of the patients were anaemic. The haemoglobin (Hb) concentration was significantly correlated with the estimated glomerular filtration rate (eGFR) ($r = 0.4$, $p < 0.001$). In multivariate analysis, eGFR, serum ferritin, age, gender, time since transplantation and centres were independently and significantly associated with Hb. Only 24% of the patients who had a Hb concentration <110 g/l were treated with an erythropoiesis-stimulating agent. The prevalence of anaemia and also the use of erythropoiesis-stimulating agents were significantly different across the different centres, suggesting substantial practice variations. ***Conclusions:*** PTA is still common and under-treated. The prevalence and management of PTA have not changed substantially since the TRESAM survey.

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Introduction

Complications of chronic kidney disease (CKD), such as anaemia, are present in a substantial proportion of kidney transplant (RTx) recipients and have a negative impact on clinical outcomes [1]. Post-transplant anaemia (PTA) is common [2–8], with a consistent prevalence of 30–40% [3, 5, 6]. The estimated prevalence of severe anaemia, potentially requiring treatment based on current guidelines, is 10–15% [3, 5]. In 2003, the TRESAM study (TRansplant European Survey on Anemia Management) collected data about PTA from centres across Europe [5].

Renal anaemia is effectively treated with erythropoiesis-stimulating agents (ESAs). Treatment benefits include improvement in quality of life, symptom relief [9] and possibly cardiovascular protection [10], although not all studies have confirmed this [11]. The DOPPS (Dialysis Outcomes and Practice Patterns Study) trial showed large international variations in anaemia management in patients on maintenance dialysis [12], but the practice patterns of PTA treatment have not been previously studied in detail.

Anaemia is associated with early post-transplant cardiovascular risk in RTx recipients [10, 13, 14]. Winkelmayer at al. [15] found no association between anaemia or haemoglobin (Hb) level and outcome. We and others, on the other hand, have demonstrated that anaemia was independently associated with mortality and graft failure [1, 16].

We expected that the prevalence of PTA has decreased and the treatment of PTA has become more consistent since the TRESAM study. To test this hypothesis, we obtained a cross-sectional dataset of 5,834 patients from 10 renal transplant units across Europe. We found that the prevalence and management practices related to PTA are quite variable and overall have remained largely unchanged over the last 5 years.

Subjects and Methods

Patients and Data Collection

This cross-sectional study used a descriptive correlational design. A convenience sample of 10 transplant centres from 4 European countries was selected. Exclusion criteria for individual patients were multiple organ transplantation, pregnancy at the time of enrolment, age <18 years at the time of enrolment and <3 months since transplant.

Demographic and laboratory data were extracted from the electronic databases of the participating centres. The following laboratory parameters were tabulated: Hb, serum creatinine, blood urea nitrogen and serum ferritin. Transplant-related data extracted from the medical records included the use of ESA and transplant 'vintage', i.e. time elapsed since the time of the transplantation. This was divided into five categories to facilitate analysis: <6 months, 6 months–1 year, 1–3 years, 3–5 years and >5 years. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula [17].

Definition of Anaemia and Iron Deficiency

We used two anaemia definitions in our analyses. First, anaemia was defined according to the anaemia guideline of the American Society of Transplantation (AST): Hb <130 g/l in adult males and 120 g/l in adult females [18]. In this work we used this definition unless stated otherwise. Anaemic patients were subsequently divided into three sub-categories to gauge severity: (I) *mild:* males: $120 < Hb \leq 130$ g/l; females: $110 < Hb \leq 120$ g/l; (II) *moderate* (as anaemia defined by the NKF-K/DOQI [19]): males: $110 < Hb \leq 120$ g/l; females: $100 < Hb \leq 110$ g/l, and (III) *severe:* males: Hb ≤110 g/l; females: Hb ≤100 g/l.

Second, the data were re-analyzed using a cut-off value of Hb <110 g/l that is suggested to trigger treatment with ESAs in patients with CKD, including kidney-transplanted patients, by current guidelines [19–21].

Iron deficiency was defined as a serum ferritin level <100 ng/ml.

Statistical Analysis

Statistical analysis was carried out using the SPSS 15.0 software. Continuous variables were compared using Student's t test or the Mann-Whitney U test, and categorical variables were analyzed with the χ^2 test. ANOVA testing with Bonferroni correction for multiple comparisons was used to analyze the relationship between continuous variables. Bivariate analysis was performed using the Pearson or Spearman correlation analysis as appropriate. For multivariate analysis linear or logistic regression was used, centres were analyzed as dummy variables.

Results

Demographics and Baseline Characteristics of the Sample

The study population included 5,834 patients; the mean age was 50 ± 14 years, 62% were males. Baseline patient characteristics are shown in table 1. The median (interquartile range) time since transplantation was 85 (106) months.

The mean age of the sub-cohorts increased significantly with increasing transplant vintage (table 1). The eGFR showed a decreasing trend across the five sub-cohorts formed according to transplant vintage.

Prevalence of Anaemia

Mean Hb for the total sample was 129 ± 17 g/l. Based on the AST criteria, overall 42% of the patients were anaemic (table 1). Furthermore, 18% of the total sample had mild, 15% had moderate and 9% had severe anaemia.

Table 1. Patients' characteristics

Time since transplantation	Total population (n = 5,834)	<6 months (n = 56)	6 months–1 year (n = 246)	1–3 years (n = 913)	3–5 years (n = 893)	>5 years (n = 3,726)	p value
Mean age ± SD, years	50 ± 14	45 ± 13	46 ± 13	47 ± 14	48 ± 14	51 ± 14	<0.001
Gender, male, %	62	64	62	64	63	61	NS*
Mean Hb ± SD, g/l	129 ± 17	120 ± 18	129 ± 18	129 ± 17	130 ± 17	128 ± 17	<0.001
Mean eGFR ± SD, ml/min/1.73 m^2	47 ± 19	50 ± 20	50 ± 16	51 ± 19	48 ± 19	46 ± 20	<0.001
Ferritin, ng/ml							
Median	114	315	198	144	134	94	<0.001
Interquartile range	219	396	482	285	273	184	
Anaemia based on AST definition, %	42	59	44	42	36	44	NS*
Anaemia based on Hb <110 g/l, %	14	29	15	14	12	14	NS*
ESA use, %	11	18	17	15	11	10	<0.001*

* p value: linear-by-linear association.

818 (14%) of the patients had Hb levels <110 g/l. The proportion of female patients with a Hb level <110 g/l was significantly higher than the proportion of males with a similar Hb level (20 vs. 11%; $p < 0.001$).

Iron Deficiency

Serum ferritin was available for 3,352 of the patients, 47% of whom had a level <100 ng/ml. Significantly more female patients had serum ferritin levels <100 ng/ml than males (50 vs. 44%; $p < 0.001$). The average serum ferritin level showed a strongly decreasing trend with increasing vintage of the sub-cohorts (table 1). Serum ferritin showed a weak negative correlation with Hb ($R = -0.102$; $p < 0.001$) and eGFR ($R = -0.145$; $p < 0.001$).

Correlates of Anaemia

Age did not show a clinically meaningful correlation with Hb levels ($R = 0.029$; $p < 0.05$). Female transplant recipients had significantly lower mean Hb than males (females 123 ± 15 g/l; males 133 ± 17 g/l; $p < 0.001$), and female gender was significantly associated with the prevalence of anaemia except when using the AST criteria of anaemia which are gender-specific.

eGFR correlated significantly with Hb in the total sample ($R = 0.4$; $p < 0.001$). Approximately one fourth of the patients (23%) had an eGFR ≥60 ml/min/1.73 m^2 (group 1). eGFR was 30–60 ml/min/1.73 m^2 in 59% of the patients (group 2) and it was <30 ml/min/1.73 m^2 in 18% (group 3). The mean Hb levels in the groups defined by eGFR were: 137 ± 15, 129 ± 16 and 116 ± 16 g/l for groups 1, 2 and 3, respectively ($p < 0.001$), and we found a similar trend between the prevalence of anaemia and CKD stages (fig. 1). eGFR correlated significantly with Hb both in group 2 ($R = 0.250$; $p < 0.001$) and in group 3 ($R = 0.236$; $p < 0.001$), i.e. in CKD stages 3–5. No association was seen between Hb and eGFR in group 1, i.e. CKD stage 1–2.

Table 2. Linear regression model of Hb as the dependent variable (adjusted R^2: 28%, $p < 0.001$)

	Level of significance	t	β
Age	<0.001	7.241	0.110
Gender (female)	<0.001	–15.670	–0.232
eGFR	<0.001	22.946	0.349
Serum ferritin	<0.001	–5.062	–0.078
Time since transplantation	<0.001	–3.886	–0.060
Centre 'J' (ref.)	–		
Centre 'H'	<0.001	–3.598	–0.071
Centre 'G'	<0.001	–3.554	–0.057
Centre 'F'	<0.001	–4.711	–0.072
Centre 'E'	<0.001	–5.430	–0.106
Centre 'D'	<0.001	–14.054	–0.268
Centre 'B'	<0.001	–9.273	–0.184
Centre 'A'	<0.001	–6.265	–0.093

Reference centre was Centre 'J' (as dummy variable), because in our sample, the prevalence of anaemia was the lowest there. From Centre 'C' and 'I' some variables are missing; consequently, patients from these centres are not included in this analysis.

Additionally, we re-analyzed our data for CKD stage 3a (59–45 ml/min/1.73 m^2) and CKD stage 3b (44–30 ml/min/1.73 m^2) [22]. eGFR correlated significantly with Hb in both sub-groups: CKD 3a ($R = 0.099$; $p < 0.001$) and CKD 3b ($R = 0.136$; $p < 0.001$). The prevalence of anaemia was 34 and 50% for CKD3a and CKD3b, respectively (fig. 1).

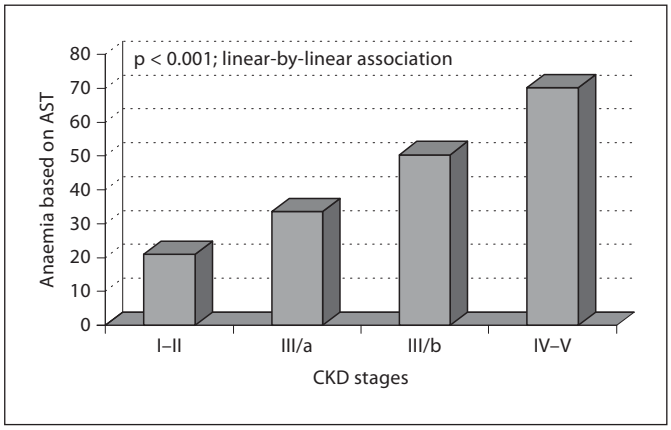

Fig. 1. Prevalence of anaemia and CKD stages in kidney-transplanted patients.

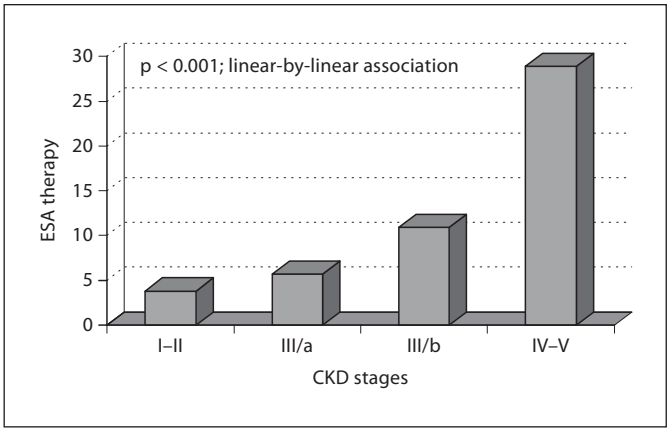

Fig. 2. ESA therapy and CKD stages in kidney-transplanted patients.

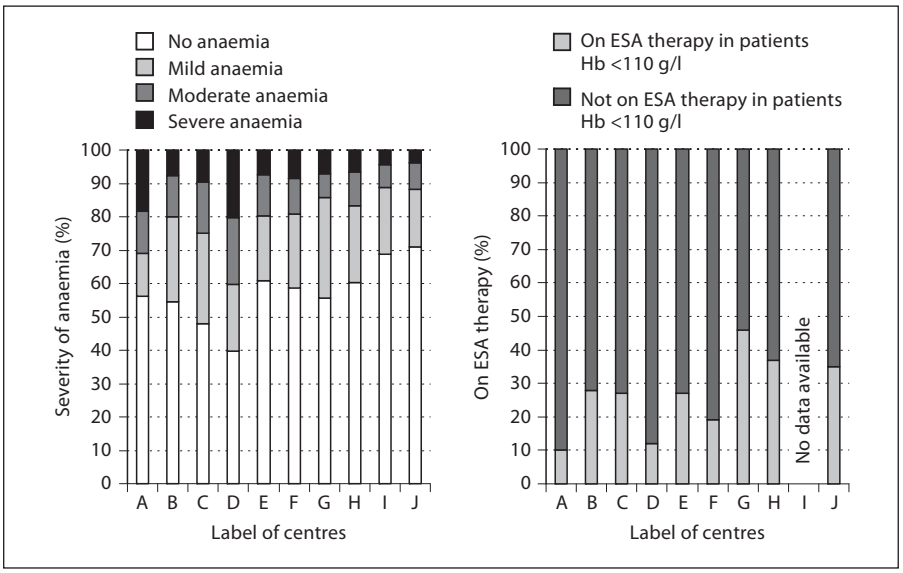

Fig. 3. Prevalence of anaemia (based on AST definition) and proportion of ESA therapy in patients with Hb <110 g/l in the different centres.

Transplant vintage is reportedly associated with Hb [5, 23]. In our sample the mean Hb was significantly lower in sub-cohort 1 (i.e. within 6 months of transplantation) compared to the remaining sub-cohorts (table 1).

Multivariate Analysis

Multivariable linear regression analysis was used to identify independent predictors of Hb. In this model (adjusted $R^2 = 0.28$, $p < 0.001$), age, gender, eGFR, serum ferritin, time since transplantation and centres were all independently associated with the Hb concentration (table 2). Qualitatively similar results were found in logistic regression models where the presence of anaemia (by each definition) was used as a dependent variable (results not shown).

Anaemia Treatment

An ESA was used in 11% of the total sample and in 17% of anaemic (by AST definition) patients. Anaemic patients receiving ESA therapy had a lower mean Hb (109 ± 12 vs. 114 ± 10 g/l; $p < 0.001$) and eGFR (30 ± 15 vs. 42 ± 18 ml/min/1.73 m^2; $p < 0.001$) than anaemic patients not receiving ESA. The percentage of ESA use increased with CKD stages (fig. 2). ESA was given to 13% of

the mildly, 15% of the moderately and 28% of the severely anaemic patients ($p < 0.001$). 76% of the patients with Hb levels <110 g/l and 67% of the patients with Hb <100 g/l were not treated with ESA. ESA use was also different according to transplant vintage (table 1). Finally, 2.6% of the patients with Hb >130 g/l were prescribed ESA therapy.

Anaemia Prevalence and Treatment by Centre

The number of patients were 87 in centre 'A', 1,535 in centre 'B', 571 in centre 'C', 673 in centre 'D', 537 in centre 'E', 341 in centre 'F', 140 in centre 'G', 809 in centre 'H', 554 in centre 'I', and 587 in centre 'J'.

The average Hb level was significantly different in the different centres ($p < 0.001$). The highest mean Hb level was 134 ± 17 g/l (centre 'J') and the lowest 121 ± 19 g/l (centre 'D'). The prevalence of anaemia was the lowest also in centre 'J' (28%) and the highest in centre 'D' (59%) (fig. 3). Similar results were found when the different anaemia definitions were used, suggesting differences in management practice.

The average eGFR was also significantly different between the centres ($p < 0.001$). The highest mean eGFR (56 ± 23 ml/min/1.73 m^2) was seen in centre 'A' and the lowest (43 ± 17 ml/min/1.73 m^2) in centre 'I'. Serum ferritin level was also different between centres.

The use of ESA therapy was also significantly different across the centres and ranged from 3% of the total patient population in centre 'A' to 22% in centre 'H'. Similarly, the proportion of ESA therapy in patients with Hb <110 g/l was also different in centres (fig. 3). 10% of the patients with Hb <110 g/l were treated with ESA at centre 'A' (the lowest) and 46% of similar patients were receiving ESA at centre 'G' (the highest). Of the patients with Hb >130 g/l, the range treated with ESA therapy was 0–17%.

Discussion

In this study we have demonstrated that the prevalence of PTA remains high and similar to what had been reported 5 years ago in the TRESAM study. The proportion of anaemic patients was 42% in this dataset (it was 39% in TRESAM). Eleven percent of the patients in this dataset were treated with ESA (5% in TRESAM) [5]. Furthermore, similar to the findings in TRESAM, more than two thirds of the patients with Hb <110 g/l had not been receiving ESA treatment. We also demonstrated that substantial practice variations exist in the anaemia management among different European centres. Most of our patients had received their transplant more than 1 year prior to their enrolment in our survey; consequently, these results are applicable to this sub-group of RTx patients.

The severity of anaemia in this cohort was also similar to the findings of the TRESAM survey [5]. Variable definitions of PTA are used in the literature [24]. Our primary anaemia definition is based on the anaemia guideline of the AST [3, 5, 6]. To have a definition that could potentially affect patient care, we also used a cut-off value of 110 g/l which is suggested to trigger treatment with an ESA in patients with CKD [4, 19, 25]. The prevalence of this anaemia in this dataset was about half of the prevalence reported by Winkelmayer et al. [4], but it is similar to the prevalence found by Yorgin et al. [25] in 2002. Different case mix, variable immunosuppressive protocols and ESA utilization may in part explain these substantially different results. It is important to emphasize that about 76% of the patients with Hb <110 g/l (67% of those with Hb <100 g/l) did not receive ESA treatment.

Although iron deficiency is one of the potential causes of PTA, it has rarely been analyzed in this context. Mix et al. [26] found that iron stores were checked in only 12% of their 240 patients. The best measure to assess iron deficiency would be the percentage of hypochromic red blood cells [27]. In this survey we did not have appropriate information about the iron status for more than one third of the enrolled patients. The observed negative correlation between serum ferritin and Hb is almost certainly due to the fact that serum ferritin is profoundly influenced by other factors, particularly by inflammation.

In contrast to previous results [3], we found a weak and clinically not meaningful correlation between age and Hb. Although the prevalence of anaemia by the AST definition was similar in males and females, the mean Hb concentration was significantly lower in females, similarly to previous results [3, 5]. Our results suggest that women are more at risk of developing severe anaemia potentially requiring treatment.

The eGFR was the strongest correlate of Hb levels even after controlling for covariables [3, 5, 6, 25]. Interestingly, however, this association was not seen in one fifth of the patients who had eGFR >60 ml/min/1.73 m^2. This suggests that PTA develops only after a substantial reduction in eGFR occurred. In the majority of the population the prevalence of anaemia showed a marked increase with declining renal function, similarly to what had been reported by Karthikeyan et al. [28]. Importantly, this association was already significant in CKD stage 3a. Furthermore, the prevalence of anaemia in CKD3a was significantly higher than in patients with CKD1 and 2.

These results suggest that even modest reductions in renal function below the threshold of eGFR of 60 ml/min/1.73 m^2 have a significant impact on Hb level. The prevalence of anaemia in patients with significantly reduced eGFR was similar to that seen in CKD patients not yet requiring renal replacement therapy [29].

In the total study sample, 17% of the anaemic patients received an ESA. This proportion was higher than previous results [5, 25, 26]. The European Best Practice Guideline for the management of transplanted patients suggests that ESA therapy should be considered when Hb is consistently <110 g/l. Even in this group, only 24% of the patients were treated with ESA, which seems low given the fact that cardiorenal anaemia syndrome is a known risk factor [30] and PTA is reportedly associated with mortality [1, 16].

Recent reports of prospective randomized studies testing the effect of ESAs in patients with CKD (the CHOIR, CREATE and TREAT studies) have suggested that targeting patients with CKD and renal anaemia to reach normal or close normal Hb levels with the use of ESAs does not confer survival benefit or even substantial improvement in health-related quality of life [11, 31, 32]. Concern about the potential risk of such treatment strategies has been raised. Furthermore, in a recent retrospective analysis of more than 1,700 RTx recipients, Heinze et al. [16] showed significantly increased mortality in patients who received ESA and had Hb >125–140 g/l. Importantly, however, the lowest mortality risk in patients receiving ESA was at Hb 125 g/l [16]. Furthermore, patients who did not receive ESA but had Hb >125 g/l had even a lower mortality risk. Finally, in an analysis of data from about 900 prevalent RTx recipients, we found that the use of ESA was not associated with increased mortality after controlling for Hb and serum erythropoietin levels in addition to sociodemographic and clinical variables [33].

Based on these results it is difficult to conclude what the optimal target for Hb level should be. The current guidelines, which suggest to initiate ESA treatment if Hb is consistently <110 g/l and maintain Hb between 110 and 120 g/l, seem to be safe. Appropriate large-scale prospective studies to define the role and targets for ESA therapy in RTx patients are needed.

Irrespective of the specific questions discussed above, we suggest that PTA still needs special attention. PTA has been repeatedly shown to be associated with an increased risk of mortality [1]. It appears from all the results briefly summarized above that the presence of PTA (and renal anaemia in patients with non-transplant CKD) is a marker of underlying processes and conditions (likely involving protein-energy wasting and others) eventually leading to poor clinical outcome. Even if increasing Hb with the use of ESAs in patients with moderately reduced Hb may not be needed, those patients will still need focused attention to identify any potential modifiable factors causing their anaemia and also to optimize the management of other potentially modifiable cardiovascular risk factors.

In the multivariate analysis, the 'centre' was independently associated with anaemia and Hb even after controlling for several covariables. In addition to potentially variable comorbidity (which we did not have information about) and immunosuppressive treatments, variable treatment practices are likely to explain some of these differences. Similar results have been reported by the DOPPS investigators for patients on maintenance dialysis [12]. Utilizing monitoring practices and target ranges suggested by appropriate guidelines [19–21], targeted continuous quality improvement practices and perhaps dedicated 'risk management clinics' for renal transplant recipients may improve the quality of treatment and perhaps also outcomes.

To our knowledge, this is the largest point-prevalence cross-sectional PTA survey ever conducted. An additional strength of the study is its multicentre, multinational design.

Several limitations, however, should also be considered. This cohort was a prevalent cohort which is subject to the problem of incidence-prevalence bias. A significant limitation of observational studies, such as ours, is that they cannot prove causal associations between predictors and outcomes. Our sample was a convenience sample and we do not claim representativeness. The non-random selection of the centres participating in the survey may be the source of selection bias; consequently, our data may not be applicable to the whole RTx population without consideration. We did not have information about several parameters (primary kidney disease, presence of diabetes, percentage of hypochromic red blood cells, transferrin saturation, serum albumin and CRP levels, comorbidity, panel-reactive antibodies, cold ischemic time, the use of drugs which effect Hb (ACE inhibitors, co-trimoxazole, CMV prophylaxis), number of blood transfusions, acute rejection episodes, intact parathormone, inflammatory markers, donor type, immunosuppression regimen and ethnicity) that may be associated with anaemia or management practices in the participating centres. Another weakness of our trial is that we did not have data about the iron status from 43% of our patients. We do not

think, however, that our main findings are systematically biased because of these limitations. Finally, we note that the large majority of the patients in this sample (95%) had their transplant more than 12 months prior to data collection; therefore, the data present are relevant to the 'late' PTA.

In summary, we found that the prevalence and management of anaemia have not changed over the last 5 years. PTA was present in 1 of 3 RTx patients and anaemia potentially requiring treatment or at least more intensive medical attention occurred in about 1 of 7 patients. Importantly, more than two thirds of these patients have not received ESA treatment for their condition. However, to date we still do not have a prospective, randomized study which would assess the potential beneficial effects of ESAs in RTx recipients. Furthermore, substantial practice variations are seen across different transplant centres in their ESA use. Finally, data about iron studies are frequently not done on a regular basis. We suggest that a more systematic approach to the detection and management of PTA and iron status is needed to improve quality of care and outcomes in this patient population.

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