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ORIGINAL ARTICLE

Anemia in children following renal transplantation—results from the ESPN/ERA-EDTA Registry

Leah A. Krischock[1] · Karlijn J. van Stralen[2] · Enrico Verrina[3] · E. Jane Tizard[4] · Marjolein Bonthuis[2] · György Reusz[5] · Farida K Hussain[6] · Augustina Jankauskiene[7] · Gregor Novljan[8] · Brankica Spasojević-Dimitrijeva[9] · Ludmila Podracka[10] · Vera Zaller[11] · Kitty J. Jager[2] · Franz Schaefer[12] · on behalf of the ESPN/ERA-EDTA Registry

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Abstract
Background Our aim was to determine the prevalence of sub-target hemoglobin (Hb) levels in children with a renal allograft and to identify potential determinants associated with these Hb levels.
Methods Data from 3669 children with a functioning renal allograft, aged <18 years between 1 January 2000 and 31 December 2012, from 20 European countries were retrieved from the ESPN/ERA-EDTA Registry, providing 16,170 Hb measurements.
Results According to the NKF/KDOQI classification and the UK-NICE guidelines, 49.8 and 7.8 % of the patients, respectively, were anemic. Hb levels were strongly associated with graft function, with Hb levels of 12.6 g/dl in children with chronic kidney disease (CKD) stage 1, declining to 10.7 g/dl in children with CKD stage 5 ($P<0.001$). Higher Hb levels were associated with the use of tacrolimus compared to ciclosporin (0.14 g/dl; 95 % confidence interval 0.02–0.27; $P=0.002$). Low Hb levels were associated with an increased risk of graft failure ($P=0.01$) or combined graft failure and death ($P<0.01$), but not with death alone (not significant).
Conclusions Anemia is present in a significant proportion of European pediatric kidney transplant recipients and is associated with renal allograft dysfunction and type of immunosuppressants used. In our patient cohort, higher Hb levels were associated with better graft and patient survival and less hypertension.

Leah A. Krischock and Karlijn J. van Stralen contributed equally to this work.

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✉ Karlijn J. van Stralen
k.j.vanstralen@amc.uva.lnl

[1] Department of Paediatric Nephrology, Sydney Children's Hospital, Sydney, Australia

[2] ESPN/ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, PO Box 22700, Amsterdam, The Netherlands

[3] G Gaslini Hospital, Genova, Italy

[4] Bristol Royal Hospital for Children, Bristol, UK

[5] Semmelweis University Budapest, Budapest, Hungary

[6] Nottingham University Hospitals, Nottingham, UK

[7] Vilnius University, Vilnius, Lithuania

[8] Children's Hospital University Medical Center, Ljubljana, Slovenia

[9] University Children Hospital, Belgrade, Serbia

[10] Department of Pediatrics, Faculty of Medicine, Slovak Medical University (SMU), Bratislava, Slovak Republic

[11] Medical University of Vienna, Vienna, Austria

[12] University of Heidelberg Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany

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Introduction

All children who have undergone renal transplantation are considered to have chronic kidney disease (CKD), irrespective of their allograft function [1, 2]. Two-thirds of pediatric renal allograft recipients have CKD stage 3 or greater [3, 4]. Anemia can persist after transplantation, with the prevalence of post-transplant anemia (PTA) varying from 22 to 82 % depending on the era of the study and the definition used [5–13]. In addition to reduced renal function, other important risk factors for PTA include medications, altered inflammatory milieu and a non-pre-emptive transplant [14, 15]. An increased risk of graft loss has been reported in anemic adult renal transplant recipients [16]. The adverse effects of anemia in CKD patients include reduced oxygen utilization, increased cardiac output and left ventricular hypertrophy, and impairment of cognitive function and quality of life [17, 18, 10]. Due to a lack of long-term outcome studies, the optimal hemoglobin (Hb) level for children following renal transplantation is unknown; similarly, whether associations between anemia and outcomes in pre-dialysis patients apply directly to the transplant population is not known [19, 20].

Many studies on PTA in children define anemia according to the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) guidelines (2007 update: http://www2.kidney.org/professionals/KDOQI/guidelines_anemiaUP/) as Hb below the 5th percentile for age and sex [21]. The 2015 UK National Institute for Health and Clinical Excellence (UK-NICE) Anaemia Management in CKD guideline suggests a target Hb of 10.0–12.0 g/dl, with a target Hb of 9.5–11.5 g/dl for children aged <2 years [22]. In 2011 the Federal Drug Administration (FDA) recommended more conservative guidelines, suggesting initiating erythropoiesis stimulation agent (ESA) treatment only when the Hb level is <10 g/dl [23]. It is important to note that these guidelines are mainly based on adult data and not on pediatric trials. As such, data relating anemia and outcomes in pediatric renal transplant recipients are needed.

Within the framework of the European Society of Pediatric Nephrology/European Renal Association and European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry [24], we performed this study to determine the prevalence of sub-target Hb levels in European children following renal transplantation. Our aim was to identify factors associated with sub-target Hb levels in this patient population and to determine associations between Hb levels and outcomes.

Materials and methods

Data are submitted to the ESPN/ERA-EDTA Registry by country. For participation in the Registry, data on the date of birth, gender, treatment modality at start of renal replacement therapy (RRT), and changes in RRT modality are required for each patient included in the population database. In this analysis we included all patients aged <18 years who had a functioning renal allograft between 1 January 2000 and 31 December 2012 and for whom data on Hb levels had been provided by the participating country. Data on Hb levels is purely voluntary, and in this study Hb data from the following countries were analyzed: Belarus, Czech Republic, Denmark, Estonia, Finland, Greece, Iceland, Lithuania, Malta, Norway, Portugal, Romania, Serbia, Russia, Slovakia, Slovenia, Spain, Switzerland, Turkey, and the UK.

Hb levels were determined according to local practice. Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine and height according to the new Schwartz formula: 0.413 × [height (cm)/serum creatinine (mg/dl)] [25]. In order to decrease selection bias, and as recommended in the STROBE Statement [26], when the variable of interest was reported for some but not all patients at the country level we used multiple imputation for missing data, resulting in five datasets. Imputations were used when at least one of the variables was provided to estimate missing Hb levels (13.8 % missing), ESA use (yes/no) (15.5 % missing) log-transformed serum creatinine (9.6 % missing), height (5.2 % missing) and albumin (4.8 % missing), and they were based on the total dataset (age at measurement, gender, cause of renal failure, time on RRT, year of transplantation, current and preceding Hb levels, ESA use, height, and creatinine and albumin levels). Based on this procedure, 3669 patients were enrolled in the study, providing 16,170 measurements. Sensitivity analyses based on the complete datasets were similar to those based on the analyses of imputed data. Sub-target Hb level was defined by both the 2007 NKF/KDOQI definition [Hb <5th percentile (age- and sex-specific)] [21] and the 2015 UK-NICE guidelines (<2 years of age: Hb <9.5 g/dl; ≥2 years of age: Hb <10 g/dl) [22]. The cause of the renal disease (primary renal disease) was divided into nine groups according to the ERA-EDTA coding system, adapted for children [27]. Systolic and diastolic blood pressure (BP) *Z*-scores were calculated according to methods published in the National High Blood Pressure Education Program (NHBPEP) Fourth Report [28] for each subject, adjusted for age, gender and height; heights below −3 *Z*-scores were converted into −3 *Z*-scores [29].

Analyses

Data on each individual in the ESPN/ERA-EDTA Registry includes several measurements over time of both the response

variable of interest (Hb level) and determinants (e.g., age, BP). As observations on any one individual over time are not independent but correlated we used multivariable linear mixed model analyses which allowed for the adjustment of multiple measurements in the same patient as well as for possible confounders. Confounders were selected based on published confounding criteria [30]. Both a random intercept and a random slope at the patient level were calculated based on time between measurements. We used multinomial generalized estimating equation models to estimate the prevalence of sub-target Hb levels, thereby correcting for the within-patient correlations, similar to a weighted average over all the available measurements within a patient. To determine the risk of unfavorable outcomes (death or graft loss), we performed Cox regression models with time-varying exposures, thereby adjusting for late entry into the risk set. Patients were followed until 31 December 2012. *P* values of <0.05 were considered to be statistically significant. All analyses were performed in SAS version 9.3 (SAS Institute, Raleigh, NC).

Results

Patient characteristics

Information was available for 3669 patients, providing 16,170 Hb measurements (median 3 measurements per patient; 5–95th centiles: 1–11 measurements per patient) (Table 1). Most patients were male (60.2 %), with renal failure due to congenital anomalies of the kidney and urinary tract (CAKUT) (47.1 %). Of the 3669 patients, 27.1 % received a pre-emptive transplant, with 68.6 % of organs coming from deceased donors. At the time of measurement most of the patients were adolescent (75.3 %; age range 13–18 years).

Sub-target Hb levels and ESA use

According to the 2007 NKF/KDOQI classification and the 2015 UK-NICE guidelines, 49.8 % [95 % confidence interval (CI) 48.3–51.2 %] and 7.8 % (95 % CI 7.2–8.4 %) of patients, respectively, had sub-target Hb levels. When the analysis was limited to cases with a complete dataset (i.e., missing values excluded), 49.6 % (NKF/KDOQI classification) and 21.3 % (UK-NICE guidelines) of patients had sub-target Hb levels. When ESA use was included in the definition of anemia, 58.1 % (NKF/KDOQI classification; 95 % CI 56.6–58.7 %) and 16.3 % (UK-NICE guidelines; 95 % CI: 15.3–17.3 %) of patients, based on the imputed dataset, were anemic. Hb levels increased with age, and males of all ages had higher mean Hb levels than females (Table 2). Over calendar time Hb levels significantly improved by 0.21 g/dl per 5 years.

Overall, 10.7 % of transplant patients were prescribed an ESA (95 % CI 9.9–11.5 %), with use increasing over the decade of the analysis [odds ratio adjusted (OR_{adj}) 1.53 per 5 years, 95 % CI: 1.36–1.73—adjusted for age, gender, time since transplantation, cause of renal failure, and eGFR]. ESA use was significantly more likely in patients younger than 5 years than in those older than 13 years (OR_{adj} 1.36 fold increased likelihood; 95 % CI 1.01–1.82).

Graft type, time since transplantation, and graft function

Hemoglobin levels were slightly but significantly higher in pre-emptive transplant patients than in patients who had dialysis before transplantation. There was no difference in Hb levels between patients who received a renal allograft from a living or a deceased donor (Table 2). Hb levels were strongly and significantly associated with graft function (Fig. 1), with Hb levels decreasing from 12.6 g/dl in those with an eGFR of >90 ml/min/1.73 m^2 to 10.7 g/dl in those with an eGFR of <15 ml/min/1.73 m^2. ESA use was also strongly related to eGFR: compared to those with an eGFR of >90 ml/min/1.73 m^2, patients with an eGFR of between 60–89, 45–59, 30–44, 15–29, and 0–15 ml/min/1.73 m^2 had an 1.3- (not significant), 2.1-, 4.5-, 17.5-, and 77.0-fold increased use of ESA, respectively (all $p<0.05$). Hb levels were significantly associated with time since transplantation, independent of the effects of eGFR. Hb levels significantly increased from 11.4 g/dl in the first months after transplantation to 12.2 g/dl after 2 years ($P<0.001$), after adjusting for age of patient, year of transplantation, gender, cause of renal failure, and eGFR (Fig. 2). ESA use was also significantly higher in the first 6 months after transplantation (OR_{adj} 1.39; 95 % CI 1.07–1.79; $P=0.001$) than between 2 and 4 years after transplantation.

Information on the use (or non-use) of cytomegalovirus (CMV) prophylaxis and of pneumocystis prophylaxis was available for 803 and 902 patients, respectively. Among those patients administered CMV prophylaxis, mean Hb levels in the first 6 months post-transplant were 0.07 g/dl lower (95 % CI −0.27 to −0.14, not significant) than those who did not receive prophylaxis, after adjustment for time since transplantation. Similarly, after adjustment for time since transplantation, mean Hb levels in the first 6 months post-transplant were 0.07 g/dl lower among patients who were administered pneumocystis prophylaxis than those who did not receive prophylaxis (95 % CI −0.53 to −0.38, not significant).

Immunosuppressive medication and Hb levels

The majority of patients received steroids as part of their immunosuppressive regimen (93 %). Only 2 % received a mammalian target of rapamycin (mTOR) inhibitor, with the majority patients using tacrolimus (70 %), ciclosporin (29 %),

Table 1 Patient characteristics

Patient characteristics	Participating patients (*N*=3669)	Total measurements (*N*=16,170)
Age at start of RTT (years)		
<2	616 (16.8)	3686 (22.8)
2 to <5	559 (15.2)	3245 (20.1)
5 to <13	971 (26.5)	4585 (28.4)
13 to <18	1523 (41.5)	4654 (28.8)
Age at measurement (years) (median)[a,b]	12.9	12.4
Sex (*n*)		
Male	2208 (60.2)	9975 (61.7)
Treatment modality at start of RRT		
HD	904 (24.6)	3801 (23.5)
PD	1715 (46.7)	7971 (49.3)
Tx	994 (27.1)	4218 (26.1)
Unknown	56 (1.6)	180 (1.1)
Type of donor (missing for 122 patients)		
Living	1115 (31.4)	4661 (29.4)
Deceased	2432 (68.6)	11,206 (70.6)
Primary diagnostic group		
CAKUT	1728 (47.1)	7711 (47.7)
Glomerulonephritis and glomerulosclerosis	489 (13.3)	1900 (11.8)
Cystic kidney disease	399 (10.9)	1835 (11.4)
Hereditary nephropathy	290 (7.9)	1578 (9.8)
HUS	146 (4.0)	623 (3.9)
Metabolic disorders	137 (3.7)	566 (3.5)
Vasculitis	66 (1.8)	222 (1.4)
Miscellaneous	230 (6.3)	1136 (7.0)
Unknown/missing	184 (5.0)	599 (3.7)
eGFR (ml/min/1.73 m^2) (median)[a]	62.5	63.1
Height *Z*-score (cm) (median)[a]	−1.81	−1.72
Systolic blood pressure *Z*-score (mmHg) (median)[a]	0.68	0.64
Diastolic blood pressure *Z*-score (mmHg) (median)[a]	0.51	0.49

Values are presented as a number with the percentage in parentheses

RRT, Renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; Tx, transplant; CAKUT, congenital anomalies of the kidneys and urinary tract; HUS, hemolytic uremic syndrome; eGFR, estimated glomerular filtration rate

[a] Weighted according to the number of measurements

[b] 50 patients under the age of 2 years were included in the study, together providing 58 measurements

mycophenolate mofetil (MMF; 56 %), or azathioprine (37 %). The most frequent combination of immunosuppressant medications was tacrolimus + MMF + steroids (39 %), followed by tacrolimus + azathioprine + steroids (20 %), ciclosporin + azathioprine + steroids (16 %), and ciclosporin + MMF + steroids (10 %). Information on antibody induction agents is not collected for the Registry.

Patients on tacrolimus had slightly higher Hb levels (by 0.16 g/dl; 95 % CI 0.07–0.26; P=0.02) than those on ciclosporin; similarly, patients on azathioprine had slightly higher Hb levels than those on MMF (0.10 g/dl; 95 % CI 0.01–0.19; P=0.04). The lower Hb levels in users of mTOR inhibitors were not significantly different from the Hb levels of non-users. Patients treated with steroids had similar Hb levels to those not receiving steroid therapy (difference −0.04 g/dl; 95 % CI −0.15–0.07). All data were adjusted for age, gender, cause of renal failure, eGFR, time since transplantation, and use of steroids and other types of immunosuppressant medications.

Table 2 Hemoglobin levels among patient subgroups

Patient subgroups	Mean unadjusted Hb levels (g/dl)	Mean adjusted Hb levels (g/dl)
Age at measurement (years)		Adjusted for sex, PRD, Tx year, eGFR, time since Tx
0–4.9	11.3 (11.2–11.4)*	11.5 (11.4–11.6)*
5–12.9	11.8 (11.8–11.9)*	11.9 (11.9–12.0)*
13–17.9[a]	12.1 (12.1–12.2)	12.2
Sex		Adjusted for Tx year, eGFR, time since Tx
Male	12.1 (12.1–12.2)*	12.2 (12.1–12.2)*
Female[a]	11.8 (11.8–11.9)	11.8
Pre-emptive		Adjusted for age, gender, PRD, Tx year, donor source, eGFR, time since Tx
Yes	12.2 (12.1–12.3)*	12.2 (12.1–12.3)*
No[a]	12.0 (11.9–12.0)	12.0
Donor source		Adjusted for age, gender, PRD, Tx year, eGFR, time since Tx
Living donor	12.1 (12.0–12.1)	12.1 (12.0–12.2)
Deceased donor[a]	12.0 (11.9–12.0)	12.1

*Significant difference at $P<0.05$

Data are presented as the mean with the 95 % confidence interval (CI) given in parentheses

Hb, Hemoglobin; PRD, primary renal disease; Tx, transplant; eGFR, estimated glomerular filtration rate

[a] Reference group

Blood pressure, use of antihypertensives and ESA

The lowest BP *Z*-scores were observed among those with an Hb level of between 9 and 10 g/dl (Fig. 3). Patients with Hb levels of >13 g/dl had significantly higher systolic and diastolic BP *Z*-scores ($P=0.03$ and $P=0.007$, respectively). The results were similar when absolute BP levels were analyzed: children with Hb levels of >13 g/dl had an absolute systolic BP that was 1.5 mmHg higher than those with Hb levels of 11–12 g/dl (95 % CI 0.91–2.20). The use of antihypertensive medication was associated with lower Hb levels (−0.12 g/dl; 95 % CI −0.19–0.06; $P<0.05$) and a more frequent use of ESA (OR 1.55; 95 % CI: 1.27–1.88; $'P<0.05$).

Adverse outcomes

Associations between Hb level and risk of death, graft loss, and death + graft loss combined are shown in Table 3. Graft loss or death with a functioning graft occurred in 651 patients. According to all guidelines, sub-target Hb levels, adjusted for age at measurement, gender, cause of renal failure, year of transplantation, eGFR, and time since transplantation, were associated with a higher risk of death + graft loss combined or graft loss alone. Additional adjustment for BP did not change these results. When using the UK-NICE guidelines the risk of death or graft loss increased by 3.8-fold (95 % CI 2.5–5.7; $P<0.001$) and by 1.7-fold (95 % CI 1.2–2.2;

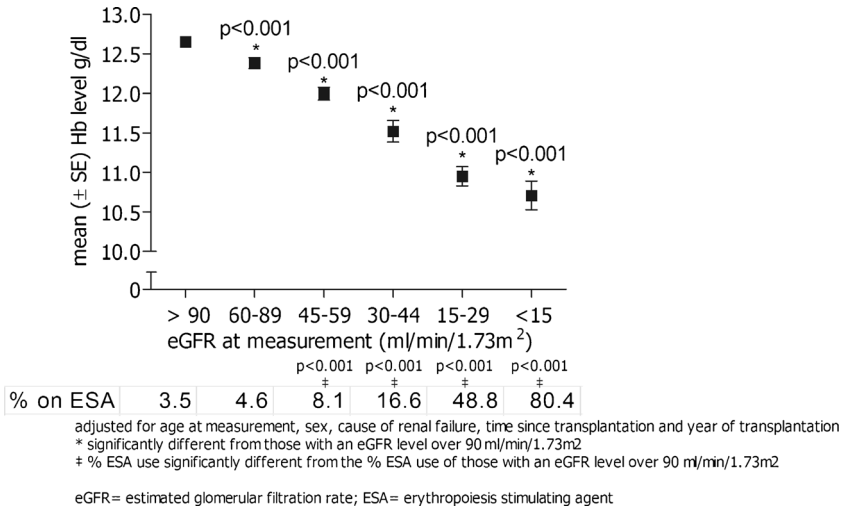
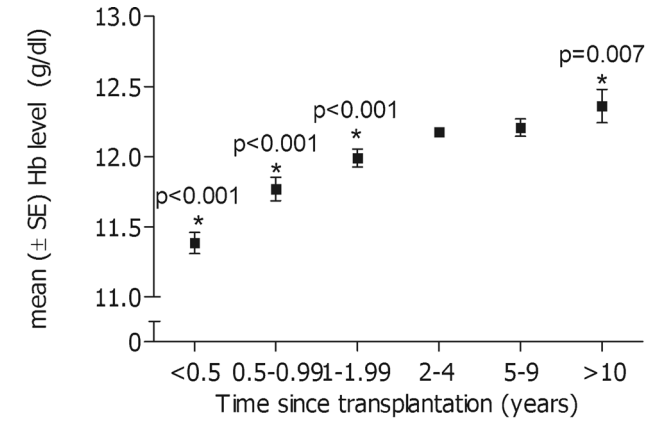


Fig. 1 Association between allograft function and hemoglobin (Hb) levels. The percentage of patients using an ESA for each eGFR group is indicated in the *table under the graph*. *SE* Standard error



% on ESA	15.4	8.7	7.1	8.5	11.6	16.1

adjusted for age at measurement, sex, cause of renal failure, eGFR and year of transplantation
* significantly different from 2 to 4 years after transplantation
‡ % ESA use significantly different from the % ESA use between 2 to 4 years after transplantation

eGFR= estimated glomerular filtration rate; ESA= erythropoiesis stimulating agent

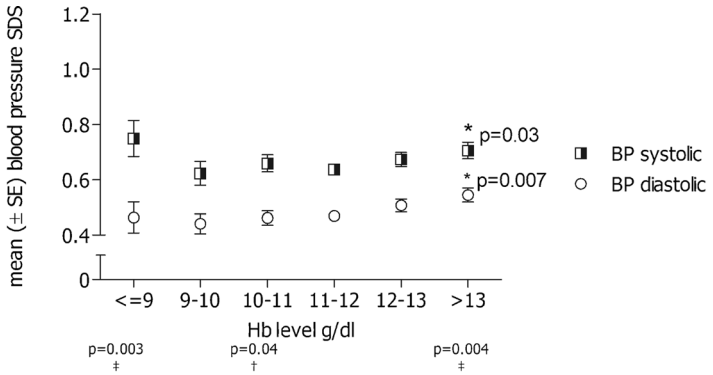
Fig. 2 Association between time since transplantation and hemoglobin (Hb) levels. The percentage of patients using an ESA at the different time periods is indicated in the *table under the graph*

P<0.001) when the NKF/KDOQI definition of anemia was used.

Discussion

Anemia is commonly observed among pediatric renal transplant patients. Using the UK-NICE guidelines (2015), in which anemia in children is defined as Hb levels of <10 g/dl in children aged 2 years or older and <9.5 g/dl in children younger than 2 years, 7.8 % of children in this study had sub-target Hb levels. When we used a definition of Hb <5th centile for age and gender, the prevalence of sub-target Hb levels in our study was 50 %, increasing to 58 % when the use of ESA was included with normal Hb levels in this definition. These data are similar to those reported in other studies using the KDOQI definition including the use of ESA, with the reported prevalence ranging between 61 and 82 % [8, 4, 13].

As expected, Hb levels were strongly associated with renal allograft function. Studies in adults have shown that patients with CKD following renal transplantation have lower Hb levels for any given level of function compared with pre-transplant CKD patients [31], suggesting that potentially modifiable factors may be at play. Hb levels were lowest in the first 6 months post-transplantation. Blood loss can occur during transplant surgery and during other invasive procedures performed more commonly soon after transplant. Moreover,



% on ESA	41.8	25.3	16.9	11.8	8.7	5.3
% on antihypertensives	60.1	63.5	56.6	52.5	53.4	56.3

adjusted for age at measurement, sex, cause of renal failure, eGFR, year of transplantation, time on transplantation, esa-use
* significantly different from Hb levels 11.1 to 12 g/dl
‡ % ESA use significantly different from the % ESA use of those with Hb levels between 11.1 and 12.0 g/dl
† % using antihypertensives significantly different from the % using antihypertensives among those with Hb levels between 11.1 and 12.0 g/dl

eGFR= estimated glomerular filtration rate; ESA= erythropoiesis stimulating agent

Fig. 3 Association between hemoglobin (Hb) levels and blood pressure (*BP*) *Z*-score. This association remained after adjustment for use of antihypertensive and immunosuppressive agents and when not adjusted for eGFR. The percentage of patients using an ESA or an antihypertensive medication for the different blood pressure levels is indicated in the *table under the graph*

Table 3 Risk of death and graft loss by hemoglobin level

Risk factors	Graft loss		Death		Death + graft loss combined	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
UK-NICE						
Anemic	4.79 (3.07–7.49)	<0.001	1.26 (0.42–3.72)	0.68	3.78 (2.53–5.68)	<0.001
Non-anemic	1.00	Reference	1.00	Reference	1.00	Reference
NFK/KDOQI						
Anemic	1.67 (1.20–2.31)	0.002	1.70 (0.87–3.32)	0.12	1.66 (1.24–2.23)	<0.001
Non-anemic	1.00	Reference	1.00	Reference	1.00	Reference
Hb groups (mg/dl)						
<9	1.89 (1.15–3.10)	0.01	2.69 (0.84–8.57)	0.09	2.05 (1.31–3.22)	0.002
9–10	1.81 (1.16–2.83)	0.01	1.74 (0.64–4.76)	0.28	1.82 (1.21–2.74)	0.004
10–11	1.26 (0.83–1.89)	0.28	2.00 (0.88–4.55)	0.10	1.37 (0.96–1.98)	0.09
11–12	1.00	Reference	1.00	Reference	1.00	Reference
12–13	0.71 (0.44–1.14)	0.16	0.69 (0.24–2.01)	0.50	0.71 (0.47–1.08)	0.11
>13	0.49 (0.28–0.85)	0.01	1.04 (0.41–2.66)	0.94	0.59 (0.37–0.93)	0.02

HR, Hazard ratio; UK-NICE 2015, UK National Institute for Health and Clinical Excellence anaemia management guideline; NKF/KDOQI 2007, National Kidney Foundation//Kidney Disease Outcomes Quality Initiative clinical practice recommendations

doses of immunosuppressive agents are likely to be highest during the first few months post-transplant, during which period antiviral agents for CMV prophylaxis and antibiotic prophylaxis for *Pneumocystis carinii* pneumonia infection are most likely to be used, possibly contributing to early PTA [32].

The choice of immunosuppressive agent(s) had a limited but statistically significant effect on Hb level. MMF and azathioprine are both associated with myelosuppression [6], although in this study Hb levels were slightly but significantly lower in patients on MMF therapy compared to those receiving azathioprine. Ciclosporin has been shown to inhibit ESA release in vitro while hematologic toxicity has only rarely been attributed to tacrolimus [6, 33]. MMF doses are lower when prescribed in combination with tacrolimus compared to ciclosporin therapy, which might also explain the lower Hb levels seen with ciclosporin use, although analyses were adjusted for other types of immunosuppression in use and information on dosing was not available. Reduced allograft function alters the metabolism of MMF, leading to higher mycophenolic acid (MPA) exposure [34], which may potentiate myelosuppression and anemia. Monitoring of the MPA level in patients with reduced GFR may allow optimization of MMF dosing. Patients treated with an mTOR inhibitor (sirolimus or everolimus) showed a trend towards lower Hb levels, although the overall number of patients on these therapies was low. mTOR inhibitors have a dose-dependent effect on red blood cell production [6, 35, 36], which is further potentiated in patients receiving both an mTOR inhibitor and MMF [37].

More patients with higher BP *Z*-scores received antihypertensive medications compared to those with lower BP *Z*-scores, which is in keeping with the possibility that the use of renin–angiotensin system antagonists, which are mildly myelosuppressive, may have affected Hb levels in this population [38], although we did not have information on the type of antihypertensive agent used. Additionally, fluid-overloaded patients may have high BP with low Hb levels due to hemodilution. Fluid overload has recently been suggested to contribute to ESA-resistant anemia in a large study of children undergoing chronic peritoneal dialysis [39]. Notably, however, the inverse association of Hb and BP persisted after correcting for eGFR. Finally, an intrinsic effect of anemia on BP is possible since tissue hypoxia leads to vasodilatation, and a resultant increase in sympathetic tone and arterial stiffness, which in turn can cause hypertension [14].

In this study, low Hb levels were associated with both patient death and graft loss. Previous studies have reported a spectrum of associations of PTA with graft and patient outcomes, including no association with graft loss or death [40], an association with graft loss only [16], and an association with increased graft loss + mortality combined [41, 20]. In our study, Hb levels of >12 g/dl were associated with neither better nor worse graft, patient or combined graft + patient survival compared to outcomes in patients with Hb levels of between 11 and 12 g/dl. It should be noted that we were unable to evaluate other anemia endpoints, such as physical exercise capacity, quality of life, or school performance, which might be improved by higher Hb levels.

Our study has several limitations. First, we obtained data from patients with highly variable treatment duration, and Hb levels were not available for all children. To minimize bias from missing data we only analyzed those patients and countries from which at least some data were reported and imputed missing data. Comparison of imputed results with complete case-only analysis did not reveal important differences, which suggests that missing data were missing at random, rather than not at random [42]. We did not have information on immunosuppression, ESA or other medication dosing, and iron status or iron supplementation, and we had only very limited information for ferritin and transferrin levels. Due to the observational character of the study, we do not claim cause–effect relationships for the factors found associated with sub-target Hb levels.

Conclusions

When defining anemia according to the 2015 UK-NICE guidelines, 8 % of European pediatric allograft recipients have sub-target Hb levels. Using the 2007 NKF/KDOQI definition increases the prevalence of sub-target Hb levels to almost half of this population. Increasing ESA use over the past decade suggests that awareness of the importance of anemia in transplant patients is improving; further optimization of ESA therapy could help to further reduce the occurrence of PTA. Higher Hb levels were associated with better graft and patient survival. In this study, important risk factors for the development of sub-target Hb levels included renal allograft function, female gender, use of antihypertensive agents, and the type of immunosuppressant used. Optimizing renal allograft function may help prevent sub-target Hb levels post-transplant, and over the past 2 decades, the use of newer immunosuppressive agents has led to improved renal allograft survival. However, anemia is a common side effect of some of these agents, such as MMF and mTOR inhibitors. Thus, continuation of iron and ESA therapy, particularly in the first few months following transplantation, should be considered in pediatric renal transplant recipients.

Future studies are needed to determine the impact of sub-target Hb levels following renal transplantation on outcomes such as school attendance and performance and patient-reported quality of life.

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Conflict of interest statement The authors declare that there are no conflicts of interest.

Ethical approval As this study is based on anonymized Registry data, ethical approval was not required.

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