

# The Prevalence and Risk Factors of Anemia in Children with Renal Transplant

## Böbrek Nakli Olan Çocuklarda Aneminin Sıklığı ve Risk Faktörleri

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### ABSTRACT

**Objective:** Anemia is commonly observed during the follow-ups of patients with renal transplantation. There is not enough information on anemia observed in children with renal transplantation. The aim of this study was to evaluate the prevalence and risk factors of anemia in children with renal transplantation on the short and long-term post-transplantation period.

**Material and Methods:** This study was performed in children who underwent renal transplant at Ege University. Anemia was defined as having a value less than 2 Standard Deviation for hematocrit levels according to age.

**Results:** In the early post-transplant period, the incidence of anemia was found as 18%. Late post transplant anemia rate was detected as 27.5% at 60 months. The incidence of anemia was 18.4%, 23.3%, 23% and 27.5%, at 24, 36, 48 and 60 months after transplantation, respectively. Anemia was detected at least once in 71 (67.6%) patients at any point of the follow-up period. There was no correlation between Angiotensin Converting Enzyme inhibitor therapy and anemia at any post-transplant time. Donor type and donor age were not significantly associated with late anemia. On the other hand, late anemia was significantly associated with a history of rejection.

**Conclusion:** Low estimated Glomerular Filtration Rate, longer duration of post-transplantation and rejection attacks are the risk factors for anemia in pediatric renal transplant recipients.

**Key Words:** Anemia, Children, Renal transplantation

### ÖZET

**Amaç:** Renal transplantlı hastaların takibinde anemi yaygın görülmektedir. Renal transplantlı çocuklarda görülen anemi hakkında yeterli bilgi bulunmamaktadır. Bu çalışmanın amacı; transplantasyon sonrası çocuklarda kısa ve uzun dönemde ortaya çıkan aneminin risk faktörlerini ve prevalansını değerlendirmektir.

**Gereç ve Yöntemler:** Bu çalışma, Ege Üniversitesi'ndeki böbrek nakilli çocuklarda yapılmıştır. Hematokrit düzeyinin yaşa göre 2 standart deviasyon altında olması anemi olarak tanımlanmıştır.

**Bulgular:** Erken post transplant dönemde anemi insidansı %18 bulundu. Geç post transplant dönemde ortalama olarak 60 ayda %27.5 oranda anemi saptandı. Anemi insidansı post transplant 24,36,48 ve 60. aylarda sırasıyla %18.4, %23.3, %23 ve %27.5 bulundu. Takip süresince herhangi bir zamanda 71 (%67.6) hastada en az bir kez anemi tespit edildi. Transplantasyon sonrası herhangi bir dönemde kullanılan ACE inhibitörü ile anemi arasında ilişki saptanmadı. Donör tipi ve yaşı ile geç anemi arasında anlamlı bir ilişki bulunmadı. Diğer yandan, geç dönem anemi rejeksiyon öyküsüyle anlamlı ilişkili bulundu.

**Sonuç:** Renal transplant alıcısı olan çocuklarda tahmini glomerül filtrasyon hızının düşüklüğü, transplantasyon sonrası sürenin uzunluğu ve rejeksiyon atağı anemi için risk faktörleridir.

**Anahtar Sözcükler:** Anemi, Çocuk, Renal transplantasyon

## INTRODUCTION

Renal transplantation provides considerable improvement in the quality of life when compared to dialysis (1,2). Advances in transplantation treatment, especially in immunosuppressive drugs, and the follow-up have shown increased patient and graft survival rates (1). However chronic immunosuppressive therapy in renal transplant recipients have both short and long-term side effects (3). Even when the grafts are functioning, their glomerular filtration rates vary. Excretory and endocrine functions of the kidneys may also be insufficient. Thus, anemia may be persistent in patients with suboptimal graft function (1, 3).

Anemia is commonly observed during the follow-ups of patients with renal transplantation (4). Increase of hemoglobin levels is expected after successful renal transplantation. However, anemia was observed in almost one-third of the cases (1, 5-7). Anemia has a negative impact on long-term outcome in kidney transplant recipients (1, 8). Although the presence of anemia is known to be a problem after renal transplantation, there is still not enough data on the prevalence (3, 5, 9, 10). Especially, insufficient data on anemia, which was associated with early and long-term transplantation period in children, was reported (4,11-13). The aim of this study is to evaluate the prevalence and risk factors of anemia in children with renal transplantation during the early and long-term post transplantation period.

## MATERIAL and METHODS

This study was performed in children who underwent renal transplant at Ege University. Children underwent re-transplantation, patients with multiple organ transplantation (liver-kidney transplants), patients who died, and patients with less than one year from the transplantation was excluded from the study.

We recorded data on age, gender, donor type, ischemia time and main causes of ESRD from the patients' charts. Also, graft function, episodes of acute rejection, immunosuppressive drugs, and graft and patient survival rates were evaluated. Current demographical, clinical and laboratory data for of the patients were evaluated including hematocrit, hemoglobin, serum creatinine and creatinine clearance.

Anemia was defined as having value less than 2 Standard Deviation of hematocrit levels according to age (13).

Patients were divided into two groups according to the duration of post-transplant period. Early post-transplant anemia (PTA) was defined as anemia occurring during the first 6 months after transplantation (PTA), while late PTA was defined as anemia occurring after 6 months. Creatinine clearance was calculated by using the Cockcroft-Gault formulae (14).

## MEDICAL MANAGEMENT

Immunosuppressive therapies included steroids, cyclosporine, tacrolimus, mycophenolate mofetil (MMF), azathioprine or sirolimus.

Desirable serum CsA levels for the first month were 350 to 400 ng/mL, and a target trough levels were 200 to 250 ng/mL 6 months after transplantation. In addition, tacrolimus trough levels for the first 2 weeks were 15 to 20 ng/mL, and its serum level was tapered to 5 to 7 ng/mL after 6 months. Antihypertensive drugs were evaluated.

### Statistical analysis

The data were analyzed using the statistical software SPSS version 13.0 (SPSS, Chicago Ill USA). The Chi-square test was used to test the difference between the proportions in two or more groups. Risk factor analysis was performed with multivariate linear regression.

## RESULTS

A total of 105 patients were included in this study. Demographic features of the patients were shown in Table I. There were 53 (50.5%) male patients and 52 (49.5%) female patients. A total of 56 (53.3%) patients received a kidney from a cadaveric donor, and 49 (46.7%) received a kidney from a living donor. The mean age of the recipients was  $95.96 \pm 78.7$  (5-218 month) and mean donor age was  $34.5 \pm 13.2$  years (1.5-64 years). Three patients died during the study. All other patients were followed-up for more than 12 months [median 69 months (range 12–181 months)].

The most common underlying kidney disease was vesicoureteral reflux (n=21). Others were focal segmental glomerulosclerosis (n=18), chronic pyelonephritis (n=11), dysplastic kidney (n=6), PUV (n=4), nephronophthisis (n=4), RPGN (n=4) and other diseases (n=37). Nephrological causes in 49.5% (n=52) of patients, urological reasons in 41% (n=43) of patients, and unknown etiology in 9.5% (n=10) of patients were found in our study (Table I).

The mean hemoglobin level was found as  $11.9 \pm 1.7$  g/dL in the first 6 months. During the 60 months of follow-up, mean hemoglobin concentrations were detected as  $11.9 \pm 1.9$  g/dl. These results were found to be significantly higher than those at the time of transplantation ( $p < 0.01$ ).

The prevalence of anemia was found as 69.5% at the time of transplantation. This rate was reduced to 39% in the first month and then gradually decreased in the course of the follow up. The incidence of anemia in the early post-transplant period (early PTA) was found as 18%. The prevalence of anemia (late PTA) was detected as 27.5% at 60 months. Among the 9 patients followed up to 120 months, 4 had anemia (44.5%). The

incidence of anemia varied after the 6th month, while a gradual decrease was seen in the first 6 months of post-transplant period. The incidence of anemia was 18.4%, 23.3%, 23% and 27.5%, at 24, 36, 48 and 60 months after transplantation, respectively (Table II).

**Table I:** Demographic features of patients.

	Mean (95% CI) or Count (Frequency)
<b>Gender</b>	
Male	53 (50.5%)
Female	52 (49.5%)
<b>Cadaveric donor</b>	56 (53.3%)
<b>Living donor</b>	49 (46.7%)
<b>Cause of ESRD</b>	
Nephrologic	52 (49.5%)
Urologic	43 (41%)
Unknown	10 (9.5%)
<b>Pre-transplant time on dialysis</b>	4.3 ± 1.5 years
<b>Hemoglobin (g/dl)</b>	12.1 (8.1-13.2)

ESRD: End-Stage Renal Disease.

Anemia was detected at least once in 71 (67.6%) patients at any point of the follow-up period. Angiotensin converting enzyme (ACE) inhibitors or ARB was used in 29 (27.6%) patients. Four patients (3.8%) were receiving ACE inhibitors at the 6th post transplant month, and 11 (10.4%) patients at 12th month. There was no correlation between ACE inhibitor therapy and anemia at any post-transplant time.

Donor type and donor age were not significantly associated with late PTA. On the other hand, late PTA was significantly associated with history of rejection and eGFR (Table III).

## DISCUSSION

Renal transplantation is the best treatment modality of choice for patients with chronic renal failure (1, 2). Patients with a well-functioning renal graft will enjoy a better quality of life compared to long-term hemodialysis or peritoneal dialysis (1, 15). Anemia is a significant complication of renal failure and is expected to resolve after transplantation (16). Hemoglobin levels generally increase after transplantation. However, anemia may persist in renal transplant recipients with suboptimal graft function (3). It

**Table II:** Risk factors of late post-transplant anemia at 60 months.

	Total population (n = 58)	Presence of anemia (n =16)	Absence of anemia (n =42)	p-Value
<b>At last visit age (years) (mean±SD)</b>	15.3±10.3	14.8±9.2	15.3±10.1	NS
<b>Transplantation time (months)</b>	95.96±78.7	94.6±70.2	90.8±75.3	NS
<b>Pre-transplant time on dialysis</b>	4.3 ±1.5	4.5±1.2	3.7±0.9	NS
<b>Creatinine clearance (mean±SD)</b>	82.8 ±10.2	58.9±14.5	79.8±9.5	P<0.01
<b>Cadaveric donor</b>	35 (53.3)	9 (56.3)	26 (61)	NS
<b>Living donor</b>	23 (46.7)	7 (43.7)	16 (39)	
<b>Donor age (years) (mean±SD)</b>	34.5±13.2	33.44±14	35.01±12.6	NS
<b>History of rejection</b>	17 (29.3)	12 (75)	5 (12)	P<0.01

**Table III:** Prevalence of anemia according to post-transplant time.

	Anemic n (%)	Non-anemic n (%)	Total patients
<b>0 month</b>	73 (69.5)	32 (30.5)	105
<b>Early post-transplant</b>			
<b>1 month</b>	41 (39)	64 (61)	105
<b>3 month</b>	25 (24)	80 (76)	105
<b>6 month</b>	19 (18)	86 (82)	105
<b>Late post-transplant</b>			
<b>12 month</b>	18 (17)	87 (83)	105
<b>24 month</b>	20 (21.7)	72 (31.9)	92
<b>36 month</b>	17 (22)	60 (78)	77
<b>48 month</b>	15 (23)	50 (77)	65
<b>60 month</b>	16 (27.5)	42 (72.5)	58
<b>120 month</b>	4 (44.5)	5 (55.5)	9

is still a common problem after solid organ transplantations (1, 13, 16).

Common causes of PTA (5, 9, 17-22) are blood loss at the time of operation, the persistent effects of uremic toxins, low EPO levels, EPO resistance, iron deficiency, and side effects of immunosuppressive drugs. Immunosuppressive drugs and decreased graft function lead to late PTA (10,22-24). So far, studies on the late PTA are not enough (1, 7, 13, 23). Published data is limited on the prevalence of PTA; it varies in different studies (1, 10, 12, 25-27).

Transplant European Survey on Anemia Management (TRESAM) has defined this value as 38.6% (1). A British study concluded that the prevalence of anemia was 53% at 12 months after the kidney transplantation (4). However, in a Japanese study on the prevalence of PTA, the reported percentage was 20% (25). An American study reported this ratio as 26% within 5 years after transplant (23). The prevalence of late PTA was 39.5% (27) in another study. Most of these were adult studies. Yorgin et al. (13) reported that the prevalence of anemia was 84.3% in the first month of the post-transplant period. They also noted that the prevalence of PTA at 6 months and 60 months was 64.2% and 82.2%, respectively. Kausman et al. (16) found the anemia prevalence as 60% in pediatric recipients. In our study, 39% of the patients were anemic at the first post-transplant month. In the early post-transplant period, anemia prevalence was found as 18%, while it was 27.5% at 60 months in the late post transplant period. In addition, 44.5% of the patients were anemic at the 120 months.

Rejection and renal dysfunction are associated with the development of PTA, which is considered as one of the major risk factors (1, 3, 23, 27-29, 30-33). Chronic allograft nephropathy can occur a long time after transplantation and that may lead to the development of PTA (27). In our study, low eGFR was found as a risk factor for PTA, at the 60 months of transplantation. This is similar to the majority of literature published on PTA suggesting renal dysfunction as a major cause of PTA especially at 60 months and 120 months.

The prevalence of PTA increases over time after transplantation. Increased prevalence of anemia in the late post-transplant was seen in comparison with the early post-transplant period as reported in the literature (23). Our results also support these data, as the incidences were 18% during the early period, and then rose to 27.5% at 60 and 44.5% at 120 months.

The effect of ACE/ARB on hemoglobin levels is a matter of debate in renal transplant recipients (12). In our study, there was no relation between ACE/ARB and late or early PTA. Some studies provide consistent results on PTA and ACEI/ARB but this study was not compatible with the others (26, 32, 34-36).

In conclusion, this study has presented data from a large cohort of pediatric renal allograft recipients from a transplantation

center. Early and late PTA in pediatric renal transplant recipients are common complications, and are under-recognized (23). Low eGFR, longer post-transplant time and rejection are the risk factors for anemia in pediatric renal transplant recipients.

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