Nephro-Urol Mon. 2011;3(3):172-176
Nephro-Urology Monthly
Journal home page: www.NUmonthly.com

# Late anemia in pediatric kidney transplant recipients: Prevalence and risk factors

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ARTICLE INFO

*Article Type:*
Original Article

*Article history:*
Received: 10 Feb 2011
Revised: 20 Feb 2011
Accepted: 5 Mar 2011

*Keywords:*
Child
Kidney
Transplantation
Anemia

ABSTRACT

*Background:* Anemia is a frequent complication among pediatric transplant recipients. However, limited published studies are currently available about anemia in these patients.
*Objectives*: We conducted a retrospective study to determine the prevalence and risk factors of late post-transplant anemia (PTA) among pediatric kidney transplant patients.
*Patients and Methods:* A total of 78 kidney transplant patients ≤ 18 years old were enrolled. Prevalence of late PTA, beyond 1 year after transplantation, in children was evaluated between 2008 and 2011. We considered anemia as hemoglobin concentration of ≤ 11 mg/dl and less than 10 mg/dl as a severe anemia. Both univariate and multivariate analyses were performed to determine the correlation of PTA with other risk factors such as renal allograft function and other laboratory parameters.
*Results:* The mean age of recipients was 10 ± 3 years (range: 3 to 18 years); 58% male and 42% female. The prevalence PTA in this survey was 15.4% (n = 12). The prevalence of late PTA was not different in both boys and girls (p = 0.38). At univariate analysis, a significant relationship was seen between serum creatinine concentrations and Hb levels (P = 0.005, r = 0.32) and there was also a significant relationship between serum Hb and cyclosporine trough blood level (p = 0.009, r = 0.29) and 2 hour post dose level of cyclosporine (p = 0.03, r = 0.29). At multivariate logistic regression after adjustment for other factors, however, renal allograft impairment was the only a risk factor for late PTA (P = 0.05, EXP (B) = 2.5; 95 % CI = 1.0- 6.3).
*Conclusions:* The prevalence of late PTA in our children was lower than previously reported in literature from both adult and pediatric transplant patients.



▸ *Implication for health policy/practice/research/medical education:*
This article focuses on anemia which can be occurred during the late post-transplant period that has received substantially less attention.

▸ *Please cite this paper as:*
Einollahi B, Rostami Z, Teimoori M, Beiraghdar F. Late anemia in pediatric kidney transplant recipients: Prevalence and risk factors. *Nephro-Urol Mon.* 2011;**3**(3):172-176.

## 1. Background

Anemia is one of the main common problems in patients with chronic kidney disease (1). Although PTA is a common problem in pediatric transplant patients (2), surprisingly limited published reports in literature are currently available. Yorgin *et al.* detected an extremely high prevalence of anemia in pediatric renal transplant recipients, only 4/175 cases (2.7%) were not anemic and 23/175 individuals had anemia during the early post-transplant period were not anemic afterwards (3). In

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another study, the prevalence of anemia in kidney recipients younger than 20 years old, was also high (61%) (4). Other investigations showed that the prevalence of PTA among renal transplant recipients varied 25–83% (3, 5, 6).

Importantly, PTA is associated with greater morbidity and mortality (7). Anemia may lead to left ventricular hypertrophy and congestive heart failure (8); hence, it results in higher risk for cardiovascular disease among pediatric transplant patients (9). Thus, PTA is an important factor that increases mortality because of cardiovascular risks in this population (10, 11). Moreover, low hemoglobin (Hb) levels are allied with amplified risk for hospitalizations and death (12). Furthermore, anemia is associated with poorer growth status in children recipients (13). Some studies have revealed that anemia may predict and accelerate the renal allograft dysfunction by restriction of oxygen delivery to kidney (14). In a study, PTA at one year after renal transplantation was an independent risk factor for death and anemic recipients had higher risk to lose the graft (15). Consequently, sufficient treatment of anemia may prevent and attenuate the progression of renal allograft impairment (8). There is scarce published data on anemia in children which proposes that this prevalence can be higher than the prevalence of anemia after transplantation in the adult renal recipients by several times (3, 16).

## 2. Objectives

This study aimed to estimate the prevalence of PTA and associated risk factors in pediatric kidney recipients.

## 3. Patients and Methods

### 3.1. Subjects

In a retrospective study, 78 pediatric kidney recipients aged ≤ 18 years old who underwent kidney transplantation for the first time with at least a minimum time of 1 year after transplantation (4 ± 2 years) were included. The prevalence of late anemia, > 1 year after transplantation, was determined and risk factors for this complication were evaluated. Data collection was done in Baqiyatallah Transplant Center, Tehran, IR Iran between March 2008 and November 2011. Living and deceased kidney transplants were both included. The present study was approved by the local Ethics Committee of the Baqiyatallah University of Medical Sciences.

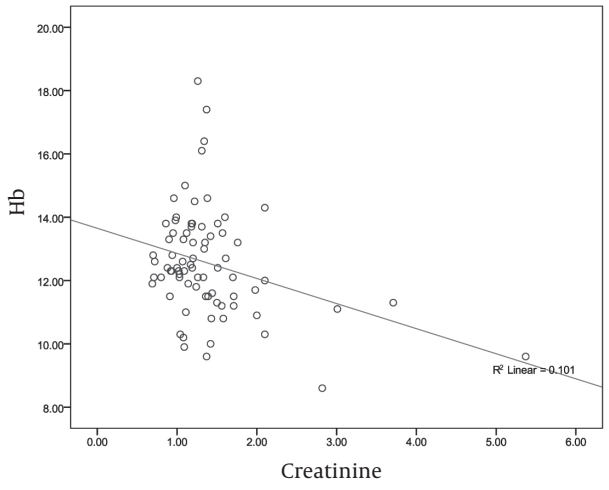


**Figure 1.** Relation between creatinine level and Hb values of children

### 3.2. Data collection

The clinical information was retrieved from both paper records and electronic databases. Data gathered for all patients included age and sex of recipient and donor; donor source (living and deceased); blood urea and serum creatinine (Cr) levels; hemoglobin (Hb); trough (C0) and 2-hr post-dose (C2) levels of cyclosporine; fasting blood sugar (FBS); lipid profile including triglycerides, cholesterols, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), serum electrolytes such as sodium, potassium, calcium and phosphorus, alkaline phosphates (ALP) and plasma uric acid level.

### 3.3. Definition

We considered anemia as Hb concentration of ≤ 11 g/dl in both genders, according to Kidney Disease Outcome Quality Initiative (KDOQI) guidelines (17); and severe anemia was defined as Hb level of ≤ 10 mg/dl. Thus, the patients were divided into three groups according to the Hb levels; non anemic group, cases with mild to moderate anemia (Hb concentration of 11 to 10 mg/dl), and those with severe anemia (Hb concentration less than 10 mg/dl).

### 3.4. Immunosuppressant regimen

Maintenance immunosuppression in all recipients was primarily based on CsA. Majority of patients also received mycophenolate mofetil (MMF) and prednisolone, except those who withdrew these drugs due to their side effects or individuals undertaken in taper of steroid pro-

**Table 1.** Baseline characteristic of patients

| Variable | |
|---|---|
| **Number of patients** | 78 |
| **Age of recipient** (yr) (mean ± SD) | 10 ± 3 |
| **Time since transplantation** (yr) (mean ± SD) | 5 ± 4 |
| **Age of Donor** (yr) (mean ± SD) | 25 ± 5 |
| **Sex of recipient** (%) | |
| **male** | 58 |
| **female** | 42 |
| **Sex of Donor** (%) | |
| **male** | 72 |
| **female** | 28 |
| **Donor source** (%) | |
| **DD** [a] | 3 |
| **LD** [b] | 97 |

[a] DD: Deceased Donor
[b] LD: Living Donor

**Table 2:** Relation of baseline characteristic of patients with anemia

| Characteristic | Non Anemia | Mild to Moderate Anemia | Severe Anemia | p-value |
|---|---|---|---|---|
| **Age of recipient** (yr) (mean ± SD) | 15 ± 3 | 15 ± 2 | 13 ± 2 | 0.35 |
| **Age of Donor** (yr) (mean ± SD) | 25 ± 6 | 23 ± 1 | 24 ± 1 | 0.61 |
| **Follow up time** (yr) (mean ± SD) | 4 ± 2 | 4 ± 2 | 4 ± 2 | 0.63 |
| **Donor Sex** [No. (%)] | | | | 0.80 |
| **Female** | 27 (36.4) | 4 (5.1) | 2 (2.6) | |
| **Male** | 39 (50) | 3 (3.8) | 3 (3.8) | |
| **Recipient Sex** [No. (%)] | | | | 0.90 |
| **Female** | 17 (89.5) | 1 (5.3) | 1 (5.3) | |
| **Male** | 41 (83.7) | 5 (10.2) | 3 (6.1) | |
| **Donor Type** [No. (%)] | | | | 0.68 |
| **Deceased** | 2 (100) | 0 (0) | 0 (0) | |
| **LURD** [a] | 49 (80.3) | 7 (11.5) | 5 (8.2) | |
| **LRD** [b] | 10 (100) | 0 (0) | 0 (0) | |

[a] LURD: Living unrelated donor
[b] LRD: Living related donor

**Table 3.** Relation of laboratory test with anemia

| | **Hb** (In all patients) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Mean ± SD** | **Correlation Coefficient** | **p-value** [a] | **Non Anemia** (mean ± SD) | **Mild to Moderate Anemia** (mean ± SD) | **Severe Anemia** (mean ± SD) | **p-value** |
| **Potassium** | 4.2 ± 0.4 | 0.02 | 0.88 | 4.2 ± 0.4 | 4.1 ± 0.3 | 4.4 ± 0.6 | 0.50 |
| **Phosphorus** | 4.4 ± 0.9 | -0.15 | 0.21 | 4.4 ± 0.9 | 4.0 ± 0.9 | 4.7 ± 0.7 | 0.44 |
| **Sodium** | 139 ± 3 | -0.03 | 0.79 | 139 ± 3 | 139 ± 2 | 138 ± 4 | 0.90 |
| **Calcium** | 9.3 ± 0.5 | 0.12 | 0.30 | 9.3 ± 0.4 | 9.1 ± 0.4 | 9.5 ± 0.6 | 0.49 |
| **Triglyceride** | 151 ± 81 | -0.02 | 0.87 | 147 ± 70 | 169 ± 71 | - | 0.03 [b] |
| **Cholesterol** | 174 ± 41 | -0.33 | 0.031 | 171 ± 37 | 187 ± 45 | - | 0.10 [b] |
| **Alkaline phosphatase** | 479 ± 388 | -0.13 | 0.38 | 485 ± 418 | 316 ± 189 | 635 ± 272 | 0.39 |
| **Blood urea** | 44 ± 19 | -0.23 | 0.04 | 43 ± 18 | 50 ± 22 | 53 ± 21 | 0.35 |
| **Uric Acid** | 6.6 ± 2.1 | 0.11 | 0.41 | 6.7 ± 2.0 | 6.5 ± 2.4 | 5.5 ± 2.6 | 0.51 |
| **Creatinine** | 1.39 ± 0.68 | -0.32 | 0.005 | 1.30 ± 0.49 | 1.47 ± 0.43 | 2.41 ± 1.78 | 0.001 |

[a] Spearman's Correlation test
[b] Due to missing date in patients with severe anemia, we used independent sample-t Test between non anemic and mild to moderate anemia groups.

tocol. According to our policy, the amount of CsA given to transplant patients was mostly based on blood levels of drug. CsA monitoring using its C0 and C2 blood levels was periodically performed at different times and dose adjusted as necessary. According to our policy, target C0 blood level at the first three months was 100 to 250 ng/ml and then tapered to 100-150 ng/ml by one year; while we used C2 target levels of 800 to 1000 ng/mL in months one to three after transplantation and C2 targets of 400 to 600 ng/mL for subsequent months.

### *3.5. Statistical analysis*

The SPSS version 17.0 for Windows was used in all the analyses. Quantitative variables were expressed as mean ± standard deviation (SD), while qualitative variables were shown by number and percentage. The kolmogorov-simirnov test showed that Hb levels were not distributed normally; hence, spearman's correlation analysis was used to study correlations between Hb concentrations with numeric variables. Comparisons between the categorical variables were also performed using the Chi square test or the Fisher exact test. Multivariate logistic regression model was performed to determine categorical and continuous risk factors for PTA. Statistical significance was considered as a p-value less than 0.05.

## 4. Results

### *4.1. Demographical setting*

A total of 78 patients were recruited within the period of study, of which 97% were from living donors (83% unrelated and 14% related) and 3% from deceased donors. The mean age of recipients was 10 ± 3 years (range: 3 to

**Table 4.** Univariate correlations between cyclosporine blood level and Hb

| | **Hb** (In all patients) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Mean ± SD** | **Correlation Coefficient** | **p-value** [a] | **Non anemia** (Mean ± SD) | **Mild to moderate anemia** (Mean ± SD) | **Severe anemia** (Mean ± SD) | **p-value** |
| **Trough level of CsA** (ng/ml) | 121 ± 74 | 0.295 | 0.009 | 124 ± 78 | 101 ± 42 | 94 ± 38 | 0.56 |
| **2-hr post dose CsA** (ng/ml) | 485 ± 140 | 0.292 | 0.03 | 495 ± 142 | 435 ± 135 | 441 ± 141 | 0.55 |

[a] Spearman's Correlation test.

18 years); 58% male and 42% female *(Table 1)*. The mean age of donors was 25 ± 5 years (range: 5 to 43 years); 72% male and 28% female. The demographic and baseline variables of these patients are shown in *table 1 and 2*. No significant differences were seen in Hb levels with sex and age of recipients *(Table 2)*.

### *4.2. Prevalence*

The prevalence of PTA beyond 1 year after transplantation was 15.4% (n = 12) of cases in this survey, mild to moderate anemia was seen in 9% (n = 7) of patients and 6.4% (n = 5) of recipients had severe anemia. The prevalence of late PTA was not different in both boys and girls (p = 0.38).

### *4.3. Univariate Analysis*

A significant and strong correlation was seen between serum Cr and Hb levels (p = 0.005, r = 0.318) *(Figure 1, Table 3)*. There was also a significant correlation between serum Hb and C0 blood level (p = 0.009, r = 0.29); C2 level was significantly related to Hb level (p = 0.03, r = 0.29) *(Ttable 4)*. No significant correlation was seen between Hb level and other biochemical parameters *(Table 3)*.

### *4.4. Multivariate regression analysis*

At multivariate logistic regression after adjustment for other factors, we found the increased plasma creatinine concentration was only a risk factor for late PTA in pediatric transplant patients (P = 0.05, EXP (B) = 2.5; 95%CI = 1.0- 6.3).

## 5. Discussion

The anemia that occurs during the late post-transplant period has received substantially less attention. In the current study, late PTA in our pediatric recipients was less prevalent after kidney transplantation as compared to that reported in adult renal transplant patients (18, 19). The prevalence of PTA has been reported from 20% to 60% in adult patients, depending on the definition used (8). It was also more common problem in pediatric studies (3, 6, 16). Late PTA was encountered in 15.4% of our patients, which is also less than that reported by Mitsnefes *et al.* (20), who used the same definition of anemia and showed that PTA was observed in 25.5% of their pediatric cases. However, our result much lower than the rates reported in two others pediatric studies (5, 21), that reported anemia in approximately 60–80% of pediatric patients from 1 to 5 years after renal transplantation. Although, they used different definitions of anemia. Thus, the lower prevalence of late PTA reported in the present study is, in part, owing to the definition of anemia. We used the KDOQI guidelines to categorize PTA as Hb < 11 g/dL (17), it may lead to underestimation of the frequency of anemia. When an Hb level of < 12 g/dL was used, 34.6% of our children had PTA. In addition, a high prevalence of anemia (70% to 80%) has been reported in pediatric cardiac (22) and liver transplant recipients (23). As expected, poor renal allograft function is a recognized predictor of anemia. In our patient population, worse renal allograft function was an important risk factor of PTA, which is comparable with the data from other studies (8, 10, 24, 25). Renal allograft impairment is one of the most common reasons of PTA, mainly as a consequence of erythropoietin deficiency. Despite the fact that cyclosporine may cause anemia following kidney transplantation (25, 26), we couldn't find any relation between cyclosporine blood level and PTA. It may due to use of the lower doses of drug 1 year after transplantation. Furthermore, we found that female gender had no more chance of PTA and they had approximately similar chance of severe anemia after renal transplantation, which is consistent with findings of de Andrade *et al.* who reported that gender difference was not an independent factor at their study (15). Conversely, Mitsnefes *et al.* (20) reported a higher prevalence of PTA in girls (32.6% versus 20.6% in boys). In addition, other studies have also reported similar higher prevalence (7, 27); however, our finding may be the result of low prevalence of anemia and small sample size of this study. Although the late PTA was not uncommon in pediatric kidney recipients, it was lower than the rates reported of the previous studies. Renal impairment was only a risk factor for late PTA in our patient population.

## Financial support

This study funded by Nephrology and Urology Research Center, Baqiayatallah University of Medical Sciences.

## Conflict of interest

None declared.

## Acknowledgments

We would like to express our thanks to Dr. Heidari for English revision of our paper.

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