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Original article

Postrenal transplant anemia and its effects on patients and graft outcomes: Seven years follow-up

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ABSTRACT

Introduction: Post-transplant anemia (PTA) is a common serious complication following kidney transplantation. It affects graft and patient survival. Anemia that presents within six months post-transplantation is defined as an early PTA. Late PTA is when anemia occurs more than six months following transplantation. Despite this, there are limited studies on the long-term impact of anemia on patient survival and graft function in kidney transplants. We conducted a retrospective study with long-term follow-up to investigate the effect of early and late PTA on patient and graft function within seven years and to estimate the prevalence of PTA at six months, two, four, and seven years postrenal transplantation along with the associated risk factors.

Method: A retrospective chart review of 145 adult patients who had kidney transplants from January 1 to December 31, 2015, and were followed up until December 31, 2022. Anemia was defined according to the World Health Organization (WHO) criteria of hemoglobin<12 gm/dl in females and<13 mg/dl in males. Pretransplant, six months, two, four, and seven years postrenal transplantation medications and laboratory data were obtained. Patients were excluded if they were pediatrics or had missing data.

Result: 180 patients were screened, and 145 patients met the inclusion criteria. The prevalence of early PTA was 8.3%. Trimethoprim-sulfamethoxazole was significantly associated with anemia within six months. The prevalence of anemia increased at two, four-, and seven-years post-transplant (24.8%, 24.8%, and 27.6%, respectively). Graft failure was significantly associated with late PTA at four and seven years (p-value < 0.001). P < 0.005, respectively). Death was reported for 3 patients, and it was significantly associated with late transplant anemia (p-value < 0.005), Cytomegalovirus was associated with anemia at 6 months and 2 years post-transplant and significantly associated with graft failure (p-value < 0.037).

Conclusion: The results of this study indicate that post-transplant anemia is associated with graft failure and patient mortality. Therefore, managing anemia post-transplant should be addressed more carefully.

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1. Introduction

Post-transplant anemia (PTA) is a serious complication following kidney transplantation. It affects graft and patient survival. (Vanrenterghem et al, 2003, Huang et al, 2015, Schjelderup et al, 2013) The prevalence of PTA reached 34 percent at different times in post-kidney transplantation. (Molnar et al, 2005) A recent study in Saudi Arabia estimated the prevalence of PTA to be about 40%. (Shilbayeh, 2022) Anemia presented within six months post-transplantation is defined as early PTA, while late PTA is when anemia occurs more than six months following transplantation. (Yorgin et al, 2022; Hricik, D.E., 2003) PTA has been undesirably linked to an increase in mortality rate as well as graft function decline. (Gafter-Gvili et al, 2017) Also, anemia is associated with an increased risk of heart failure in renal transplant patients. (Rigatto,2002) There are multiple risk factors for anemia in renal transplant patients, including iron deficiency, which is the most reported and contributes to early PTA, late PTA, deficiency of erythropoietin (EPO) (Ganz, T., 2003), bone marrow depression, the use of prophylactic agents such as valganciclovir, trimethoprim-sulfamethoxazole (Winkelmayer et al, 2004), immunosuppressive medications, azathioprine, mycophenolate mofetil, (Joist, 2006) female gender, and lower estimated glomerular filtration rate (eGFR) at six months. (Gafter-Gvili etal, 2017) Despite this, there are limited studies on the long-term impact of anemia on patients and graft function in kidney transplants. We designed a retrospective, single-center study with long-term follow-up to investigate the impact of early and late PTA on patients and graft survival within seven years. In addition, we aimed to assess the prevalence of PTA at six months, two, four, and seven years postrenal transplantation. **Definitions**: According to the World Health Organization (WHO), anemia is a hemoglobin level below 12 g/dl for females and<13 in males. (Blanc, B., 1968) We classify anemia severity as follows: Mild anemia: hemoglobin levels range from 10 g/dL to the lower limit of normal; moderate anemia: Hb ranges from 8 to<10 g/dL; and severe anemia: Hb is below 8 g/dL. (Blanc, B., 1968) Our primary objectives were to assess early and late PTA (within six months, two, four, and seven years) in patients' survival and graft function. Our secondary objectives were to estimate the prevalence of PTA at six months, two, four, and seven years postrenal transplantation in Saudi Arabia.

2. Methods

2.1. Study design

This is a retrospective single-arm cohort study of all patients with end-stage renal disease who underwent kidney transplantation from January 1, 2015, to December 31, 2015, at King Faisal Specialist Hospital and Research Center-Jeddah, with a seven-year follow-up period. We screened 180 patients, and 145 were eligible for inclusion in the study (Flow Chart 1).

2.2. Data collection

Data were obtained from patients' electronic files, which contained the age of the patients, gender, date of transplant, diabetes, hypertension, blood group, causes of end-stage renal disease (ESRD), type of dialysis, time of dialysis, and body mass index (BMI) before kidney transplantation and 6- and 12-months post-transplantation. Anemia workup involved hemoglobin (g/dl), MCV (g/dl), RDW, iron, ferritin, vitamin B12, folic acid, and estimated glomerular filtration rate. The use of tacrolimus, cyclosporine, mycophenolate, prednisone, angiotensin-converting enzyme inhibitors (ACEIs) / Angiotensin II receptor blockers (ARBS), beta-blocker, diuretics, statin, anti-platelet, trimethoprim-sulfamethoxazole, and valganciclovir were documented. The outcomes of the research include graft failure, death, and patient survival days. The Institutional Review Board (IRB) approval was obtained from King Faisal Specialist Hospital and Research Centre (KFSH&RC-J) number (2022–37).

2.3. Study setting and participants

King Faisal Specialist Hospital and Research Centre-Jeddah (KFSH&RC-J) is an internationally recognized, 350-bed tertiary health care institution in western Saudi Arabia. The information was collected from the renal transplant unit (RTU), the outpatient renal transplant clinic, and the medical floor.

2.4. Inclusion/exclusion criteria

We included all patients older than 18 years old who received kidney transplantation at KFSHRC-Jeddah from January 1, 2015, to December 31, 2015, with a seven-year follow-up period. We

Flow chart 1:

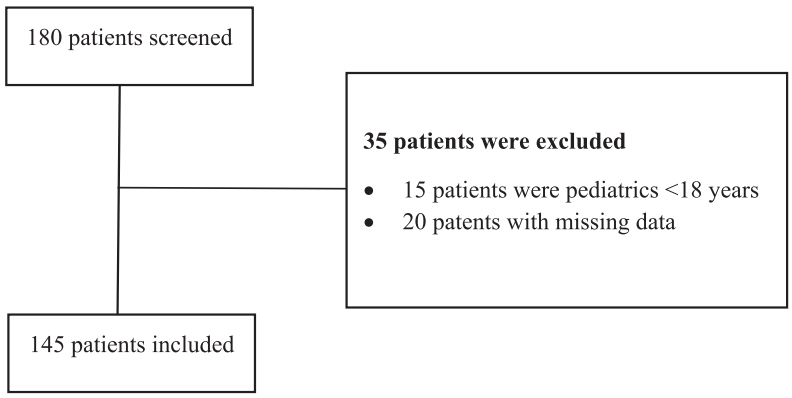

Chart 1. Flow-chart of patient selection.

excluded pediatrics<18 years old and patients with missing information.

2.5. Data analysis

This study was analyzed using IBM SPSS version 23 (IBM Corp., Armonk, N.Y., USA). A simple descriptive statistic was used to define the characteristics of the study variables through a form of counts and percentages for the categorical and nominal variables. Continuous variables are presented as means and standard deviations. To establish a relationship between categorical variables, this study used a chi-square test. Cox regression analysis was used to build a predictive model for time-to-event data. The model produces a survival function that predicts the probability that the event of interest has occurred at a given time t for the given values of the predictor variables. The shape of the survival function and the regression coefficients for the predictors are estimated from the observed subjects; the model can then be applied to new cases that have measurements of the predictor variables. Lastly, a conventional p-value < 0.05 was the criterion to reject the null hypothesis.

3. Results

3.1. Patients' demographics

One hundred and forty-five patients were included in the study period from January 1 to December 31, 2015, and followed up for seven years. The mean age of the participants was 42 ± 13.9 years, and the mean body mass index (BMI) at surgery was 25.9 ± 8.2 kg/m2. One hundred twenty-six (86.9%) of the patients received a living- kidney transplant, and only 19 patients (13.1%) received a deceased donor's kidney. Regarding the blood group of the patients who received a renal transplant, almost half of them were blood group O+ (72 patients, 49.7%), followed by the A + blood group (44 patients, 30.3%), then the B + blood group (23 patients, 15.9%). Regarding the co-morbidities, 66 patients (45.5%) had hypertension and 117 patients (80.7%) had diabetes mellitus (Table 1; general characteristics of the 145 study samples). Anemia profile prerenal transplantation showed the mean hemoglobin 11.9 ± 6.5 gm/dl, red blood cells (RBCs) 3.97 ± 0.9 cells/mcL, mean corpuscular volume (MCV) 88.6 ± 6.3 fL, red cell distribution (RDW) 14.46 ± 2 percent, iron 14 ± 7.4 micromol/L, and ferritin 558.21 ± 873.6 Âµg per liter. Anemia was present in 101 (69.7%) patients before transplantation; 66 (45.5%) of the patients had mild anemia, 32 (22.1%) had moderate anemia, and 3 (2.1%) had severe anemia. (Table 2).

3.2. Outcomes: Primary objective

Early anemia, which occurred six months postrenal transplantation, was present in 12 (8.3%) patients; 10 (6.9%) had mild anemia, 2 (1.4%) had moderate anemia, and none had severe anemia. The mean hemoglobin was 13.9 ± 5.7 gm/dl, red blood cells (RBCs) 5.11 ± 1 cells/mcL, mean corpuscular volume (MCV) 82.7 ± 14fL, red cell distribution (RDW) 13.81 ± 2.5 percent, iron 8.18 ± 4.4 micromol/L, and ferritin 1923.56 ± 3970.8 Âµg per liter. (Table 2) Medications at six months postrenal transplantation are present in the supplementary (Table 1). All patients maintained, at least, dual immunosuppression, which consist of tacrolimus, and prednisone 145 patients (100%), 140 patients (96.6%) maintained mycophenolate, while only one patient-maintained cyclosporine (0.7%). Twenty patients (13.8%) received ACEI, or angiotensin-receptor blockers (ARBs), 59 patients (40.7%) were on beta-blockers, 9 patients (6.2%) on diuretics, 47 patients (32.4%) on statins, 57 patients (39.3%) on anti-platelet, regarding the prophylaxis; 142 patients received trimethoprim (97.9%), and 141 (97.2%) received valganciclovir. Trimethoprim-sulfamethoxazole was significantly associated with early PTA within six months (p-value 0.019) (supplementary Table 1.1). Late PTA was present in 36 (24.8%) two- and four-years post-transplantation. It occurred in 40 patients (27.6%) seven years post-transplantation (Tables 2). Medications administered two, four-, and seven-years post-transplantation are presented in Tables 2, 3, and 4supplementary . None of them were significantly associated with late PTA.

3.3. Secondary objective

Regarding the outcomes of interest, 15 (10.3%) patients suffered from graft failure within seven years and were back on dialysis; two of them (1.4%) returned to dialysis within six months, six patients within two years, and four patients within four years. Of the others, three returned to dialysis within a seven-year period. Death occurred among three patients (2.1%) within seven years. The patients who died after the transplantation lived around 2286.67 ± 113.2 days, with the maximum living 2389 days, while

Table 1
Characteristics of the 145 Study Samples.

Demographics		Without anemia n (%)	Anemia within 7 years	P value
Age (yrs) mean ± SD		42.48 ± 13.7	42.32 ± 14.6	0.418
BMI (kg/m2) mean ± SD		26 ± 9	25.8 ± 5.7	0.418
Gender	Male	81 (77.9)	23 (22.1)	0.009*
	Female	23 (56)	18 (43)	
Diabetes	Yes	86 (73)	32 (27)	0.63
	No	18 (67)	9 (33)	
Hypertension	Yes	43 (65)	23 (35)	0.139
	No	61 (77)	18 (23)	
Type of organ	Living	33 (26)	93 (74)	0.175
	Cadaveric	11 (58)	8 (42)	
Induction therapy	Basiliximab	74 (73.3)	27 (26.7)	0.55
	ATG	30 (68)	14 (32)	
Blood group	A+	31 (71)	13 (29)	0.964
	B+	16 (70)	7 (30)	
	O+	54 (74)	19 (26)	
	AB+	3 (75)	1 (25)	
ABO incompatibility	Yes	2 (100)	0 (0)	0.37
	No	102 (71.3)	41 (28.6)	

Table 2
Anemia work up prior renal transplant and 6 months, 2, 4, 7 years post renal transplantation.

Parameters	Pre-transplant:	6 months post-transplant	2 years post-transplant	4 years post-transplant	7 years post-transplant
	Mean ± SD				
Hemoglobin (gm/dl)	11.91 ± 6.5	13.57 ± 2.9	13.84 ± 2	13.65 ± 2.2	13.72 ± 3.8
RBC (cells/mcL)	3.97 ± 0.9	5.11 ± 1.0	5.27 ± 0.8	5.08 ± 0.7	4.96 ± 0.8
MCV (fL)	88.62 ± 6.3	82.47 ± 14	83.44 ± 8.9	85.1 ± 7.6	85.44 ± 6.1
RDW (%)	14.46 ± 2	13.81 ± 2.5	14.61 ± 1.8	14.25 ± 1.4	14.16 ± 1.6
Iron (umol/l)	14.08 ± 7.4	8.18 ± 4.4	10.63 ± 5.7	15.02 ± 27.9	9.67 ± 6.4
Ferritin (mcg/l)	558.21 ± 873.6	1923.56 ± 3970	296.97 ± 3902	428.23 ± 572.4	380.38 ± 384.5
Vitamin B12 (pg/ml)	657.28 ± 932	258.85 ± 193	383.40 ± 224	539 ± 694.7	357.58 ± 186.7
	Number (%)				
Presence and Severity of anemia	**Yes** 101 (69.7)	12 (8.3)	36 (24.8)	36 (24.8)	40 (27.6)
	No 44 (30.3)	133 (91.7)	109 (75.2)	109 (75.2)	105 (72.4)
	No 44 (30.3)	133 (91.7)	109 (75.2)	109 (75.2)	105 (72.4)
	Mild 66 (45.5)	10 (6.9)	30 (20.7)	29 (20)	27 (18.6)
	Moderate 32 (22.1)	2 (1.4)	6 (4.1)	4(2.8)	12 (8.3)
	Severe 3 (2.1)	0 (0)		3(2.1)	1 (0.7)

Table 3
Anemia with graft failure and patients' death.

Graft Failure		Total	Anemia		p-value
			Yes	**No**	
<=6 month	Yes	2	0(0%)	2(100%)	0.6
	No	143	12(8.4%)	131(91.6%)	
2 years	Yes	6	3(50%)	3(50%)	0.14
	No	139	33(23.7%)	106(76.3%)	
4 years	Yes	4	4(100%)	0(0%)	<0.001[a]
	No	141	32(22.7%)	109(77.3%)	
7 Years	Yes	3	3(100%)	0(0%)	0.005[a]
	No	142	37(26.1%)	105(73.9%)	
		Anemia 7 years	**p-value**		
		Yes	**No**		
Total	145	40(27.6%)	105(72.4%)	–	
Death	Yes	3	3(100%)	0(0%)	0.005[a]
	No	142	37(26.1%)	105(73.9%)	
	N	**Mean**	**SD**		
Survival days	3	2286.67	113.2		

a-significant using Chi-Square Tests at < 0.05 level.

Table 4
Effect of CMV, induction therapy in the incidence of anemia, graft failure, patients' death.

Variable		Anemia							
		6 months post	**P value**	**2 years**	**P value**	**4 years**	**P value**	**7 years**	**P value**
Viral infection (CMV)	Yes	7	0.001*	6	0.003*	4	0.08	4	0.08
	No	1		2		4		4	
Induction	Basiliximab	30	0.98	27	0.26	24	0.89	27	0.5
	ATG	13		8		20		14	
Induction		Graft failure				Death			
		Yes	No	P value		Yes	No		P value
Basiliximab		10	91	0.79		2	99		0.9
ATG		5	39			1	43		
CMV	Yes	12	5	0.037*		0	8		0.672
	No	3	125			3	134		

the minimum is 2165 days. Anemia was significantly associated with graft failure at four and seven years (p-value < 0.001. P < 0.005, respectively) (Table 3). Factors affecting anemia are present at different time points, and BMI is present at different time points, as are blood group incompatibility, diabetes, HTN, and use of medications. None of these were statistically significant (supplementary Table 5). However regarding the cytomegalovirus infection it was significantly associated with anemia at 6 months and 2 years post transplants, and it was associated with graft failure as well (P.value 0.001, 0.003 and 0.037* respectively).

4. Discussion

Anemia is a common complication following kidney transplantation and has a significant effect on patient and graft survival. While almost all previous studies have shown a significant correlation with early transplant anemia and graft survival, results regarding the association between early and late anemia, graft function and mortality for long term are inconsistent. (Vanrenterghem et al, 2003; Molnar et al, 2005) In this study, we evaluated early and late post-transplantation anemia in patients

and graft function. Anemia was present in 69.7% of our study population prior to transplantation, compared to a study conducted in the Aljouf region in Saudi Arabia, which showed 96% of dialysis patients had anemia ranging from mild to severe. (Thar et al, 2020) In our study, only 8.3% of patients presented with early PTA; however, the risk increased in the second, fourth-, and seventh-years post-transplantation, compared to a previous study that also assessed PTA and graft function. (Shibagaki, Y., Shetty, A., 2004; Yorgin et al, 2002) Our study found that early anemia is less common compared with previous studies, which found that almost 41.1% of the subjects presented with early anemia six months after transplantation while on our study early anemia presented on 8.3% of the subjects. (Shibagaki, Y., Shetty, A., 2004) The higher percentage in their study is explained by the race factor, since anemia is more prevalent among African Americans, (Shibagaki, Y., Shetty, A., 2004) while our study included only the Saudi population. It is important to note that although 15.6% of the patients in the same study displayed delayed graft function, they did not specify the time they experienced this event (Shibagaki, Y., Shetty, A., 2004). In our study, graft failure presented for only 1.4% at six months and for 4.31% at two years, then returned to 2.8% and 2.1% at four and seven years, respectively, which could not be explained by the presence of anemia alone since transplant patients could suffer from infection, rejection, and fluctuation at the level of immunosuppression medications. Another retrospective study determined that there was a strong association between 5-year anemia and graft function after kidney transplantation, with 30.4% of patients suffering anemia versus 24.8% in our study over four years and 27.6% in seven years. PTA was linked to worse future kidney graft function and graft loss. (Kolonko et al, 2009) Two other prospective cohort studies with different follow-up periods ranging from three to four years post-transplant assessed mortality and graft failure in anemic patients compared to non-anemic patients, mortality and graft failure were higher in anemic patients (Molnar MZ et al, 2007; Ott et al, 2008), which was consistent with our findings. In our study, anemia increased over four to seven years, but an analysis of other two retrospective cohorts showed that the frequency of PTA declined during the first four to six years post-transplantation. (Gafter-Gvili et al, 2017, Huang et al, 2015) Our study demonstrated that, after seven years of follow-up, anemia rates increased from 8.3% in the first six months to 27.6% in the seventh year, indicating that anemia rates increase with time. The prevalence of anemia is associated with graft failure (p-value < 0.001, <0.005 at 4 and 7 years, respectively). A significantly higher death rate was found at seven years post-transplant in patients with late transplant anemia. A total of three anemic patients who had the following risk factors died: older age, hypertension, and diabetes mellitus. Two of them were overweight and had high lipid profile: low density lipoprotein and triglyceride levels, there are several limitations to consider on our study. First, being single-center study, convenient sample, and the retrospective nature of this study limits us to only demonstrating an association between the severity of anemia and outcomes, not causality. In addition, defining anemia by hemoglobin levels retrospectively is prone to error due to inaccurate entry in the patients' medical records. Lastly, more diversity among racial groups will make the study more generalizable and stronger.

5. Conclusion

The results of this study indicated a lower incidence of early PTA compared with other studies; however, a higher incidence of late transplant anemia was seen. There was a link between PTA, graft failure, and patient death. Therefore, PTA should be managed more carefully, particularly late anemia.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.101696.

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