Hematological disorders after renal transplantation: A single-center study

Revsa Evin Canpolat Erkan[a,*], Ramazan Danis[b]

[a]Dicle University, Faculty of Medicine, Department of Medical Biochemistry, Diyarbakır, Türkiye
[b]University of Health Sciences, Gazi Yaşargil Educational and Research Hospital, Department of Nephrology, Organ Transplant Center, Diyarbakır, Türkiye

Abstract

Aim: Post-transplantation anemia (PTA) and post-transplantation erythrocytosis (PTE) are the most common hematological problems in patients after renal transplantation. Hematological disorders need to be corrected to improve the mortality and morbidity status of patients and to maintain cardiac and graft functions. The objective of this study is to determine the prevalence of PTA and PTE in kidney transplant (KT) patients in our region in our organ transplant center.

Materials and Methods: 212 renal transplant patients who underwent KT in a single center between 2012 and 2020 were included in the study. Demographic, clinical, and laboratory data of renal transplant patients at preoperative and postoperative months 6 and years 1, 2, 3, 4, and 5 were evaluated.

Results: We determined the prevalence of PTA to be 28.16% (Early PTA 25.62%), and the prevalence of PTE to be 4.22%. The PTA group consisted of 40 patients, 33 females and 7 males, with a mean age of 30.5 years, while the PTE group consisted of only 6 male patients with a mean age of 21. Female predominance was observed in the PTA group (33, 82.5%), and male predominance (6, 100%) was observed in the PTE group. While there was no correlation between PTA and graft loss, there was a statistical correlation between PTE and graft loss (p<0.001). There wasn't relationship between the groups in terms of mortality, tacrolimus, cyclosporin A, and erythropoietin use (p>0.05). We found a negative correlation between hemoglobin levels and urea and a positive correlation between albumin, Ca, and tacrolimus levels.

Conclusion: PTA is a common condition, especially in female patients, and its prevalence increases over the years if the necessary care is not taken in the follow-up, and complications that may occur can be prevented with early diagnosis and treatment. Even if the prevalence of PTE is low, especially young male patients should be followed, and treatment should be started early to prevent a possible complications.

Introduction

In addition to complications related to graft rejection and immunosuppressive treatment, hematological disorders are also frequently observed in patients after kidney transplantation. Post-transplantation anemia (PTA) and post-transplantation erythrocytosis (PTE) are the most common hematological problems [1].

Anemia, which is one of the most common complications of chronic kidney disease, is defined as a hemoglobin (Hb) level below 12 g/dL in women and 13 g/dL in men. Even after kidney transplantation, PTA rates have a high prevalence of 20% to 60% (2). Some authors suggest classifying PTA as early (up to 6 months) and late (after 6 months and up to 5 years) [2,3]. Many factors have been associated with PTA, including iron deficiency, infections, impaired kidney function, re-transplantation, use of immunosuppressive and renin-angiotensin axis active drugs, donor age and low erythropoietin [4]. Anemia needs to be corrected to maintain cardiac functions and, thus, graft functions and to improve patient survival. There are also observational studies showing that PTA is closely associated with graft function and mortality [5, 6]. One study has shown that targeting hemoglobin (Hb) levels to >13 g/dL prevents the deterioration of chronic allograft nephropathy [7]. Existing studies show that correction of anemia with antihypertensive and immunosuppressive drugs slows the deterioration of renal function of chronic phase allograft

*Corresponding author:
Email address: drevinerkan@gmail.com (Revsa Evin Canpolat Erkan)

nephropathy for more than three years [5].

PTE is defined as a hemoglobin (Hb) level of >17 gm/dl or a hematocrit level of >51%, and its prevalence varies between 8-20%, according to various sources [1]. PTE is usually seen in the first two years of transplantation, and in 25% of patients it goes into remission spontaneously within two years of its onset [8]. Risk factors predisposing to the formation of PTE include male gender, smoking, affected native kidneys (excessive erythropoietin production by the remaining native kidney), diabetes, renal artery stenosis of the native or transplanted kidney, and a history of acute rejection [9, 10]. Although the pathogenesis of PTE has not been fully elucidated, the Renin-Angiotensin System (RAS), angiotensin-1 receptor, angiotensin-II receptor activation, endogenous androgens, growth factors such as insulin-like growth factor 1 (IGF-1), and serum-soluble stem cells (sSCF) are among factors causing an increase in erythropoietin sensitivity [8, 11]. Depending on the increase in blood viscosity in PTE, the risk of stroke and thromboembolic conditions (thrombophlebitis, deep vein thrombosis, pulmonary embolism) increases. Due to such risks, PTE should be treated without delay. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers are the first line of treatment, while phlebotomy is the second line [8, 10, 11].

Data on the relationship between the severity of anemia and patient and graft outcome, as well as the distribution of specific etiologies for anemia and their relationship to outcomes, are unfortunately limited. We aim to help guide diagnosis and treatment protocols by examining the preoperative and postoperative levels of PTA and PTE, which pose a risk in terms of mortality and morbidity, and determining their effects on graft rejection and graft functions. Moreover, with this study, we will show the prevalence of PTA, PTE, and EPO treatment in our hospital.

Materials and Methods

Subjects and study design

Of the 212 renal transplant recipients who underwent KT at the Organ Transplantation Unit of the Training and Research Hospital between 2012 and 2020, 199 transplant patients were included in the study due to the exclusion of 11 patients under the age of 18 and 2 patients with missing data. Ethics Committee approval was obtained Gazi Yaşargil Training and Research Hospital Ethics Committee for the study (No: 25/09/2020 - 568).

Clinical and laboratory data of renal transplant patients at preoperative and postoperative months 1 and 6, and years 1, 2, 3, 4, and 5 were evaluated.

Demographic-Clinical data: Age, gender, height, weight, type of dialysis before transplantation, duration of dialysis, total rejection, delayed graft function, mortality plasmapheresis, use of EPO, erythrocyte transplantation, phlebectomy, immunosuppressive drugs, graft rejection, type of donor, donor age, and donor association. Laboratory tests: Complete blood, routine biochemistry, protein-creatinine in spot urine, ferritin, tacrolimus, cyclosporine A.

Definition

The study included patients who had a first kidney transplant, no other organ transplants, at least one year of follow-up and sufficient data in the outpatient follow-up file. According to the World Health Organization (WHO) criteria for PTA and the American Society of Transplantation Guidelines, hemoglobin (Hb) levels were defined to be below 12 g/dL in women and below 13 g/dL in men; however, as the guidelines indicated a minor difference between men and women, Hb for PTA was standardized to 12 g/dL in our study. In 2009, the Kidney Disease Improving Global Outcomes (KDIGO) organization defined Hgb as > 17 g/dL or Hct as > 51%, regardless of gender, to establish a consensus in terms of diagnostic criteria and management for PTE.

Patients with Hb level <12 g/dL in the post-transplant year 2 were classified as PTA group, while those with Hb level >17 g/dL were classified as PTE group, the rest were considered as the control group. Furthermore, an early PTA group was formed at 6 months and a late PTA group at 2 years. Since the literature review was based on the 2nd year for late PTA, we also organized the late PTA data according to the 2nd year in our study.

Patients with a history of acute rejection in the previous 3 months, previous diagnosis of malignancy, pregnancy or breastfeeding status, hemorrhagic diathesis, Hb levels <10 g/dL with ESA, CVD and/or history of coronary artery disease, infection, and critical allergies were excluded from the study.

Patients with insufficient data for preoperative and postoperative follow-ups due to not coming in for follow-up, as well as patients who had erythrocytosis prior to kidney transplantation for PTE and erythrocytosis for other reasons such as respiratory, cardiovascular, and myeloproliferative disorders, were excluded from the study.

Statistical analysis

SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) for Windows was used for statistical analysis of the data obtained from patient files and hospital computer system records. Data were presented as percentage (%), mean ± standard deviation (SD), median, min-max value, and correlation coefficient (r).

The Kolmogorov-Smirnov test was used to determine the distribution of the data. A comparison of more than two groups was performed using the one-way ANOVA test. Analysis between the significant ones was performed with post hoc tests (Dunnett t, Dunnett C). Discrete variables between more than two groups were analyzed using the Kruskal-Wallis test. The Mann-Whitney U test with a Bonferroni correction was applied to the parameters that were determined to be significant in the analysis. The chi-square test was used to compare categorical variables, and the relationship between numerical variables was evaluated with Pearson correlation analysis. $p < 0.05$ was considered statistically significant.

Results

For the study, 212 patients were analyzed retrospectively. Eleven patients were younger than 18 years of age, and

Table 1. Demographics and baseline characteristics in year 2.

		Control (96)	PTA (n=40)	PTE (n=6)	p	Total (199)
Gender n, (%)	Female	29 (30.2)[a]	33 (82.5)[ab]	0[ab]	0.000	84(42.2)
	Male	67(69.8)[a]	7 (17.5)[ab]	6(100)[b]		115(57.8)
Age at the time of transplant (years)		36(15-65)[a]	30.5 (16-68)[a]	21 (18-31)[a]	**0.013**	34.29 (15-72)
Weight (kg)		64.36±14.84	56.26±11.27	63.53±5.12	**0.008**	61.56 ±14.48
Length (cm)		167 (131-183)[a]	158 (140-175)[a]	173 (166-177)[a]	**0.000**	164 (131-194)
Age of donor (years)		41.28±10.59	45.40±12.49	41.83±5.91	0.179	43.76
Type of donor n, (%)	Living	86(89.6)	33(82.5)	6(100)	0.33	167 (83.9)
	Cadaver	10(10.4)	7(17.5)	0		32 (16.1)
Donor relationship to recipient n, (%)	Partner	36(42.4)	5(14.3)	0		54 (27.1)
	Parent-child	30(35.3)	17(48.6)	5(83.3)		69 (34.7)
	Sibling	15(17.6)	8(22.9)	1(16.7)	0.152	29 (14.6)
	grandmother-father grandchild					
	3rd degree relative	1(1.2)	1(2.9)	0		3 (1.5)
Duration of dialysis, months		2 (0-134)	0 (0-103)	16.5 (12-127)	0.247	29.75 (0-204)
Dialysis types n, (%)	Preemtive	34(35.4)	21(52.5)	1(16.7)		68(34.2)
	HD	59(61.5)	17(42.5)	5(83.3)	0.325	115(57.8)
	CAPD	2(2.1)	2(5)	0		7(3.5)
	HD+CAPD	1(1)	0	0		1(0.5)
Total rejection n, (%)		3(3.1)	2(5)	0	0.82	6(2.5)
Delayed graft function n, (%)		0	1 (%2.5)	0	0.279	2 (%1)
Graft loss n, (%)		0[a]	1(2.5)	1 (16.7)[a]	**0.003**	4 (2)
Tacrolimus n, (%)		96(100)	39(97.5)	6(100)	0.27	189 (95)
Siklosporin A n, (%)		0	1(2.5)	0	0.27	3 (1.5)
Mortality n, (%)		5(5.2)	1(2.5)	0	0.67	10(5)
Plazmaferez n, (%)		9(9.4)	3(7.5)	1(16.7)	0.76	18 (9)
EPO treatment n, (%)		6(6.3)	0	0	0.23	7 (3.5)
Erythrocyte transp. n, (%)		4(4.2)	10 (25)	0	0.061	19 (9.54)
Flebektomi n, (%)		7(7.3)	0	4 (66.7)	0.380	13 (6.53)

HD: Hemodialysis, CAPD: Continuous Ambulatory Peritoneal Dialysis, EPO: Erythropoietin; *p < 0.05 a, b, c, … The difference between the values indicated with different letters on the same line is statistically significant.
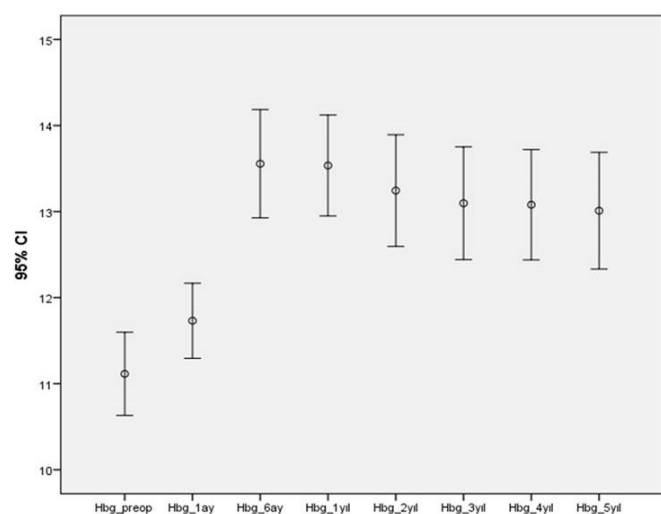

Figure 1. Five-year hemoglobin behavior (Hb;g/dL) after renal transplantation (RT).

two patients with missing data on their follow-up were excluded from the study. Of the 199 renal recipients evaluated, 84 (42.2%) were female and 115 (57.8%) were male. The PTA group included 40 patients with a mean age of 30.5, with 33 females and 7 (17.5%) males, and the PTE group included 6 male patients with a mean age of 21. Female predominance was observed in the PTA group, and male predominance was observed in the PTE group. At the time of transplantation, the PTE group consisted of younger patients with a mean age of 21 (18-31) years (p<0.013). Living donor dominance was observed in the PTA and PTE groups. While there was no relationship between PTA and graft loss, there was a high degree of statistical significance between PTE and graft loss (p<0.001). It was determined that erythropoietin was used in 7 (3.5%) patients, and according to the evaluations performed in the 2nd year, it was given only to 6 (6.3%) patients in the control group while it was never used in the PTA group. There was no relationship between the groups in graft loss, mortality, Tacrolimus-Cyclosporine A use, plasmapheresis, erythropoietin use, erythrocyte transplantation, phlebectomy, or other demographic data (p>0.05). Demographic

Table 2. Clinical and Biochemical Characteristics.

	Control (96)	PTA (n=40)	PTE (n=6)	p
Baseline hematological parameters				
HGB preop, g/dL	11.14±2.02	10.89±1.60	12.03±1.47	0.358
HGB 6 month, g/dL	14.26±1.68[a]	11.65±1.86[a]	17.79±0.91[a]	**0.000**
HGB, 1 year g/dL	14.23±1.76[a]	11.81±1.71[a]	16.84±1.13[a]	**0.000**
HGB, 2 year g/dL	14.6(12-17)[a]	10.6 (8-12)[a]	17.8 (17-18)[a]	**0.000**
HGB, 3 year g/dL	14.24±1.39[a]	10.49±1.29[a]	17.35±0.77[a]	**0.000**
HGB, 4 year g/dL	14.3 (10.6-16.7)[a]	10.7 (8.2-13)[a]	16.8 (16-18)[a]	**0.000**
HGB, 5 year g/dL	14.10±1.65[a]	10.70±2.24[a]	16.10±0.96[a]	**0.000**
HTC (%)	43.77±3.85[a]	31.76±6.98[a]	55.75±3.59[a]	**0.000**
RBC (10^6/μL)	5.18±0.67[a]	4.29±0.53[a]	6.76±0.91[a]	**0.000**
Baseline laboratory parameters				
CR preop (mg/dL)	5.5 (1.94-12.90)	5.5 (1.98-10.99)	5.7 (2.97-9.16)	0.863
CR (mg/dL)	0.96 (0.77-1.69)	1.1 (0.62-1.16)	1.18 (0.91-1.28)	0.757
GFR preop (ml/dk/1.73m^2)	13.5 (4-42)	12.5 (5-27)	13 (7-14)	0.316
GFR (ml/dk/1.73m^2)	82.8 (37.8-125)	77.9 (10-179)	86.5 (74-102)	0.65
Protein (g/dL)	7.37±0.41	7±0.26	8.2	0.278
Albumin (g/dL)	4.79±0.23[a]	4.1±0.1[b]	4.89±0.29[ab]	**0.007**
Glukoz (mg/dl)	105 (73-180)	85 (82-87)	87 (72-103)	0.383
Urea (mg/dL)	31 (22-44)	30 (26-47)	25 (17-32)	0.091
Cholesterol (mg/dL)	167±31.5	186±39	176±30	0.827
Triglycerides (mg/dL)	122 (75-257)[a]	104 (101-203)[a]	157 (108-269)	**0.047**
Fe (μg/L)	76 (17-177)[a]	34 (13-84)[a]	40 (35-46)	**0.000**
UIBC (μg/L)	252±105	299±130	334±59	0.251
Ca (mg/dL)	9.41 (8.68-11.6)[a]	9.3 (7.2-9.9)[a]	10.48 (10.4-10.6)[a]	0.000
P (mg/dL)	3.1 (2.2-4.1)	3.3 (3.1-4.9)	2.8 (2.5-3)	0.671
Mg (mg/dL)	1.78±0.16	1.15±0.24	1.77±0.04	0.768
Spot Urine Protein (%)	10 (2-123)	17 (1.3-360)	11.3 (3-22)	0.152
Spot Urine Creatinin (%)	37.7 (11.6-259)	57.7 (24-93)	89.4 (21-142)	0.350
Ferritin preop (μg/L)	357 (6-2086)	320 (6.6-804)	684 (253-861)	0.412
Tacrolimus (ng/ml)	5.78 (3.52-9.51)	5 (2.62-6.75)	5(4.49-5.61)	0.176

RBC: Red Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, CR:Creatinine, GFR: Glomerular Filtration Rate, UIBC: Unsaturated Iron Binding Capacity. *p < 0.05 a, b, c, … The difference between the values indicated with different letters on the same line is statistically significant.

and basic characteristics of the patients are shown in Table 1.

We determined the albumin level to be higher and statistically significant in the PTE group compared to the control and PTA groups (p<0.005). We found a lower serum Ca level in the PTA group and a higher level in the PTE group compared to the control group (p<0.001). Triglyceride and Fe levels in PTA patients were determined to be lower and statistically significant (p<0.05, p<0.001). Although the Mg level was also found to be lower, it was not statistically significant. PTE patients were younger than PTA patients and had higher GFR, albumin, and triglyceride levels and a younger living kidney donor. There was no significant difference between the groups in other blood test findings (Table 2).

While the mean hemoglobin level before transplantation was 10.98±1.96 g/dL and the frequency of anemia was 70.35%, the mean hemoglobin level and anemia frequency in the second year after transplantation were found to be 13.4±2.13 g/dL - 28.16%. The mean hemoglobin level and the frequency of anemia before the transplantation, at the 6th month, 1st year, 2nd year, 3rd year, 4th year, 5th year

after the transplantation are shown in Table 3 and Figure 1.

While there was a negative correlation between donor age and 6 month and 1 year hemoglobin (r:-0.181, p:0.019 , r:-0.187, p:0.022) and GFR (r:-0.287, p:0.016) levels, there was a positive correlation between creatinine (r: 0.237, p:0.008) and protein (r:0.316, p:0.039) levels (p<0.05). There was a negative correlation between hemoglobin levels and urea (r:-0.xxx, p:0.0xx), while there was a positive correlation between albumin (r:0.229, p:0.006), Ca (r:0.343, p:0.000), and tacrolimus (r:0.175, p:0.046) levels.

Discussion

Our study showed that, the frequency of early and late PTA was 25.62% (51/199) and 28.16% (40/142), while the frequency of PTE was 4.22% (6/142), which was consistent with previously predicted studies.

There are varying definitions of PTA in the literature. The CAPRIT study by Choukroun et al. showed that the normalization of anemia with a target Hb level of 13.0-15.0 g/dL corrected the decrease in graft kidney function [7]. On the other hand, Heinze et al. state that Hb concen-

Table 3. Clinical and Biochemical Characteristics at Pre-KT and 1 Post-KT.

| | Pre-KT n=199 | Post-KT | | | | | |
		6. Month n=199	1. year n=175	2. year n=142	3. year n=120	4. year n=85	5. year n=62
Baseline hematological parameters							
Anemia,	%70.35	%25.62	%24.57	%28.16	%25.83	%32.94	%30.64
(%), n	140	51	43	40	31	28	19
HGB g/dl	10.98±1.96	13.5±2.31	13.4±2.21	13.4±2.13	13.2±2.22	13±2.39	13±2.58
RBC (10^3/uL)	3.7±0.73	4.8±0.89	5.0±0.83	5.0±0.83	4.9±0.84	4.8±0.94	4.9±0.90
WBC (10^3/uL)	7.2±2.25	8.1±3.21	8.2±2.55	8.4±2.17	8.7±2.44	9.0±2.92	8.8±2.29
PLT (10^3/uL)	205±63.7	249±69.2	269±83.8	271±84.9	265±72.4	260±68	260±74.2
Baseline laboratory parameters							
Creatinine (mg/dL)	5.72±2.1	1.58±4.1	1.18±0.5	1.17±0.6	1.59±4.6	1.2±0.8	1.55±1.8
GFR (ml/dk/1.73m2)	11.9±6.22	75.9±26.43	80.79±23.94	82.07±23.92	77.3±23.58	59.73±24.05	73.51±21.75
Protein (g/dL)	7±0.8	7±1	7.1±0.5	7.2±0.6	7.2±0.6	7.2±2.1	7.3±0.7
Albumin (g/dL)	4.2±0.6	4.5±0.4	4.5±0.3	4.5±0.3	4.5±0.4	4.5±1.2	4.4±0.4
Glukoz (mg/dl)	101±33.7	96±41.4	98±45.8	95±35.9	93±33	97±35.8	100±38.9
Urea (mg/dl)	89±49.7	35±17.3	33±14.3	33±16.4	34±21.1	36±25.9	40±29.7
Cholesterol(mg/dL)	165±43.7	179±43.5	171±35.6	168±36.3	163±37.5	167±37	173±36.3
Triglycerides,(mg/dL)	155±95.4	180±97.8	156±71.9	147±78	149±66.9	145±90.8	159±70.8
Fe(µg/L)	75±40.3	71±43.5	69±46	62±37.7	64±41.8	66±43.6	67±40.9
UIBC(µg/L)	165±62.5	214±89.3	234±98.9	268±108.2	265±106	269±79.5	236±85.5
Ca(mg/dL)	9±1	9.5±0.6	9.6±0.5	9.4±0.7	9.4±0.6	9.3±0.7	9.2±0.7
P(mg/dL)	6.7±27.8	3.2±0.7	3.2±0.7	3.2±0.7	3.1±0.5	3.1±0.7	3.1±0.5
Mg(mg/dL)	2.3±1.2	1.7±0.3	1.7±0.2	1.8±0.2	1.7±0.2	1.8±0.6	1.8±0.6
Tacrolimus	11.69±3.8 (1. Month)	7.7±3.1	5.9±2.5	5.5±1.9	5.8±1.7	5.3±1.7	5.3±1.6

WBC: White Blood Cell, RBC: Red Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, GFR: Glomerular Filtration Rate, UIBC: Unsaturated Iron Binding Capacity.

trations above 14 g/dL are associated with increased mortality [12]. In our study, an Hb level below 12 g/dL was defined as PTA, and an Hb level above 17 g/dL was defined as PTE [13, 14, 15].

There is a wide range of PTA prevalence after kidney transplantation, ranging from 20% to 60% [2]. In a study titled TRESAM conducted in 16 European countries, the prevalence of PTA was found to be 38.6% [16], and in a cohort study with 1139 kidney transplant recipients (RTA) the prevalence was determined to be 36% [4]. In the study consisting of the four major ethnicities of the USA, the PTA was found to have a slightly higher prevalence of 62.1% compared to other studies [6]. While Iwamoto et al. found the prevalence of anemia to be 77.4% at month 6 and 48.8% at month 24 [17], in a prospective study, the prevalence of PTA at post-transplant months 6 and 12 was found to be 35.5% and 25%, respectively [18]. In a study by Gafter-Gvili et al., the prevalence of PTA was 51.3% at 6 months (early PTA) and 36.6% at 2 years (late PTA), and they determined that female gender was an independent predictor for 6-month early PTA [19]. In Turkey, Ünal et al. determined the PTA prevalence to be 49.3% [20], while Merdin et al. found 6-month PTA prevalence to be 28.8% [21]. Özgür et al. determined it to be 36.9%. Moreover, they found the mean Hb level of the patients to be 10.8 g / dL before transplantation, the frequency of anemia to be 76.3%, and the rates of anemia at the postoperative months 1, 3, 6, and 12 to be 70%, 40%, 36%, and 34%, respectively. In the study, PTA was reported in

43% of female patients and in 33% of male patients [22].

Of the studies conducted for PTE, in a study conducted with 1304 kidney transplant patients, the PTE incidence was 12.9% [8], while the incidence of PTE was found to be 5% in another study conducted in a large kidney transplant group with 4317 patients. It was determined that male gender is a 3-fold risk factor for the development of PTE and that patients receiving kidney grafts after starting dialysis sessions are in the risk group for PTE, while elderly recipients are at lower risk [23]. In the study, which had the highest PTE prevalence of 28.4%, they attributed this to male predominance, the presence of native kidneys, and absence of acute rejection episode [10]. While Özgür et al. determined the prevalence of PTE as 11.7%, [22], Koçak et al. determined the prevalence of PTE as 23.2% which was statistically significant in male gender and living donor kidney recepients (p<0.001, p< 0.05) [24]. A meta-analysis reported that the prevalence of PTE can be up to 10-16%, male gender is dominant (p<0.001) and the risk of developing PTE is higher in transplants from cadaveric donors [25].

While we found many studies on PTA in our literature review, studies on PTE were limited. According to the data of our study, he frequency of anemia before transplantation was 70.35%, while the frequency of anemia in month 6 and years 1, 2, 3, 4, and 5 after transplantation was 25.62%, 24.57%, 28.16%, 25.83%, 32.94%, and 30.64%, respectively. Based on these findings, the rates of anemia in the transplant patients we analyzed did not decline over

time, and in fact increased in years 4 and 5. We found the prevalence of PTA at 28.16% (early PTA at 25.62%) which is consistent with the literature but slightly lower than the studies conducted in Turkey. In fact, when PTA patients in the 4th and 5th years were examined, the rate of patients who had anemia in the first 2 years and whose anemia did not improve was 75% in the 4th year and 85% in the 5th year. The prevalence of PTE was 4.22%, which was lower than previous studies, and the closest prevalence to our study was the study by Alzoubi et al. who found it to be 5%. Consistent with previous studies, there was a relationship between PTA and the female gender, while the group with PTE consisted of only male patients. In addition, patients with PTA and PTE consisted of younger patients (30.5 (16-68), 21 (18-31), p<0.01) compared to the patients in the control group. The fact that the PTE group consisted of young male patients and the PTA group consisted of female patients also created a statistically significant difference in terms of height, weight, and hemoglobin levels (p<0.001, p<0.01, p<0.001, respectively). In our study, living donor transplantation was predominant in all groups. We believe that the reason for this is the lack of awareness of organ transplantation in Turkey and the families' unwillingness to accept intervention on their deceased relatives.

Many studies have shown that there is a relationship between anemia, and graft failure [4, 16, 19] and mortality [4, 19, 26]. In a study conducted by dividing PTA into 3 categories according to hemoglobin (Hb) values—severe, mild, and non-PTA—a 6 times higher risk of death was predicted for mild PTA and a 10 times higher risk of death was predicted for severe PTA [27]. In another study, a higher prevalence of PTA (77.1%) was determined in patients experiencing DGF and it was emphasized that there was a significant relationship between DGF and PTA [6]. In a study conducted with pure red cell aplasia (PRCA), it was stated that the risk of graft rejection increased in patients with severe anemia after transplantation and who had multiple blood transfusions [28]. In a study conducted in Japan, a significant correlation was found between PTA and kidney graft function. It was noted that although kidney graft function decreased when Hb levels were 11 g/dL, younger recipient ages and good kidney function had a positive effect on recovery from anemia [17]. Eisenga et al. found in the univariate analysis performed in their study that anemia, iron deficiency anemia, and iron deficiency were associated with all-cause mortality [29]. It was also found that RTAs with corrected anemia had a significantly lower rate of graft loss, and that even targeting hemoglobin values of ≥ 120 g/L reduced serum creatinine levels, graft loss rate, and all-cause mortality. It was observed that elevated hemoglobin levels reduce creatinine levels, even in cases of anemia where RTA is not completely corrected [2]. Contrary to these studies, in the ALERT study, it was reported that hemoglobin levels did not have any relationship with all-cause mortality [30]. There was no relationship between PTA and mortality, and DGF and graft loss in our study. In the meta-analysis of Mekraksakit and the studies of Alzoubi and Hofstetter conducted with PTE patients, it was reported that PTE had no effect on mortality or graft rejection [8, 23, 25]. In our study, while no

relationship was found between PTE and mortality, there was a statistical relationship with graft loss (p<0.001). We think that we obtained such a statistical result due to the fact that we had only 6 PTE patients due to a small PTE sample size and that we experienced graft loss in 1 patient.

Similar to Chang et al., who found a significant relationships between PTA and the use of immunosuppressants tacrolimus, sirolimus and thymoglobulin, Ataş et al. also concluded that there is a relationship between PRCA and tacrolimus [6, 31]. In a study by Winkelmayer et al., a positive correlation was found between the use of tacrolimus and anemia [32]. Augustine et al. reported in their study that there was a decrease in Hb levels in the first year in RTA patients and that sirolimus-based therapy was an independent factor of anemia [33]. In our study, 39 (97.5%) PTA patients used tacrolimus, 1 (2.5%) used cyclosporin A, and 6 (100%) PTE patients used tacrolimus. There was no relationship between the groups in terms of tacrolimus and cyclosporine A use (p>0.05). There was only a positive correlation between hemoglobin level and tacrolimus (p<0.05).

In the 2-year follow-up of kidney transplant recipients with anemia in the epoetin beta-treated group and the untreated group 3 months after transplantation, Pile et al. detected significantly higher hemoglobin concentrations in the epoetin beta-treated group than in the untreated group (12.3 ± 0.18 vs. 9.99 ± 0.22 g / dL; p<.0001). They stated that the use of RHuEPO was safe and well tolerated, with no increase in cardiovascular or thrombotic events [34]. In a prospective study, it was observed that 41.3% of patients received recombinant erythropoietin (rEpo) therapy in the first months after transplantation, and that Epo levels on the day of transplantation were an independent factor for anemia at months 6 and 12 post-transplant [18]. In the TRESAM study, it was found that the mean Hb level in patients receiving epoietin therapy was significantly lower than in patients not receiving [16]. Kitamura et al. observed a high PTA in the ERI group 1 year after the transplantation, according to the ESA responsive index (ERI= weekly pre-transplant ESA dose/(hemoglobin x body weight)) formula they used [35]. In contrast to these studies, Japanese researchers reported in their study that anemia gradually improved after transplantation, and in the majority of cases, this improvement occurred without the use of ESA [17]. In our study, it was determined that 7 (3.5%) participants used erythropoietin, and it was never used in the PTA group according to the evaluations performed in the 2nd year (it was also determined that erythrocyte transfusion was performed in 10 PTA patients). Therefore, no relationship was found between PTA, erythropoietin use, and erythrocyte transfusions (p>0.05).

Gafter-Gvili et al. reported that eGFR decreases over time in patients with anemia, while eGFR decreased in anemic patients, eGFR increased in non-anemic patients [19]. In a study by Özgür et al., there was no difference in creatinine levels between the groups before transplantation; while the creatinine level in months 1, 3, 6, and 12 after transplantation was significantly higher in the PTA group compared to the PTE and control groups (p <0.05), GFR values were significantly lower (p <0.05) [22]. In a study by Ünal et al., it was determined that, while Hb value was

positively correlated with creatinine clearance and serum albumin level, it was negatively correlated with serum creatinine level, proteinuria amount, and cyclosporine level. In multivariate analysis, creatinine clearance and serum albumin levels were found to be independent risk factors for PTA [20]. In the TRESAM study, it was reported that there was a strong relationship between Hb levels and serum creatinine and creatinine clearance and that serum creatinine was > 2 mg/dL in the majority of anemic patients [16]. In our study, creatinine levels were found to be higher and the GFR ratio was found to be lower, although statistically not significant, in PTA patients compared to control patients. Moreover, the rate of protein and creatinine in the spot urine was found to be higher than in the control group.

The strengths of our study are that it presents data over a wide time period of five years and that both PTA and PTE patients were evaluated together. The primary limitation of our study was that it was a retrospective study; consequently, some patients did not attend their follow-up appointments regularly, and even if they did, there was no consistency in the requested examinations, and there were data collection issues such as incomplete computer data entry. Furthermore, the PTE group consisted of a small number of patients, and our results cannot be generalized to the entire kidney transplant population as our study consisted of a single-center data group.

Conclusion

In conclusion, PTA is a condition that is common, particularly in female patients, and its prevalence increases over the years if it is not followed-up properly. Along with anemia, problems with kidney function may also occur. Even if the prevalence of PTE is low, especially young male patients should be followed up regularly, and their treatment should be started without delay since it causes complications and adversely affects the prognosis.

Ethical approval

The study was approved by the Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (No: 25/09/2020 - 568).

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