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Prevalence of Long-term Anemia and Erythrocytosis in Kidney Transplant Patients: A Cross-sectional Study

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Abstract: Objective: While numerous reports have characterized the prevalence and risk factors of acute post-transplantation anemia (PTA) and erythrocytosis (PTE), there is a scarcity in the published reports regarding their chronic forms. We conducted the present study to investigate the prevalence and risk factors of PTA and PTE. **Materials and Methods**: This study was a cross-sectional descriptive study was carried out on 81 kidney transplant recipients in the renal transplant clinic at Sohag University Hospital during the period from February 2018 to February 2019. **Results**: We found that the prevalence of PTA was 44.4%, mainly normocytic anemia; almost one-third of anemic patients had severe anemia. On the other hand, 11.1% of the patients had erythrocytosis. Patients with history of rejection, higher number of rejection episodes. and cell-mediated rejection were more likely to have PTA. In addition, patients with PTA were more likely to receive anti-thymocyte globulin, intravenous immunoglobin (IVIG), rituximab, and plasmapheresis. Patients with more decline in kidney functions had higher risk of PTA and PTE. Regarding the impact of PTA and PTE on patients' outcomes, we found that patients with PTA and PTE were more likely to have impaired graft function than patients with normal hematological parameters. On multivariate analysis, only history of hypertension and hyperparathyroidism were independent predictors of PTA. **Conclusion**: In conclusion, chronic PTA and PTE are common in transplant recipients. Therefore, it is recommended that physicians involved in renal transplantation consider the investigation and follow-up of transplant recipients for PTA and adopt appropriate preventive and therapeutic measures.
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Keywords: Chronic Kidney Disease; Kidney transplantation; Cytopenia; Hematological abnormalities.

1. Introduction:

End-stage renal disease (ESRD) is the final stage of chronic kidney disease (CKD) that is characterized by irreversible declines in kidney function to the extent of an estimated glomerular filtration rate (eGFR) of less than 15 mL/minute/1.73 m^2 or the necessity of dialysis, irrespective of eGFR(1). The global prevalence of ESRD was reported to be 0.1% in 2016, with a notably higher prevalence in the United States (USA), Canada, and Japan(2); in addition, the incidence of ESRD in the USA is expected to increase by at least 30% in 2030(3). Diabetes, hypertension, and glomerulonephritis are among the commonest causes of ESRD(4). Renal replacement therapy, including hemodialysis and peritoneal dialysis, is the commonest form of management of ESRD, especially in developing countries. However, dialysis patients can represent a major public health burden owing to the high rate of hospitalization and healthcare cost (4,5). Moreover, the prognosis of ESRD patients on dialysis is poor with a reported 5-year survival rate of 35%(6).

Since its introduction in 1954, renal transplantation has revolutionized the treatment paradigm of ESRD. With the progressive advances in its techniques and the better understanding of the role of immunosuppressive agents, the outcomes of renal transplantation have improved significantly(7); previous reports showed that renal transplant recipients had better survival and quality of life than dialysis patients(8). In addition, renal transplantation significantly reduces the overall cost of treatment of ESRD, compared to dialysis(9). However, renal transplantation is not a risk-free procedure with a considerable proportion of patients suffer from a wide range of short and long-term complications. Classic complications of renal transplantation include graft rejection, infection, cardiovascular, and urological complications(10).

Hematological abnormalities are common following renal transplantation, renal transplant recipients exhibit higher frequencies of anemia, cytopenia, erythrocytosis, and lymphoproliferative disorder than the general population(11). Post-transplantation anemia (PTA) and post-transplant erythrocytosis can be either acute (≤ six months after

transplantation) or chronic (> six months after transplantation)(12). While numerous reports have characterized the prevalence and risk factors of acute PTA and PTE, there is a scarcity in the published reports regarding their chronic forms. Thus, we conducted the present study to investigate the prevalence and risk factors of PTA and PTE.

2. Materials and Methods:

The study's protocol gained the approval of the local ethics and research committee of Sohag University Hospital, Sohag, Egypt. Written informed consents were obtained from eligible patients before the beginning of the study.

Study Design, Setting and Participants:

This study was a cross-sectional descriptive study was carried out on 81 kidney transplant recipients in the renal transplant clinic at Sohag University Hospital during the period from February 2018 to February 2019. Adults (> 18 years old) patients were included if they received kidney transplantation for more than six months before the study's enrollment. We excluded patients with multiple organ transplantation, patients on hemodialysis due to temporary or permanent failure of transplantation, patients with history of hematological abnormalities, and/or patients with history of recent bleeding or blood transfusion. Pregnant women were excluded as well. A non-probability consecutive sampling technique was employed to recruit eligible patients.

Data collection and Study's Visits:

The following data were collected from eligible patients: demographic characteristics, history of chronic diseases, causes of ESRD, mode and duration of dialysis, donors' characteristics, history of graft rejection or dysfunction, previous medications, the presence of systemic infection, and the findings of routine laboratory findings. The laboratory investigations included complete blood count (CBC), kidney function tests, serum uric acid, serum electrolytes, urine analysis, iron profile, and parathormone hormone. CBC and its parameters were done on the CELL-DYN RubyTM System Operator.

The primary outcome in the present study was the incidence of PTA and PTE in kidney transplant patients. Anemia was defined as a reduction in hemoglobin level to less than 13g/dL in males and 12g/dL in females. The anemia was graded into mild (defined as hemoglobin >12 and <13g/dL for males and >11g/dL and less than <12 g/dL for females), moderate (defined as hemoglobin >11g/dL and less than ≤12 for males and >10g/dL and ≤ 11g/dL for females), and sever (defied as hemoglobin less than 11 and 10g/dL for males and females, respectively) degrees(13). Erythrocytosis was defined as hematocrit (Ht) above 52% males, and Ht above 50% in females or hemoglobin concentration >17 g/dl(14).

Statistical Analysis:

The statistical analysis was conducted using Statistical Program for Social Science (SPSS) version 20.0. The mean± standard deviation (SD) was used to describe quantitative data; while, qualitative data were expressed as frequency and percentage. The association analysis was conducted using Mann Whitney test for continuous data and Pearson Chi-square for qualitative data. A p-value of less than 0.05 was considered statistically significant.

3. Results:

The present cross-sectional study included 81 kidney transplant recipients with a mean age of 40.4±12.41 years; the majority of patients were males (81.5%) The mean of duration after transplantation was 61.17±58.51 months. Regarding study outcomes, the mean hemoglobin level was 12.96±2.377 g/dL and the mean hematocrit level was 39.43±7.736%. We found that 44.4% of our study group had anemia, 38.3% had normocytic anemia and 6.2% had microcytic anemia. Regarding the degree of anemia, 17.3% of patients had severe anemia, also 17.3% had mild anemia and 9.9% had moderate anemia. 11.1% of our study group had erythrocytosis (**Figure 1**).

There were no statistically significant differences between the anemic group and the non-anemic group regarding demographic data, smoking, and BMI. (**Table 1**).

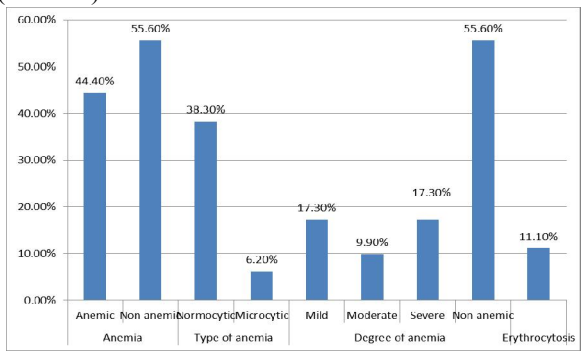

Figure (1): Characters of Anemia

Table 2 shows that there were no statistically significant differences between anemic group and non-anemic group regarding each of age, sex of donor, number, duration and type of transplantation, mode of dialysis, duration of dialysis, and duration of last rejection episodes. On the other hand, there were statistically significant differences between both groups regarding the history of rejection, number of rejection episodes. and type of rejection. There were statistically significant differences between the anemic group and the non-anemic group regarding the history of immunosuppressive drugs (**Figure 2**).

Table (1): Comparison between Anemic group and the non-anemic group regarding demographic data:

Item		Anemic	Non anemic	P-value
Age	Mean ±SD	43.22±14.4	38.13±10.1	0.066
Sex	Male	32(88.9%)	34(75.6%)	0.125
Occupation	Employed	25(69.4%)	33(73.3%)	0.700
Residence	Rural	23(63.9%)	29(64.4%)	0.959
Smoking	Smoker	6(16.7%)	5(11.1%)	0.267
BMI	Normal	22(61.1%)	26(57.8%)	0.950
	Underweight	1(2.8%)	2(4.4%)	
	Overweight	7(19.4%)	11(24.4%)	
	Obese	6(16.7%)	6(13.4%)	
Cause of ESRD	Hypertension	10(27.8%)	4(8.9%)	0.067
	Glomerulonephritis	6 (16.7%)	6(13.3%)	
	Obstructive nephropathy	1(2.8%)	3(6.7%)	
	Obstetric cause	1(2.8%)	1(2.2%)	
	SLE	0(0%)	2(4.4%)	
	Polycystic kidney	3(8.3%)	3(6.7%)	
	Analgesic nephropathy	1(2.8%)	0(0%)	
	Unknown causes	9(25%)	20(44.4%)	
	Amyloidosis	1(2.8%)	2(4.4%)	
	Pylonephritis	4(11.1%)	4(8.9%)	

Table (2): Comparison between anemic group and non-anemic group regarding data of transplantation:

Item		Anemic	Non-anemic	P-value
Mode of dialysis	**Hemodialysis**	32(88.9%)	42(93.3%)	0.694
Duration of dialysis	**Mean ±SD**	13.42±8.09	21.51±10.2	0.213
Duration of transplantation	**Mean ±SD**	67.83 ±15.61	55.84±20.3	0.363
Type of transplantation	**Living related**	12(33.3%)	24(53.3%)	0.078
Groups of transplantation	**6-12 m**	5(13.9%)	9(20%)	0.579
	12-60 m	17(47.2%)	23(51.1%)	
	>60 m	14(38.9%)	13(28.9%)	
Number of transplantation	**Single**	35(97.2%)	44(97.8%)	1.000
Sex of donor	**Male**	19(52.8%)	24(53.3%)	0.960
Delayed graft function		3 (8.3%)	0 (0%)	0.084
History of rejection		19 (52.8%)	4 (8.9%)	**<0.001**
Number of rejection episodes	**0**	17 (47.2%)	41 (91.1%)	**<0.001**
	1	12 (33.3%)	4 (8.9%)	
	2	7 (19.4%)	0 (0%)	
Duration of last rejection episodes	**Mean ±SD**	12.14±7.8	6.44±1.23	0.337
Type of rejection	**Cell mediated**	13 (36.1%)	4 (8.9%)	**<0.001**
	Antibody mediated	6 (16.7%)	0 (0%)	
	No rejection	17 (47.2%)	41 (91.1%)	

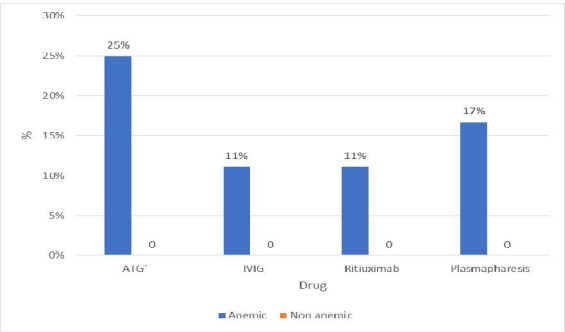

Figure (2): Comparison between Anemic group and non-anemic group regarding the therapeutic history

There were significant differences between anemic group and non-anemic group regarding transferrin saturation, total iron-binding capacity (TIBC), ferritin level, serum uric acid, eGFR, serum creatinine, presence of proteinuria, parathormone hormone (PTH) level, serum phosphorus, serum iron, and serum calcium level. In both groups, the majority of patients had normal serum transferrin and TIBC,

but ferritin levels increased in 58.3% of the anemic group while it was normal in 84.4% of the non-anemic group. Proteinuria was present in 66.7% of the anemic group but not present in any patient in the non-anemic group. Regarding stages of eGFR, the majority of anemic patients had stage 3 and 4 but non-anemic patients had stages 1 and 2 only. In the anemic group, serum creatinine was commonly > 2 mg/dl. In addition, 94.4% of the anemic group had hyperparathyroidism but only one patient in the non-anemic group had hyperparathyroidism. The majority of patients in both groups had normal Ca and phosphate levels (**Table 3**).

Table (3): Comparison between the anemic group and the non-anemic group regarding Laboratory investigations:

Item		Anemic	Non-anemic	P-value
WBCs	**Normal**	34 (94.4%)	43(95.6%)	1.000
	Leucopenia	1 (2.8%)	2 (4.4%)	1.000
	Leucocytosis	1 (2.8%)	0(0%)	0.444
Platelets	**Normal**	36 (100%)	44(97.8%)	1.000
	Thrombocytosis	0(0%)	1(2.2%)	
HCT level	**Mean±SD**	32.63±4.18	33.88±5.16	**<0.001**
Ca level	**Mean ±SD**	8.94±0.92	9.39±0.51	**0.007**
Phosphorus level	**Mean ±SD**	4.33±1.28	3.44±0.57	**<0.001**
PTH level	**Mean ±SD**	300.52±130.61	62.48±27.47	**<0.001**
Serum Creatinine	**<1**	3 (8.3%)	21 (46.7%)	**<0.001**
	1-2	12 (33.3%)	24 (53.3%)	
	>2	21 (58.3%)	0 (0%)	
eGFR	**Mean ±SD**	39.58± 19.85	86.11±15.72	**<0.001**
Stages of eGFR	**Stage 1**	2 (5.6%)	18 (40%)	**<0.001**
	Stage 2	5 (13.9%)	27 (60%)	
	Stage 3	16 (44.4%)	0 (0%)	
	Stage 4	13(36.1%)	0 (0%)	
Proteinuria		24 (66.7%)	0 (0%)	**<0.001**
Hyperuricemia		12 (33.3%)	1 (2.2%)	**<0.001**
Hypoalbuminemia		2 (5.6%)	0 (0%)	0.194
Iron	**Normal**	29 (80.6%)	44(97.8%)	**0.01**
	Decreased	6 (16.7%)	1 (2.2%)	
	Increased	1 (2.8%)	0 (0%)	
Ferritin	**Normal**	15(41.7%)	38(84.4%)	**<0.001**
	Decreased	0 (0%)	1(2.2%)	
	Increased	21(58.3%)	6 (13.3%)	
TIBC	**Normal**	23 (63.9%)	42 (93.3%)	**<0.001**
	Decreased	12 (33.3%)	3 (6.7%)	
	Increased	1 (2.8%)	0 (0%)	
Transferrin level	**Mean ±SD**	30.75±13.06	37.04±10.95	0.07

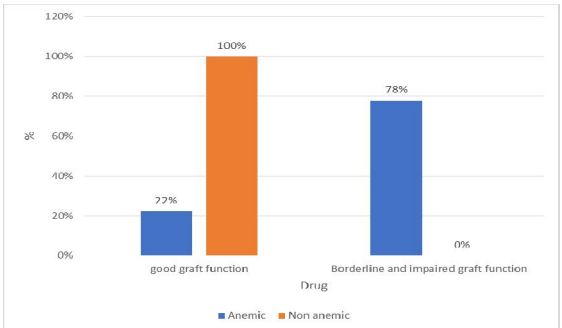

Figure (3): Comparison between the anemic group and the non-anemic group regarding Graft function

There was a statistically significant difference between anemic group and non-anemic group regarding graft function as 77.8% of anemic patients had borderline and impaired graft function, but 100% of non-anemic patients had good graft function (**Figure 3**).

There were statistically significant differences between erythrocytosis group and non-erythrocytosis group regarding PTH level, serum creatinine, eGFR and presence of proteinuria; 48.6% of non-erythrocytosis group had hyperparathyroidism but 100% of erythrocytosis group had normal PTH. Patients of erythrocytosis group had only eGFR stage

1 and 2 but non-erythrocytosis group had up to stage 4. In the erythrocytosis group, the majority of patients had creatinine < 1 mg/dl but the majority of non-erythrocytosis group had creatinine between 1-2 mg/dl. Regarding proteinuria, 33.3% of non-erythrocytosis group had proteinuria but no patients (0%) in the erythrocytosis group had proteinuria (**Table 4**).

Table (4): Comparison between Erythrocytosis group and non-Erythrocytosis group regarding Laboratory investigations:

Item		Erythrocytosis	Non-Erythrocytosis	P-value
Ca level	**Mean ±SD**	9.36±0.56	9.171±0.777	0.467
Phosphorus level	**Mean ±SD**	3.47±0.56	3.885±1.08	0.275
PTH level	**Mean ±SD**	57.66±12.5	182.10±58.95	**0.009**
Serum creatinine	**<1**	5 (55.6%)	19 (26.4%)	**0.028**
	1-2	4 (44.4%)	32 (44.4%)	
	>2	0 (0%)	21 (29.2%)	
e GFR	**Mean ±SD**	91.11± 15.43	62.22±29.61	**0.005**
Stages of e GFR	**Stage 1**	5 (55.6%)	15 (20.8%)	**0.009**
	Stage 2	4 (44.4%)	28 (38.9%)	
	Stage 3	0 (0%)	16 (22.2%)	
	Stage 4	0 (0%)	13 (18.1%)	
Proteinuria		0 (0%)	24 (33.3%)	**0.052 (S)**
Hyperuricemia		0 (0%)	13 (18.1%)	0.342
Hypoalbuminemia		0 (0%)	2 (2.8%)	0.789
Iron	**Normal**	9 (100%)	64(88.9%)	0.317
	Decreased	0 (0%)	7 (9.7%)	
	Increased	0 (0%)	1 (1.4%)	
Ferritin	**Normal**	8(88.9%)	45(62.5%)	0.125
	Decreased	0 (0%)	1(1.4%)	
	Increased	1(11.1%)	26 (36.1%)	
TIBC	**Normal**	9 (100%)	56 (77.8%)	0.128
	Decreased	0 (0%)	15 (20.8%)	
	Increased	0 (0%)	1 (1.4%)	
Transferrin level	**Mean ±SD**	39.29±11.21	33.61±16.32	0.315

There was a statistically significant difference between erythrocytosis group and non-erythrocytosis group regarding graft function as 77.8% of anemic patients had borderline and impaired graft function, but 100% of non-anemic patients had good graft function (**Figure 4**).

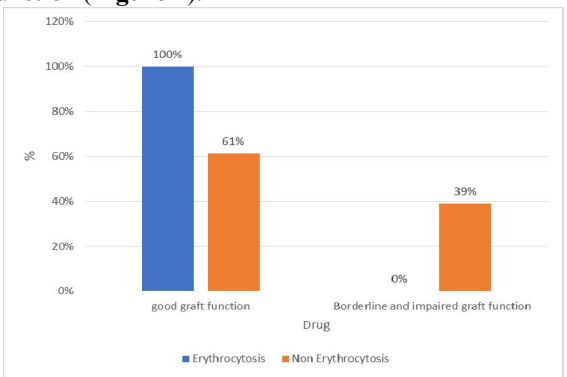

Figure (4): Comparison between Erythrocytosis group and non-erythrocytosis group regarding Graft function

The regression analysis showed that no factors could be considered as independent factors that predict cases from controls in erythrocytosis groups, while we found that each of history of hypertension, HCT level, and PTH hormone considered as independent factors that predict cases from controls in anemic groups (**Supplementary file no. 1**).

4. Discussion:

While numerous reports have characterized the prevalence and risk factors of acute PTA and PTE, there is a scarcity in the published reports regarding their chronic forms. Thus, we conducted the present study to investigate the prevalence and risk factors of PTA and PTE. In the present study, we found that the prevalence of PTA was 44.4%, mainly normocytic anemia; almost one-third of anemic patients had severe anemia. On the other hand, 11.1% of the patients had erythrocytosis. Patients with history of rejection, higher number of rejection episodes. and cell-mediated rejection were more likely to have PTA.

In addition, patients with PTA were more likely to receive anti-thymocyte globulin, intravenous immunoglobin (IVIG), rituximab, and plasmapheresis. Patients with more decline in kidney functions had higher risk of PTA and PTE. Regarding the impact of PTA and PTE on patients' outcomes, we found that patients with PTA and PTE were more likely to have impaired graft function than patients with normal hematological parameters. On multivariate analysis, only history of hypertension and hyperparathyroidism were independent predictors of PTA.

PTA is a common finding which can persist for up to five years after transplantation. On the other hand, PTE presents in 10-20% of kidney transplant recipients(15). In the present cross-sectional study, we found that the prevalence of PTA was 44.4%, mainly normocytic anemia; almost one-third of anemic patients had severe anemia. On the other hand, 11.1% of the patients had erythrocytosis. In agreement with our findings, Wu and colleagues(16) reported that 38.3% of renal transplant recipients had at least one episode of PTA over a 5 years period. A more recent report from Australia showed that the prevalence of PTA was 45.6%, mainly moderate-to-severe anemia(17). In their survey over 16 European countries, Vanrenterghem and colleagues(18) reported that the overall prevalence of PTA was 38.6%. Other studies reported a PTA prevalence of 45%(19) and 36.2%(20). However, other reports showed lower prevalence of PTA. For example, the MOST study demonstrated that only 22.7% of the renal transplant recipients had PTA(21). Imoagene-Oyedeji and colleagues(22) reported that the prevalence of PTA was 20% at 12 months after transplantation. Regarding the prevalence of PTE, a retrospective review of 500 renal transplant recipients reported that the prevalence of PTE was 20%(23).

Several risk factors were implicated in the development and persistence of PTA. Normal graft function is expected to restore the normal level of erythropoietin (EPO) and, subsequently, the normal hemoglobin level; thus, graft dysfunction and EPO resistant are thought to be the most important determinants of the development of PTA(24). In addition, prolonged exposure to immunosuppressive agents can lead to chronic suppression of erythropoiesis and higher susceptibility to viral infection(25,26). Other risk factors for PTA include transplant rejection (which can lead to sharp decline in erythropoiesis and inflammatory response), nutritional deficiencies, and blood ABO-incompatible transplantation(11). In the present study, we found that patients with history of rejection, higher number of rejection episodes. cell-mediated rejection, impaired renal function, history of chronic immunosuppressive exposure, and hyperparathyroidism were more likely to have PTA. Similar to our findings, a large cohort study found that impaired renal functions was associated with higher risk of PTA(27). Elsayed and colleagues(19) reported that higher number of graft rejections, impaired renal function, and infections were associated with increased risks of PTA. Similar findings were reported by other studies(17,18).

The impact of PTA and PTE on the outcomes of transplant recipients has been a matter of debate over the past few years. Numerous reports linked PTA to increased risks of mortality and graft dysfunction in transplant recipients; while other reports showed no significant association(28–30). In the present study, we found that patients with PTA and PTE were more likely to have impaired graft function than patients with normal hematological parameters.

We acknowledge that the present study has a number of limitations. The study was conducted in one center only which may affect the generalizability of our findings. Another limitation is the small sample size which can further affect the generalizability of our findings.

In conclusion, chronic PTA and PTE are common in transplant recipients. We found that patients with history of rejection, higher number of rejection episodes. cell-mediated rejection, impaired renal function, history of chronic immunosuppressive exposure, and hyperparathyroidism were more likely to have PTA. Therefore, it is recommended that physicians involved in renal transplantation consider the investigation and follow-up of transplant recipients for PTA and adopt appropriate preventive and therapeutic measures. In addition, we recommend further studies on more large number of patients with focus on the link between post-transplantation cytopenia and mortality.

Conflict Of Interest:

All authors confirm no financial or personal relationship with a third party whose interests could be positively or negatively influenced by the article's content.

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