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ORIGINAL ARTICLE

Early and Late Post Transplantation Anemia in Kidney Transplant Patients: A Retrospective Study

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Abstract

***Background**: The post-transplantation anemia is commonly reported nationally and internationally. Anemia following kidney transplant is causing many co-morbidities and poor prognosis of transplant.*
***Objective**: To assess the early and late post transplantation anemia in kidney transplant recipient and identifying risk factors related anemia.*
***Methodology**: This study was a retrospective observational study implemented in Nephrology department of Erbil Teaching Hospital and Paky private hospital in Erbil city-Kurdistan region/Iraq during the period of three years from 1st of May, 2019, to 30th of April, 2022 on convenient sample of fifty patients underwent kidney transplant. The anemia was diagnosed according to World Health Organization (<13mg/dl in men and <12mg/ dl in women). The diagnosis of graft failure was done by nephrologists and kidney transplant physician. The patients were followed retrospectively within last 6 months.*
***Results**: All studied patients had early and late PTA. The mean eGFR was significantly increased late post-transplant. The means of hemoglobin, hematocrit, MCV, RDW, iron, serum ferritin, TSAT and folic acid levels were significantly increased late post-transplant of kidney. On other hand, means of transferrin, vitamin B12 and TSH levels were significantly decreased late post-transplant of kidney. The positive dialysis history and graft failure are the common risk factors affecting anemia prevalence post-transplantation.*
***Conclusions**: The prevalence of early and late post-transplant anemia is high. However, the serum hemoglobin and iron levels are increased long term after kidney transplant.*

Keywords**: **Post-transplantation anemia, Early, Late, Hemoglobin level

1. INTRODUCTION

The anemia is a chronic disorder affecting one-third of population all over the world in which the hemoglobin (Hb) level and/or red blood cells (RBCs) count are under normal ranges that negatively affect the physiological processes of human body (1,2). The anemia is a serious public health problem accompanied by many co-morbidities especially for women and children (3), low productivity in adults (4) and independent risk factor for all-cause mortality in developing countries (5). The anemia is linked to many chronic debilitating disorders such as chronic kidney disease (CKD) (6). In patients with CKD, the pathophysiology is complicated as it is attributed to low erythropoietin hormone productivity, short life span of RBCs and inflammatory effect. The anemia of CKD patients is accompanied by poor outcomes and low survival of patients . It was shown that anemia prevalence increases with worsening of CKD and the anemia prevalence was correlated positively to estimated glomerular filtration rate of CKD patients (7,8). Post-Transplant anemia (PTA) is a common complication of kidney transplant with range of 20% to51% (9–14). Prevalence of PTA is dependable on anemia definition and time of anemia following transplant (15). It was shown that kidney transplant has a direct impact on development of anemia as compared to general population (16). The severe anemia was reported in 8.5% of patients post-transplant and the common risk factors aggravating anemia are graft dysfunction, infections and the use of some drugs and cytototoxic agents (11). The PTA is different from anemia caused by CKD that need modified management approach (16). The etiology of PTA is classified into PTA attributed to reduced production of RBCs, elevated rates of RBCs destruction, or RBCs loss (17). The PTA is categorized into early and late PTA in regard to time of diagnosis. Early PTA could be diagnosed in 80% of patients few months postoperatively that reduced to 20% as late PTA 12 months postoperatively (18). Preoperatively, the anemia is prevalent and related to chronic kidney disease and depletion of iron stores. Early PTA is diagnosed within first 6 months post-transplantation and is related commonly to preoperative anemia and iron depletion in addition to intraoperative hemorrhage, high frequency of blood sampling postoperatively and the dilution effect of hydration aggressively (18). On other hand, late PTA is diagnosed more than 6 months after kidney transplant and attributed mainly to graft dysfunction (19).

The late PTA is shown among 23% to 36% of post-transplant patients and can be presented late to 8 years post-transplant (10,20). In addition to graft function, the infection, iron deficiency, immunosuppressant effect and other factors might lead to late PTA (10,13). Many authors reported the link between graft dysfunction and PTA. One meta- analysis study revealed association of anemia with graft failure but inconclusive association was recorded between PTA and death of patients with functioning graft (21). In many studies, the PTA was negatively associated with long-term outcomes like increased all-cause mortality rates (14,22,23), graft failure (12,24), congestive heart failure (25) and reduced estimated glomerular filtration rate (eGFR) (14,20). Unfortunately, most of literatures discussing the PTA etiology were not assessing the severity level except on study classified the hemoglobin levels in relation to graft failure (24). Late PTA is related commonly to iron deficiency, renal dysfunction, frequent transplantations, donor's age, infection, immunosuppressant use, renin angiotensin axis agents' use, and reduced erythropoietin level (26). The PTA etiology mainly iron deficiency anemia is directly related to long-term prognosis (27). In Iraq, the kidney transplant has started since about 50 years ago and the outcome of kidney transplant is improving in last year's. However, long-term patient follow-up requires more qualitative care (28). In Kurdistan region, the kidney transplant started since 2006 with developing outcomes and prognosis (29). More than half of Iraqi patients on hemodialysis had functional iron deficiency anemia lead to altering in response to erythropoiesis- stimulating agents (30). It was shown that Iraqi patients subjected to renal transplantation is prevalent with anemia. PTA among Iraqi patients is related mainly to graft dysfunction in addition to effect of immunosuppressant agents (31). However, there is a scarcity in national literatures discussing the early and late PTA hemoglobin level with other factors. For that, this study aimed to assess the early and late post transplantation anemia in kidney transplant recipient and identifying risk factors related anemia.

2. METHODOLOGY

The design of present study was a retrospective observational study implemented in Nephrology department of Erbil Teaching Hospital and Paky private hospital in Erbil city-Kurdistan region/Iraq during the period of three years from 1st of May, 2019, to 30th of

April, 2022. The studied population was all patients underwent kidney transplant during study duration. Inclusion criteria were adult patients (age≥ 18 years) underwent kidney transplant during study duration in last three years and completed registry and investigations of studied patients. Exclusion criteria were younger age patients, patients underwent second kidney transplant, patients with hematological malignancies, incomplete or missing data and lost to follow up. The study ethics were implemented in regard to Helsinki Declaration by documented approval of health authorities and confidentiality of data. A convenient sample of fifty patients underwent kidney transplant was enrolled in current study after eligibility to inclusion and exclusion criteria. Data of patients were collected retrospectively by researcher through a prepared questionnaire designed by the researchers according to previous literatures (5,6,11,14). The questionnaire included general characteristics of patients underwent kidney transplant (age, age at transplant, gender, body mass index and original renal disease), dialysis history and outcome of patients underwent kidney transplant (dialysis history, dialysis duration, duration of hospitalization, clinical co-morbidities, graft failure, cardiovascular complications and mortality) and investigations measures early and late post-transplant (estimated glomerular filtration rate, hemoglobin level, hematocrit level, mean corpuscular volume, red cell distribution width, platelets, leukocyte, serum iron, serum ferritin, transferrin level, transferrin saturation, vitamin B12 level, folic acid level and thyroid stimulating hormone level). Early post-transplantation anemia was defined as anemia occurred at first 6 months following kidney transplant, while late post-transplantation was defined as anemia occurred after first 6 months following kidney transplant (18,19). The anemia was diagnosed according to World Health Organization (WHO) definition depending on hemoglobin level (<13mg/dl in men and <12mg/ dl in women) (32). All investigations were implemented in Erbil Teaching Hospital and Paky private hospital. The diagnosis of graft failure was done by nephrologists and kidney transplant physician by calculating eGFR according to (CKD-EPI; 2009) and by kidney biopsy. The patients were followed retrospectively within last 6 months. All patients with anemia were managed accordingly by nephrologists in the hospitals. The patients' information were entered and interpreted statistically by SPSS program-Suitable statistical

tests (Fishers exact test) for data were implemented accordingly and p value of ≤0.05 was significant.

3. RESULTS

In this study, fifty patients with kidney post-transplant were enrolled with mean age of (47.4 years) and mean age of transplant of (44.8 years). Male patients were more than females (56% vs. 44%). Mean body mass index of patients was (25.1 Kg/m2) and the common original renal disease was unknown (32%); followed by diabetes mellitus (30%) and hypertension (22%), etc. (Table 1). The dialysis history was positive in 90% of patients and mean duration of dialysis before transplant was (5.1 months, while mean duration of hospitalization following transplant was (6.1 days). Clinical co-morbidities were absent in 42% of studied patients, while common co-morbidities were HT & DM (20%), HT (18%), DM (8%), etc. Graft failure was reported in 10% of patients post-transplant and CVD complications in 14% of them, while all studied patients had early and late PTA and no mortality was reported. (Table 2). The mean eGFR was significantly increased late post-transplant ($p=0.001$). The means of hemoglobin, hematocrit, MCV, RDW, iron, serum ferritin, TSAT and folic acid levels were significantly increased late post-transplant of kidney ($p<0.001$). On other hand, means of transferrin, vitamin B12 and TSH levels were significantly decreased late post-transplant of kidney ($p<0.001$, $p<0.001$, $p=0.007$, respectively). The means of platelets and leukocytes were not significantly different early and late post-transplant ($p>0.05$). (Table 3). The means of eGFR, hemoglobin and iron levels were significantly increased late post-transplant of kidney in patients with positive dialysis history ($p<0.001$). The means of eGFR, hemoglobin and iron levels were not significantly different early and late post-transplant in patients with negative dialysis history ($p>0.05$). (Table 4). No significant differences were observed between patients with graft failure and patients with no graft failure regarding age ($p=0.36$), age at transplant ($p=0.28$), gender ($p=0.44$), body mass index ($p=0.6$) and original renal disease ($p=0.56$). (Table 5). No significant differences were observed between patients with graft failure and patients with no graft failure regarding dialysis history ($p=0.43$), duration of hospitalization ($p=0.48$) and clinical co-morbidity ($p=0.75$). There was a significant association between longer dialysis duration and graft failure ($p=0.007$). (Table 6). The

means of eGFR, hemoglobin and iron levels late post-transplant were significantly lower in patients with graft failure ($p<0.05$). (Table 7).

Table 1. General characteristics of patients with kidney post-transplant.

Variable		No.	%
Age (year)	<40	13	26
	40-49	13	26
	50-59	15	30
	≥60	9	18
	Mean (SD):	47.4 (13)	-
Age at transplant (year)	<30	8	16
	30-39	8	16
	40-49	13	26
	≥50	21	42
	Mean (SD):	44.8 (13)	
Gender	Male	28	56
	Female	22	44
BMI	Normal	32	64
	Overweight	11	22
	Obese	7	14
Original renal disease	Unknown	16	32
	DM	15	30
	HT	11	22
	FSGS	6	12
	Membranous neuropathy	1	2
	IgA neuropathy	1	2

SD: standard deviation of mean, BMI: Body mass index, DM: diabetes mellitus, HT: hypertension, FSGS: Focal segmental glomerulosclerosis

Table 2. Dialysis history and outcome of patients with kidney post-transplant.

Variable		No.	%
On dialysis	Yes	45	90.0
	No	5	10.0
Duration of dialysis (months)	<6	28	62.2
	≥6	17	37.8
	Mean ± SD	5.1±2.3	-
Duration of hospitalization	Mean ± SD	6.1 ± 1	-
	< one week	33	66.0
	≥ one week	17	34.0
Clinical comorbidities	HT	9	18.0
	DM	4	8.0
	HT & DM	10	20.0
	HT & CVA	1	2.0
	HT, DM & CVA	5	10.0
Graft failure		5	10.0
Cardiovascular complications		7	14.0
Early PTA		50	100.0
Late PTA		50	100.0
Mortality		0	0.0

SD: standard deviation of mean

Table 3. Distribution of investigations measures early and late post-transplant

Variable	Post-transplant				P. value
	Early		Late		
	Mean	SD	Mean	SD	
eGFR (ml/min/1.73 m^2)	62.6	13.1	74.7	19.4	0.001 S
Hemoglobin (g/d)	7.90	1.12	10.5	1.2	<0.001 S
Hematocrit (%)	25.1	4.5	33.6	5.1	<0.001 S
MCV (fL)	78.0	6.6	83	4.9	<0.001 S
RDW (%)	13.4	1.6	15.8	1.3	<0.001 S
Platelets (x10^3)	221.8	72.1	230.2	54.2	0.50 NS
Leukocyte (x10^3)	7.40	2.0	7.9	1.7	0.17 NS
Iron (mcg/dl)	53.7	14.4	71.2	20.7	<0.001 S
S. ferritin (ng/ml)	79.3	74.3	244.5	123.8	<0.001 S
Transferrin (mg/L)	397.1	101.1	342.7	77.3	<0.001 S
TSAT (%)	14.5	4.9	21.2	5.5	<0.001 S
Vitamin B12 (pg/ml)	616.2	183	353.7	161.6	<0.001 S
Folic acid (ng/ml)	5.20	1.8	8.0	2.0	<0.001 S
TSH (mIU/L)	3.68	3.7	2.4	2.5	0.007 S

S: Significant, NS: Not significant, SD: standard deviation of mean

Table 4. Distribution of investigations measures early and late post-transplant according to dialysis history.

Variable	Post-transplant				P. value
	Early		Late		
	Mean	SD	Mean	SD	
Positive dialysis history					
eGFR (ml/min/1.73 m^2)	62.1	13.7	75.8	18.6	0.001 S
Hemoglobin (g/d)	7.9	1	10.6	1.2	<0.001 S
Iron (mcg/dl)	54	14.9	71.2	21.3	<0.001 S
Negative dialysis history					
eGFR (ml/min/1.73 m^2)	66.8	3.7	65	26	0.8 NS
Hemoglobin (g/d)	8.4	1.6	9.7	1.2	0.29 NS
Iron (mcg/dl)	50.6	8.4	71.6	15.2	0.09 NS

S: Significant, NS: Not significant, SD: standard deviation of mean

Table 5. Distribution of general characteristics according to graft failure.

Variable		Graft failure				P. value
		Yes		No		
		No.	%	No.	%	
Age (Year)	<40	0	0	13	28.9	0.36 NS
	40-49	1	20	12	26.7	
	50-59	2	40	13	28.9	
	≥60	2	40	7	15.6	
Age at transplant (Year)	<30	0	0	8	17.8	0.28 NS
	30-39	0	0	8	17.8	
	40-49	1	20	12	26.7	
	≥50	4	80	17	37.8	
Gender	Male	2	40	26	57.8	0.44 NS
	Female	3	60	19	42.2	
Body mass index	Normal	4	80	28	62.2	0.6 NS
	Overweight	1	20	10	22.2	
	Obese	0	0	7	15.6	
Original renal disease	Unknown	2	40	14	31.1	0.56 NS
	HT	0	0	11	24.4	
	DM	3	60	12	26.7	
	FSGS	0	0	6	13.3	
	Membraneous	0	0	1	2.2	
	IgA neuropathy	0	0	1	2.2	

NS: not significant

Table 6. Distribution of dialysis characteristics according to graft failure.

Variable		Graft failure				P. value
		Yes		No		
		No.	%	No.	%	
On dialysis	Yes	4	80.0	41	91.1	0.43 NS
	No	1	20.0	4	8.9	
Duration of dialysis	<6 months	0	0.0	28	68.3	0.007 S
	≥6 months	4	100.0	13	31.7	
Duration of hospitalization	< one week	4	80.0	29	64.4	0.48 NS
	≥ one week	1	20.0	16	35.6	
Clinical co-morbidities	None	2	40.0	19	42.2	0.75 NS
	HT	0	0.0	9	20	
	DM	1	20.0	3	6.7	
	HT & DM	1	20.0	9	20	
	HT & CVA	0	0.0	1	2.2	
	HT, DM & CVA	1	20.0	4	8.9	

S: Significant, NS: Not significant

Table 7. Distribution of late post-transplant investigations according to graft failure

Variable	Graft failure				P. value
	Yes		No		
	Mean	SD	Mean	SD	
eGFR (ml/min/1.73 m^2)	20.2	4.50	80.8	6.60	0.001 S
Hemoglobin (g/d)	7.6	0.60	10.9	0.70	<0.001 S
Iron (mcg/dl)	52.0	15.7	73.4	20.2	0.20 S

S: Significant, SD: standard deviation of mean

4. DISCUSSION

The post-transplant anemia is frequently registered in many transplant centers globally. Correcting anemia following transplant is essential in yielding better outcomes of kidney transplant, avoidance of complications and improving health and life related quality of patients (33).

In the current study, all studied patients had early and late anemia post-transplantation of kidney. This finding is higher than results of Al-Lami et al. (31) study in Iraq on 112 patients

after kidney transplant which showed that early anemia was shown in 25% of patients. Additional our study findings regarding early and late PTA are also higher than results of Gafter-Gvili et al. (14) single center retrospective cohort study in Palestine on 266 patients after kidney transplant which recorded the early PTA in 51.3% of patients and late PTA in 36.6% of them. This high difference might be attributed to fact that 90% of studied patients were on dialysis in addition to effect of iron depletion, clinical co-morbidity with other chronic diseases and immunosuppressant effect. Although high prevalence of anemia, our study revealed a significantly increase in serum hemoglobin, hematocrit, MCV and RDW levels from early to late post- transplant period. These findings are in agreement with results of Lim et al. cross sectional study in Australia which reported an increase in serum hemoglobin, hematocrit, MCV and RDW levels after 12 months post-transplant compared to the levels after 6 months post-transplant. Many authors reported the reduction in anemia prevalence 6 months after transplant as compared to pre-transplant and further reduction in anemia prevalence 12 months post-transplant as compared to 6 months post-transplant (34–36).

Our study found that serum iron, serum ferritin, TSAT and folic acid levels were significantly increased late post-transplant of kidney ($p<0.001$). These findings are consistent with results of Zheng et al. (37) retrospective study in USA which revealed a significant increase in serum iron, serum ferritin, TSAT and folic acid levels one year after kidney transplant. In our study, mean of transferrin level was significantly decreased late post-transplant of kidney ($p<0.001$). Similarly, Schechter et al. (38) reported low transferrin level at late post-transplant kidney as compared to early post-transplant.

The current study found the mean vitamin B12 level was significantly decreased late post-transplant of kidney ($p<0.001$). This finding coincides with results of Pontes et al. (39) study in Brazil which documented high prevalence of vitamin B12 deficiency late post-transplant of kidney. In present study, mean of TSH level was significantly decreased late post-transplant of kidney ($p=0.007$). Schairer et al. (40) study in Austria revealed a negative relationship between TSH level and eGFR of patients after kidney transplant.

Our study found that mean eGFR was significantly increased late post-transplant ($p=0.001$). This finding is parallel to results of many literatures such as Ali et al. (28) study in Iraq and

Baek et al. (41) study in South Korea which all documented an increase in eGFR of patients one year after kidney transplant. In present study, means of eGFR, hemoglobin and iron levels were significantly increased late post-transplant of kidney in patients with positive dialysis history ($p<0.001$), while means of eGFR, hemoglobin and iron levels were not significantly different early and late post-transplant in patients with negative dialysis history ($p>0.05$). Regarding eGFR, our study finding is similar to results of Schold et al. (42) study in USA. Regarding hemoglobin and iron levels, our study findings are close to results of Afzali et al. (43) study in UK which revealed that hemoglobin and iron levels were significantly reduced in pre-transplant phase by dialysis, which improved obviously after kidney transplant.

The current study found a significant association between longer dialysis duration and graft failure ($p=0.007$). This finding coincides with results of Aufhauser et al. (44) study in USA which reported that longer duration of pre-transplant dialysis is associated with poor outcomes of kidney transplant. Our study showed that mean eGFR in late post-transplant was significantly lower in patients with graft failure ($p=0.001$). Consistently, Clayton et al. (45) study in Australia reported significant relationship between eGFR decline and graft failure. In current study, means of hemoglobin and iron levels late post-transplant were significantly lower in patients with graft failure ($p<0.05$). These findings are similar to results of Malyszko et al. (46) study in Poland which stated that late post-transplant anemia was related to graft failure.

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5. CONCLUSIONS

The prevalence of early and late post-transplant anemia is high. However, the serum hemoglobin and iron levels are increased long term after kidney transplant. The positive dialysis history and graft failure are the common risk factors affecting anemia prevalence post-transplantation. This study recommended earlier treatment of anemia with strict monitoring of blood indices to avoid complications.

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Ethical Clearance:

All ethical issues approved by the authors from the local authorities. Patients enrollment and data collection were in accordance with the World Medical Association (WMA), declaration of Helsinki, The Ethical Principles for Medical Research Involving Human Subjects, 2013

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