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ORIGINAL ARTICLE

Assessment of the Risk Factors and Different Lines of Treatment of Anemia in Kidney Transplant Recipients

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ABSTRACT

Background: This study aimed to screen the prevalence, etiologies of post transplantation anemia PTA, its implication on graft function and efficacy of different approaches in the management of anemia in a cohort of kidney transplant recipients. **Methods:** We studied 320 kidney transplant recipients; 160 cases (anemic patients) and 160 control (normal Hb group). Univariate and multivariate analysis were done to evaluate the risk of anemia. A prospective investigation of various etiologies of anemia post renal transplantation were done. complete blood picture, Iron indices, kidney function. Management of anemia according to condition was administered either by iron therapy or erythropoietin stimulating agents (ESA) therapy. Re-evaluation was done after 3 months of continuous treatment by laboratory, radiological and clinical assessment. Resistant cases managed by bone marrow biopsy or modify immunosuppression. **Results:** Our cohort included 320 patients with multiple risk factors that showed statistical significance by Univariate analysis. The risk factors of PTA in our study were female gender (P value< 0.001), odds ratio OR (3.1), old age (P value 0.001), low pre-transplant Hemoglobin P value (0.002), acute rejection (P value< 0.007), OR (2.5), number of acute rejections (P value 0.04) OR (4.9), chronic rejection (P value 0.004) OR (2.1), Bacterial infections (P value 0.047) OR (2.1). Low iron indices were also risk factors; ferritin, P value (0.005), transferrin saturation (TSAT) P value (0.040) and were associated with Low estimated glomerular filtration rate (eGFR) (at 0,3,6,12,24 months) in anemic patients (89.7 ± 31.1, 85.3 ± 31.6, 84.1 ± 32, 81.8 ± 31.3, 80.9 ± 32.5) respectively. **Conclusion:** The risk factors of PTA in our study were female gender old donors, acute rejection, chronic rejection, number of acute rejections, bacterial infections and low iron indices associated with progressive decline eGFR.

Keywords: Anemia; Kidney Transplant; Post transplantation anemia**.**

INTRODUCTION

Post-transplant anemia (PTA) is a common issue in kidney transplant recipients. Important factors associated with PTA are a reduced allograft function [1]. The PTA likely contributes to graft loss [2]. Evaluation of anemia should be undertaken when hemoglobin fails to normalize by 3 months after transplantation [3]. Anemia was defined by WHO as hemoglobin concentration <12 g/dl in women and <13 g/dl in men [4]. Transplant recipients differ from other patients with chronic kidney disease because they bear the additional burden of therapy with immunosuppressive drugs that may directly exacerbate anemia [5]. Other factors commonly associated with PTA include recipient age, female gender and donor age [6]. More recent data have suggested strong associations of anemia with graft failure and mortality [7]. Anemia correction in kidney transplant recipients KTR slows the decline in GFR and improves quality of life (Qol) [8]. We aimed from this study to identify risk factors for development of anemia post transplantation and study efficacy of different approaches in the management of anemia in renal transplant recipients. We studied anemia in kidney transplant recipients with normal or near serum creatinine and we excluded kidney transplant recipients with compromised kidney function from our study, and others studied patients with compromised kidney function.

METHODS

In our study prospective cohort study, we performed screening of the prevalence, various etiologies of PTA; its implication on graft function and rejection episodes and efficacy of different approaches in the management of anemia in a cohort of kidney transplant recipients We studied 320 kidney transplant recipients; 160 cases (anemic patients) and 160 control (normal Hb

group). This study was carried out in Urology and nephrology center, Mansoura university, and included patients who underwent kidney transplantation and completed follow up for ≥ 3months and were still anemic. Patients with compromised graft function, pregnant female recipients, recipients with acute blood losses and recipients with active malignancy or on chemotherapy treatment were excluded.

Univariate and multivariate analysis were done to evaluate the risk of anemia. A prospective investigation of various etiologies of PTA were done. Investigation of multiple laboratory data including complete blood picture, Iron indices, and kidney function, glomerular filtration rate (eGFR) was estimated by Modification of Diet in Renal Disease Study Group (MDRD) equation [9].

-Anemia was defined as Hemoglobin less than 13, and 12 g/dl in male, and female respectively [10]. Anemia was managed according to each condition either by:

-Oral iron therapy for iron deficiency: ferritin <100 ng/mL, and total saturation of transferrin (TSAT) < 20% [11] ; oral iron ferrous fumarate tablet 375mg/ day .

-Intravenous iron was administered to patients with severe iron deficiency (transferrin saturation [TSAT] <12 %, severe anemia in asymptomatic patients with [Hb] <9 g/dL(male) and <8g/dl (female). IV iron was calculated according to iron deficit.

-Erythropoietin stimulating agents (ESA) therapy was administered to patients with normal iron indices or persistent anemia after correction of iron indices, or both. The dose of Epoetin A was 80-120 IU / Kg per week. Re-evaluation was done after 3 months of continuous treatment by both laboratory, radiological and clinical assessment .

-Resistant cases were managed by bone marrow biopsy or modification immunosuppression by reducing the dose of the antimetabolite, typically by 50%.

The study protocol was submitted for approval by Mansoura urology and nephrology center Mansoura university medical research ethics committee. Informed consent was obtained for each patient in the study.

STATISTICAL METHODS

All analyses were performed with SPSS software (SPSS: An IBM company, version 21.0, IBM Corporation, Armonk, NY, USA). Different groups were compared by different statistical tests according to data type. Univariate analysis: Student t-test: to compare symmetrically distributed continuous data between 2 groups. Chi-square test: categorical data. Q-Q plot test used to determine the normality of data distribution. Multivariate analysis: Linear regression test: for continuous data between 2 groups. Logistic regression: for categorical data.

RESULTS

Anemic and control groups were compared regarding demographic data and baseline characteristics. There was a statistically significant difference regarding recipient sex as most of anemic group were females and control group were males (p: 0.0001). The age of donors was higher, pre-transplant hemodialysis duration, need for iron therapy, number of blood transfusions, all were higher in anemic group compared to control group with statistical significance. The body mass index was higher in control group than anemic group with statistical significance (p: 0.013) (Table 1) .

The type of maintenance immunosuppression was comparable in both groups (Table 2). Acute rejection types, both (cellular and vascular) were significantly higher in anemic group (p: 0.016). Number of rejection episodes was significant higher in anemic group than normal Hb. Group (p: 0.0075). Chronic rejection was significant higher in anemic group (p: 0.0001). (Table 3) .

Post-transplant medical complications prevalence was comparable among both groups except for bacterial infection which was higher among anemia group (p: 0.0005) (Table 3) .

Serum creatinine and creatinine clearance were compared at baseline, but serial follow up of serum creatinine supplementary figure (1) and creatinine clearance at (3 months, 6 months, 12 months and 24 months) had significant rise of serum creatinine and significant drop of eGFR in anemic group (statistically significant) (Table 4).

The serum Hb. was significantly lower in anemic group than control group at baseline of study. During serial follow up, serum Hb. showed significant rise and improvement but still significantly lower than control group (Table 5) (supplementary figure 1) .

Iron indices were significantly impaired in anemia group (Table 5).

Secondary evaluation: After 3-month follow-up (3 months after study initiation). Out of 77 patients received oral iron, 40 patients showed full improvement of iron indices and anemia. Ten patients showed improvement of iron indices but no improvement regarding anemia. They started ESA therapy. 27 patients did not show good response to oral iron regarding iron indices or hemoglobin levels. They started IV iron. (Figure 2).

Tertiary evaluation: (6 months after study initiation), 22 patients out of 27 received iv iron in the secondary evaluation showed improvement of iron indices and anemia. Five patients started ESA

therapy. Twelve patients out of 20 received ESA therapy after secondary evaluation showed improvement. 8 patients were resistant to anemia The resistant 5 patients proceeded for GIT endoscopy and the result showed significant findings then was managed by gastroenterologist. The other 3 patients were managed by immunosuppression modification (Figure 2). Five cases were excluded from the study after diagnosis of malignancy during work-up for anemia management. Bone marrow biopsy was performed, and the patients were diagnosed as hematological malignancy (Supplementary Table 1) .

Multiple risk factors showed statistical significance by univariate analysis. These factors were entered multivariate as shown in (Supplementary Table 2) and we found that the most important risk factors for PTA were sex of recipient (female), age of donor, acute rejection, chronic rejection, and bacterial infection.

Table 1: demographic data and baseline characteristics among studied groups

	Anemic group (160 KTRs) No. (%)	Normal Hb. group (160 KTRs) No. (%)	p value
Recipient age (years) mean±SD	27 ± 9.2	28 ± 10.5	0.45
Recipient Sex (female)	84 (52.5%)	42(26.2%)	0.0001
Donor age (years) mean±SD	41.3 ± 9.24	37 ± 9.3	0.001
Donor Sex (male):	68 (42.5%)	68 (42.5%)	0.605
Special habits (Smoker):	7 (4.4%)	7 (4.4%)	0.786
BMI (Kg/m2) mean ±SD	7 ± 4.5	24.9 ± 4.1	0.013
Hypertension	60 (37.5%)	86(55.8%)	0.004
Diabetes	1 (0.625%)	1 (0.625%)	0.5
Hepatitis C	10 (6.2%)	28 (17.5%)	0.022
Hemodialysis:	144 (90%)	150 (93.8%)	0.22
Hemodialysis Duration (years) mean±SD	1.8 ± 0.7	1.6 ± 0.7	0.011
Erythropoietin use:	85 (53.1 %)	64 (40%)	0.019
Pre-transplant iron therapy:	91 (56.87%)	70 (43.65%)	0.012
Pre-transplant hemoglobin mean±SD	9.8 ± 1.44	11.3 ± 0.9	0.0002
Prior blood transfusion:	56 (35.5%)	49 (30.6%)	0.405
Number of blood transfusion units mean±SD	1.84 ± 0.5	1.4 ± 0.2	0.001
Blood group: Same different	122 (76.2 %) 38 (23.8 %)	127 (79.4 %) 33 (20.6 %)	0.501

KTRs: Kidney transplant recipients

Table 2: Primary plan for immunosuppressive medications

	Anemic group (160 KTRs) No. (%)	Normal Hb. group (160 KTRs) No. (%)	p value
Induction therapy:	155 (96.9%)	151 (94.4%)	0.274
Type of induction: **ATG** **Basiliximab**	 3 (1.9%) 152 (95%)	 7 (4.4%) 144 (90%)	0.161
Steroid-based	97 (60.6 %)	104 (65 %)	0.418
Cyclosporine-based	19 (11.9 %)	20 (12.5 %)	0.864
Tacrolimus-based	137 (85.6 %)	133 (83.1 %)	0.538
mTORI –based	20 (12.5 %)	21 (13.1 %)	0.867
Mycophenolate-based	125 (78.1 %)	120 (75 %)	0.509
Azathioprine-based	14 (8.8 %)	20 (12.5 %)	0.276

mTORI: mammalian taget of rapamycin inhibitor
ATG: Antithymocytes globulins

Table 3: post-transplant medical complications

	Anemic group (160 KTRs) No. (%)	Normal Hb group (160 KTRs) No. (%)	p value
Acute rejection: **No** **Acute cellular rejection** **Vascular rejection**	 133 (83.125 %) 24 (15%) 3 (1.875%)	 148 (92.5 %) 10 (6.25%) 2 (1.25%)	 0.016
Number of rejection episodes: **0** **1** **≥ 2**	 133 (83.125%) 9 (5.6%) 18 (11.25%)	 148 (92.5%) 8 (5%) 4 (2.5%)	 0.0075
Acute tubular necrosis	6 (3.8%)	6 (3.1%)	0.759
Chronic rejection	17 (10.625%)	6 (3.75%)	0.0001
Hypertension	18 (11.2%)	30 (18.8%)	0.06
Diabetes	3 (1.9%)	6 (3.8%)	0.310
Hepatic impairment	8 (5%)	10 (6.2%)	0.627
Bacterial infection	16 (10%)	8 (5%)	0.0005
Viral infection	10 (6.2%)	9 (5.6%)	0.813
CMV infection	7 (4.5 %)	4 (2.6 %)	0.407

CMV: Cytomegalovirus

Table 4: Serum creatinine and creatinine clearance follow-up over 2 years after transplantation

	Anemic group (160 KTRs) No. (%)	**Normal Hb. group (160 KTRs) No. (%)**	**p value**
S.cr at baseline (mg/dl) mean±SD	1.1 ± 0.33	0.25	0.179
S.cr 3 months (mg/dl) mean±SD	1.24 ± 0.41	1.12 ± 0.25	0.002
S.cr 6 months (mg/dl) mean±SD	1.31 ± 0.65	1.12 ±0.25	0.01
S. cr 12 months (mg/dl) mean±SD	1.40 ± 0.92	1.13 ± 0.28	0.001
S.cr 24 months (mg/dl) mean±SD	1.51 ± 1.36	1.13 ± 0.28	0.001
eGFR at baseline (ml/min) mean±SD	89.7 ± 31.1	95.7 ± 26	0.069
eGFR-3 months(ml/min) mean±SD	85.3 ± 31.6	95 ± 25.2	0.003
eGFR-6 months (ml/min) mean±SD	84.1 ± 32	95.5 ± 27	0.001
eGFR-12 months (ml/min) mean±SD	81.8 ± 31.3	94.3 ± 25.2	0.0001
eGFR-24 months (ml/min) mean±SD	80.9 ± 32.5	95 ± 25.2	0.0001

s.cr : serum creatinine
eGFR: estimated glomerular filtration rate

Table 5: Serum hemoglobin follow-up as mean±SD

	Anemia group (160 KTRs) No. (%)	**Normal Hb. group (160 KTRs) No. (%)**	**p value**
CBC characteristics at baseline			
Hemoglobin (g /dl) mean±SD	10.6 ± 1.3	14.5 ± 1.7	0.001
WBC count (10^3/uL) mean±SD	8 ± 3.2	10.5 ± 2.8	0.281
Platelets number (10^3/uL) mean ±SD	253 ± 90	234 ± 75	0.047
MCV(fL) mean±SD	81.8 ± 16.5	83 ± 6.3	0.380
hematocrit (%) mean ± SD	31.2 ± 4.2	42 .2 ± 5.6	0.0001
Hemoglobin follow up			
At baseline (gm/dl)	10.6 ± 0.3	14.5 ± 1.7	0.0001
After 3 months (gm/dl)	12.4 ± 2.3	14.55 ± 1.7	0.002
After 6 months (gm/dl)	12.14 ± 1.05	14.4 ± 1.34	0.0001
After 1 year (gm/dl)	12.2 ± 1.08	14.4 ± 1.3	0.0001
After 2 year (gm/dl)	12.4 ± 1.05	14.4 ± 1.3	0.0001
Iron studies			
Serum iron (ug /dl) mean±SD	65.62 ± 32.1	99.1 ± 42.1	0.0001
Serum ferritin (ng/ml) mean±SD	297±25	384.5 ± 42.5	0.0001
TSAT % mean±SD	19.3 ± 3.2	30.1 ±5	0.001
TIBC (ug/dl) mean±SD	301 ± 67.5	291.5 ± 11.8	0.04

CBC: complete blood count.
WBC: White blood cells
MCV :Mean corpuscular volume.
TSAT: Total iron binding capacity
TIBC: Total iron binding capacity.

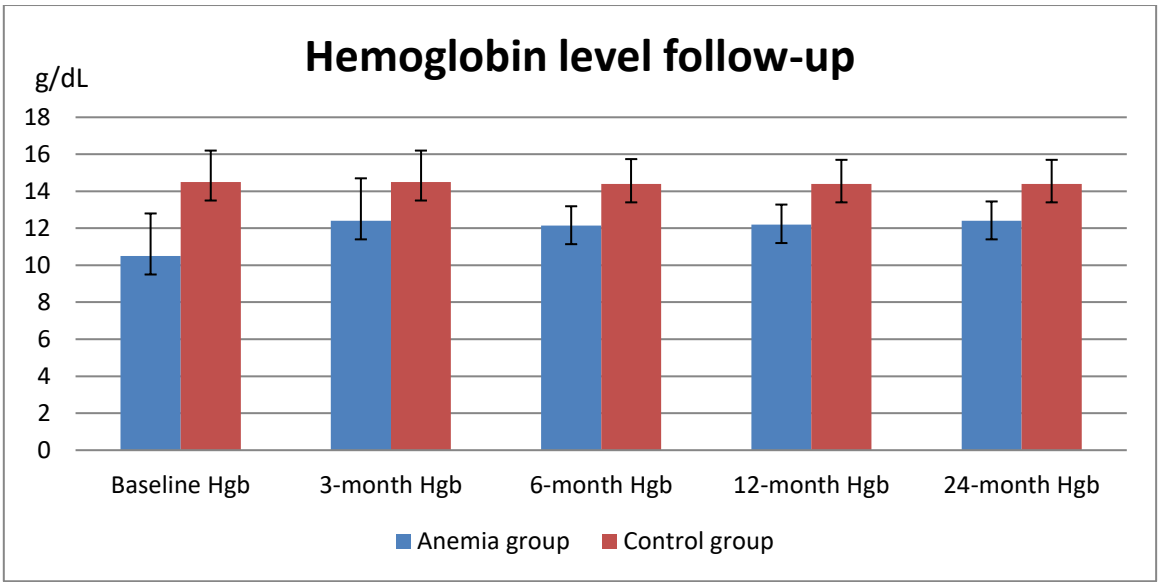

Figure 1: Hemoglobin level serial follow-up

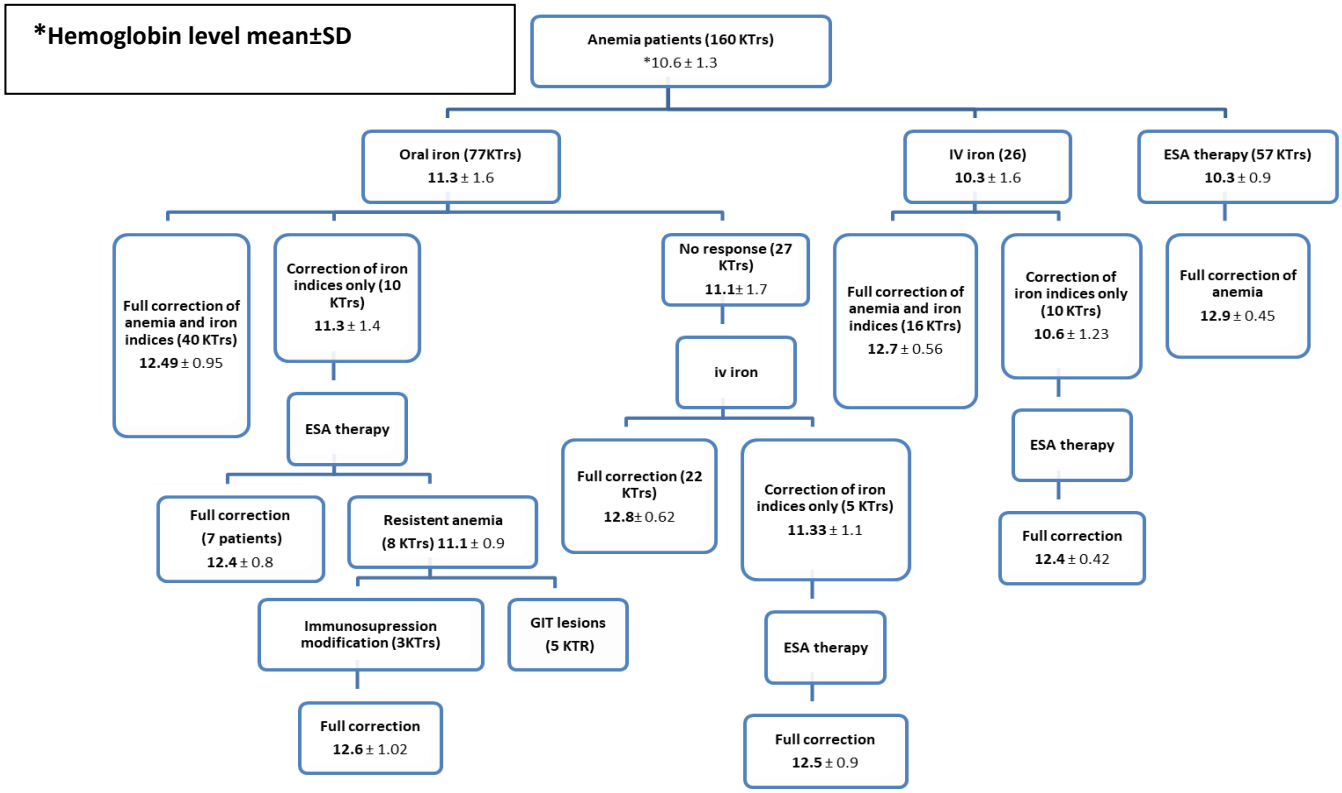

Figure 2: Response to different lines of treatment

DISCUSSION

PTA is a common issue in kidney transplant recipients. Important factors associated with PTA are a reduced allograft function, side effects of immunosuppressive drugs, iron deficiency, infections, older donor age, rejection [1]. As only one kidney is transplanted, kidney function seems to be only partially restored [12].

Many studies revealed the prevalence of anemia at 3 months to be common; (40 %) [13], 39% [14], and 42% [15].

Gafter-Gvili et al, reported high incidences of anemia that approached 40 percent at one year post

transplant, and the prevalence of PTA at 6 months was 51.3% and at 2 years was 36.6% [13]. This difference between our study and other studies may be explained by strict exclusion criteria in our study, as we excluded patients with compromised graft functions and serum creatinine more than 2 mg/dl.

There was a statistically significant difference regarding recipient sex, as most of anemic group were females and control group were males (p value: 0.0001) and this was supported by many studies as Imoagene-Oyedeji et al, who showed that female gender was one of the major determinants of anemia post kidney transplantations [10] and this may be explained by resumption of menstrual blood flow in some women of reproductive age which usually occurs at 6 months after transplant and may result in a threefold higher rate of anemia than observed in their male counterparts, and also approved by other studies [14 , 15 and 16].

The age of donors was higher in anemic group compared to control group with statistical significance , similarly , in a large European survey of patients, six months to five years post-transplant, lower hemoglobin (Hgb) levels were associated with increased donor age (particularly >60 years) [5 and 11] this association of age with anemia may be explained by the fact that old donors may be more liable to DGF, interstitial fibrosis and tubular atrophy[17] .

In this study we found that, the body mass index was higher in control group with statistical significance, and this may be due to improved nutrition in non-anemic group [18].

Hemoglobin levels pre-transplantation were significantly lower among anemia group compared to non-anemic group, similarly, Huang et al, found that higher pre-transplantation Hb level protected against PTA [11].

Induction therapy and the maintenance immunosuppression were comparable with non-significant difference between anemic and normal Hb groups, contrary to many studies which showed that the antimetabolites cause marrow suppression and can also result in anemia [10] and [19]. Sirolimus causes marrow suppression and anemia, particularly early after initiation [20]. Another study supported our result [21], and this may be explained using potent immunosuppression during induction and maintenance as tacrolimus which allowed the use of lower dose of antimetabolite; Mycophenolate mofetil (MMF), this was guided CBC, GIT upsets and acute Rejection especially in early period post transplantation.

Type and number Acute rejection types were significantly higher in anemic group, Chronic rejection was significant higher in anemic group, and this was supported by many studies as [22 and 11].

Bacterial infections were higher among anemia group with statistical significance (p value:0.0005) by univariate analysis and this was also approved by another study [23]. Infection has also been associated with an increased risk of anemia and this may lead to inflammation-induced hepcidin expression in the liver through cytokines, including interleukin (IL)-6 and bone morphogenetic protein (BMP) [7]. Infections were associated with an increased risk of anemia [24]. Other studies suggest that iron deficiency can increase susceptibility to bacterial infection. Lower TSAT was associated with a higher risk of bacteremia, even after correction for chronic diseases [25]. CMV infections were higher in anemic group and supported by another study [26].

Graft function follow up, serum creatinine and eGFR were compared at base line but serial follow up of serum creatinine and eGFR at (3 months, 6 months, 12 months and 24 months) showed a statistically significant rise of serum creatinine and significant drop of eGFR in anemic group. And this was supported by many studies as in one retrospective study, the degree of post-transplant anemia was positively correlated with graft loss [27].

Iron indices were significantly impaired in anemia group and percentage of iron deficiency was 63 % in anemic patients and this may be explained by low-grade inflammation, medications, frequent sampling, increased blood losses by return of menstrual cycle in females, increase iron consumption by use of ESA [16]. Many studies confirmed that iron deficiency is the most common contributor to PTA as the prevalence iron deficiency anemia was 43% [28] ,34.7% [21]. Iron therapy was used in 3/4 of cases and IV iron used for rest of cases. 2/3 of cases responded to oral iron. On other side, all patients received iv iron showed full improvement of iron indices. So, the choice between oral and intravenous (IV) iron depends on a number of factors including the acuity of the anemia, costs and availability of different iron replacement products [29].

One limitation of this study was regarding ESA therapy, as our patients received ESA therapy either short, intermediate, or long acting depending on their availability, and this did not enable us to evaluate the differential effect of each type of ESA on post-transplant anemia separately. On the other hand, several studies evaluated the use of ESA therapy in KTR [30, 31]. As KDIGO guidelines recommended that if ESA is initiated, the iron

status should be determined and iron stores should be repleted, as with CKD patients [32].

By multivariate analysis, we found that the most important risk factors for post-transplant anemia were sex of recipient (female), age of donor, acute rejection, number of acute and chronic rejection, number of acute rejections, and bacterial infection. Low iron indices were significant risk factors in anemic group by multivariate analysis. Declining of renal function was a significant risk factor for anemia as rising of serum creatinine and declining of eGFR by multivariate analysis.

CONFLICT OF INTEREST: None
FINISH DISCLOSURE: None

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SUPPLEMENTARY TABLES AND FIGURES

Table S1: Bone marrow biopsy and GIT endoscopy results

Procedure	Result
Bone marrow biopsy	1- Multiple myeloma. 2- Non-Hodgkin's lymphoma. 3- Chronic lymphocytic leukemia. 4- chronic myeloid leukemia. 5- Aplastic anemia.
GIT endoscopy	1- chronic active focally erosive duodenitis. 2- chronic active erosive gastritis with helicobacter pylori infection 3- vascular polypoidal lesions 4- tubule-villous adenoma at sigmoid lesion with low grade dysplasia. 5- celiac disease.

Table S2: Multivariate analysis for significant risk factors of anemia (categorical data):

Risk factor	B estimate	Pearson Correlation (r^2)	Confidence Interval		Odds ratio OR. (%)	P value
			Lower	Upper		
Sex of recipient (female)	-1.66	0.269	-0.343	-0.119	3.1	**0.001**
Pre transplant hypertension	0.227	0.163	-0.203	0.008	0.5	0.069
ESA therapy	-0.71	-0.132	0.024	0.234	1.7	**0.016**
Acute rejection	-1.2	-0.140	-0.179	-0.029	2.5	**0.007**
Number of Acute rejections	1.5	-0.137	0.001	0.094	4.9	**0.044**
Chronic rejection	-2.1	-0.133	0.506	-0.099	3.05	**0.004**
Bacterial infection	-0.72	-0.095	-0.309	0.09	2.1	**0.047**
Age of donor	-0.045	-0.189	1.772	6.812	0.95	**0.001**
Number of blood transfusion	0.033	-0.065	-0.105	1.738	1.033	0.082
Creatinine after 3 months	-1.6	-0.173	0.081	0.259	0.19	**0.001**
Creatinine after 6 months	-0.4	-0.194	-0.396	-0.131	0.63	**0.001**
Creatinine after 12 months	0.45	-0.197	0.131	0.549	1.057	**0.001**
Creatinine after 24 months	-0.61	-0.193	0.237	0.776	1.054	**0.001**
eGFR 3 months	-0.03	0.169	0.237	0.776	0.97	**0.001**
eGFR 6 months	-0.024	0.189	-19.569	-4.939	0.97	**0.001**
eGFR 12 months	0.034	0.216	7.458	22.418	1.035	**0.001**
eGFR 24months	0.027	0.233	-25.04	-9.338	1.027	**0.001**
Serum iron	0.03	0.393	-46.783	-26.44	1.03	**0.001**
Serum ferritin	0.001	0.103	-317.219	6.812	1.001	**0.005**
TSAT	0.002	0.149	59.5	1.451	1.002	**0.040**

ESA: Erythropoietin stimulating agents
HCV: Hepatitis C virus

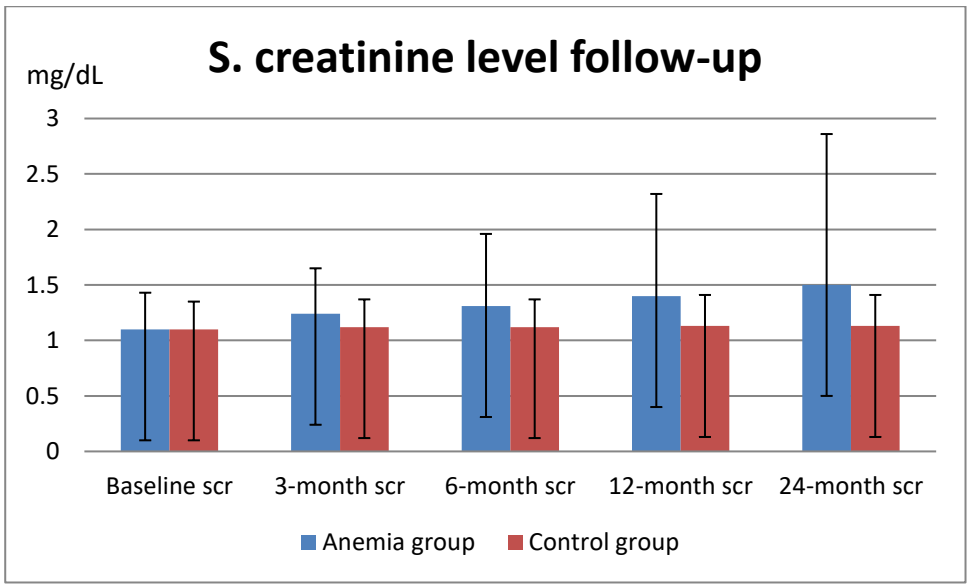

Figure S1: s. creatinine level serial follow-up