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Factors Associated with Post-Transplant Anemia among Renal Transplant Recipients with Functioning Grafts in Sana'a City, Yemen

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ABSTRACT

Objective: To assess the factors associated with anemia in renal transplant recipients with functioning grafts in Sana'a city, Yemen.

Methods: One hundred and thirteen adult renal transplant recipients with functioning grafts were enrolled in this study in the period from Janury to December 2014. Biodata and clinical data were collected using a pre-designeddata collection sheet. Hemoglobin (Hb) concentration was measured, and anemia was defined as Hb concentration less than13.0 g/dLin males and less than 12.0 g/dL in females. The factors associated with anemia were analyzed, and independent predictors of post-transplant anemia (PTA) among renal transplant recipients were identified using a multivariable logistic regression model.

Results: PTA was detected in 23.0% of renal transplant recipients with functioning grafts. Bivariate analysis showed a significant association of PTA with age of 50 years or older (Odds ratio (OR) = 2.7; 95% CI: 1.10–6.72; *P* = 0.03), history of acute rejection (OR = 3.6; 95% CI: 1.17–11.28; *P* = 0.019) and delayed graft function (OR = 6.2; 95% CI:1.60–24.16; *P* = 0.004). Multivariable analysis using a logistic regression model identified history of acute rejection (adjusted OR = 3.9; 95% CI: 1.11–12.94; *P* = 0.034) and delayed graft function (adjusted OR = 4.6; 95% CI: 1.07–19.81; *P* = 0.04) as independent risk factors for PTA among recipients. However, no association was found between PTA and recipient's gender, graft source, immunosuppressive protocols, erythropoietin treatment or use of antihypertensive drugs.

Conclusions: The prevalence of PTA among Yemeni renal transplant recipients is high, with history of acute rejection and delayed graft function being the independent risk factors. 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.

Keywords: Post-transplant anemia, Kidney transplantation, Renal transplant recipient, Risk factor, Yemen

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1. Introduction

Anemia is an important risk factor for cardiovascular diseases and is related to left ventricular hypertrophy in renal transplant recipients. Moreover, severe anemia is shown to be strongly associated with reduced patient and graft survival (1–3). Therefore, early treatment of post-transplant anemia (PTA) may improve clinical outcomes in renal transplant recipients. Chronic anemia is commonly observed in patients with kidney dysfunction. The primary cause of anemia in this situation is the reduced production of erythropoietin (EPO) hormone by the kidneys. Renal transplantation is the treatment of choice for patients with end-stage kidney disease. Following successful renal transplantation, PTA is corrected *via* endogenous production of EPO by the renal transplant. However, such renal transplants may not function optimally in the majority of renal transplant recipients, leading to a high rate of PTA (4, 5).

PTA prevalence rates were reported to range from 20.0% to 60.0%, depending on the criteria used for defining anemia (6–13). For instance, PTA was reported to be prevalent among 39.5% of Sudanese renal transplant recipients (14). In Egypt, 74.0% and 45.0% of renal transplant recipients were reported to show PTA within three and six months after renal transplantation, respectively (15). In addition, PTA prevalence rates ranging between 20.0% and 49.3% have been reported from several countries in Asia, Europe and the Americas (4, 6–13).

Etiology of PTA is multi-factorial, where reported causes include blood loss either secondary to the transplantation surgery or during outpatient follow up for monitoring the renal allograft, insufficient diet that results in iron, vitamin B12 and folate deficiencies, infectious agents (e.g. cytomegalovirus or parvovirus B19 infection), donor age, different immunosuppressive regimens, acute rejection episodes, the degree of renal function and use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) (6, 8, 11, 16–19).

To the best of our knowledge, no published data are available on the prevalence and risk factors for PTA among Yemeni renal transplant recipients, which are necessary for the management of post-transplant complications. Therefore, the present study aimed to assess the prevalence and risk factors associated with PTA among renal transplant recipients with functioning grafts.

2. Methods

2.1. Study design, setting and subjects

This cross-sectional study was conducted in Al-Thawra Modern General Hospital (AMGH) in Sana'a city in the period from Janury to December 2014. One hundred and thirteen renal transplant recipients who had undergone renal transplantation at the Kidney Center of the hospital were recruited. All recipients had transplantation surgery before four months or longer and were subjected to immunosuppressive treatment to prevent graft rejection. Serum creatinine levels of all included recipients were less than 2 mg/dL, indicating functioning grafts. Patients who underwent a second renal transplantation, pregnant women, recipients aged less than 18 years were excluded from the study.

2.2. Data and sample collection

Five milliliters of venous blood were collected from each participant. In addition, data about recipient's gender and age, donor-recipient relationship, immunosuppressive regimens, use of ACEIs and ARBs, EPO treatment prior to renal transplantation, graft function and history of

acute rejection episodes were collected using a pre-designed data collection sheet.

2.3. Hemoglobin measurement

Hb was measured using an automated ADVIA® 2120i Hematology System (Siemens Healthcare Diagnostics, Dublin, Ireland). Anemia was defined as Hb concentrations less than 13.0 g/dL in males and less than 12.0 g/dL in females as established by the World Health Organization and adopted by the American Society of Transplantation (20).

2.*4. Statistical analysis*

Statistical analyses of data were performed using the Statistical Packages for Social Sciences (SPSS) software, version 13.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and proportions. Differences or associations between variables were tested using Pearson's chi-square test, which were considered statistically significant at *P* values <0.05. A bivariate logistic regression model was developed to identify the possible risk factors associated with PTA, and odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were reported. To identify the independent predictors of PTA, a multivariable logistic regression model was developed for variables with *P* values <0.07, and adjusted ORs with their 95% CIs were reported.

3. Results

3.1. Characteristics of renal transplant recipients

Table (1) shows the characteristics and PTA prevalence rates among renal transplant recipients in AMGH in Sana'a. The majority of recipients were males (63.7%; 72/113), aged less than 50 years (70.8%; 80/113), had a late PTA (71.7%; 81/113) and receiving renal transplants from a living related donor (77.9%; 88/113). On the other hand, 59.3% (67/113) of renal transplant patients received a triple therapy of cyclosporine A (CsA), mycophenolate mofetil (MMF) and prednisone, while 40.7%(46/113) received tacrolimus (Tac), MMF and prednisone. In addition, the majority of recipients had no history of acute graft rejection (86.7%; 98/113), receivedtreatment with ACEIs/ARBs (62.0%; 70/113), but did not receive EPO treatment (65.5%; 75/113). Regarding the graft function, immediate and delayed functions were observed in 91.2% and 8.8% of renal transplant recipients, respectively.

Table 1. Characteristics and prevalence of PTA among renal transplant recipients attending the Kidney Center of AMGH, Sana'a city (2014)*

Characteristic	*n* (%)
Gender	
Male	72 (**63.7**)
Female	41 (**36.3**)
Age (years)	
<50	80 (**70.8**)
≥50	33 (**29.2**)
PTA type	
Early	7 (**22.0**)
Late	19 (**23.0**)
Donor type	
Living related donor	88 (**77.9**)
Living unrelated donor	25 (**22.1**)
History of acute rejection	
Yes	15 (**13.3**)
No	98 (**86.7**)
Immunosuppressive drugs used	
CsA with MMF and prednisone	67 (**59.3**)
Tac with MMF and prednisone	46 (**40.7**)
Treatment with ACEIs/ARBs	
Yes	70 (**62.0**)
No	43 (**38.0**)
Pre-transplant EPO treatment	
Yes	39 (**34.5**)
No	74 (**65.5**)
Graft function	
Immediate	103 (**91.2**)
Delayed	10 (**8.8**)

* Total number of recruited renal transplant recipients is 113; CsA, cyclosporine A; MMF, mycophenolate mofetil; Tac, tacrolimus; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; EPO, erythropoietin.

Prevalence of PTA in the study was 23%. Seven (22.0%) of renal transplant recipients had early anemia (occured within 4–12 months post-transplantation) while 19 (23.0%) of renal

recipients had late anemia (occured one year post-transplantation).

3.2. Factors associated with PTA

Bivariate analysis showed a significant association of PTA with age of 50 years or older (OR= 2.7; 95% CI: 1.10–6.72; *P* = 0.030), history of acute rejection (OR = 3.6; 95% CI: 1.17–11.28; *P* = 0.019) and delayed graft function (OR = 6.2; 95% CI: 1.60–24.16; *P* = 0.004). However, no statistically significant association was observed between PTA and gender, treatment with CsA, Tac, or ACEIs/ARBs, graft source, pre-transplantation treatement with EPO (Table 2). On the other hand, multivariable analysis identified history of acute rejection (adjusted OR = 3.9; 95% CI: 1.11–12.94; *P* = 0.034) and delayed graft function (adjusted OR = 4.6; 95% CI: 1.07–19.81; *P* = 0.040) as independent risk factors for PTA (Table 3).

Table 2. Bivariable analysis of factors associated with PTA among Yemeni renal transplant recipients attending the Kidney Center of AMGH, Sana'a city (2014)

Variable	*N*	**Anemia *n*(%)**	**OR** (95% CI)	***P* value**
Gender				
Female	41	6 (**14.6**)	Reference	
Male	72	20 (**27.8**)	**2.2** (0.82–6.15)	0.110
Age (years)				
<50	80	14 (**17.5**)	Reference	
≥50	33	12 (**36.4**)	**2.7** (1.10–6.72)	0.030*
Donor type				
Living related donor	88	20 (**22.7**)	Reference	
Living unrelated donor	25	6 (**24.0**)	**1.1** (0.38–3.05)	0.890
History of acute rejection				
No	98	19 (**19.4**)	Reference	
Yes	15	7 (**46.7**)	**3.6** (1.17–11.28)	0.019*
Immunosuppressive drugs used				
CsA	66	17 (**25.8**)	Reference	
Tac	47	9 (**19.1**)	**0.68** (0.27–1.70)	0.410
Treatment with ACEIs/ARBs				
Yes	70	18 (**25.7**)	Reference	
No	43	8 (**18.6**)	**0.72** (0.35–1.52)	0.380
Pre-transplantation EPO treatment				
Yes	39	5 (**12.8**)	Reference	
No	74	21 (**28.4**)	**2.7** (0.93–7.83)	0.060
Graft function				
Immediate	103	20 (**19.4**)	Reference	
Delayed	10	6 (**60.0**)	**6.2** (1.60–24.16)	0.004*

N, Number of renal transplant recipients; n, anemic patients; OR, Odds ratio; CI, confidence interval; CsA, cyclosporine A; Tac, tacrolimus; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; * statistically significant at *P* value <0.05.

Table 3. Multivariable analysis of factors associated with PTA among Yemeni renal transplant recipients attending Kidney Center of AMGH, Sana'a city(2014)

Variable	**Adjusted OR** (95% CI)	***P* value**
History of acute rejection	**3.9** (1.11–12.94)	0.034
Delayed graft function	**4.6** (1.07–19.81)	0.040

OR, Odds ratio; CI, confidence interval.

4. Discussion

Anemia remains a common renaltransplant complication. The prevalence of PTA among Yemeni renal transplant recipients with functioning grafts was 23%. Early anemia represents 22.0%, while late anemia represents 23.0%. Such a high PTA prevalence rate is in line with the published literature that PTA represents a common problem among renal transplant

recipients (6–11, 14, 15). However, the PTA prevalence rate concluded by the present study is lower than those reported by several previous studies elsewhere (6–11, 14, 15). This could be attributed to the inclusion criteria adopted in the present study, where only renal transplant recipients with functioning grafts were recruited. With this respect, Iwamoto et al. (21) reported a significant correlation between PTA and poor kidney graft function.

The significant association of recipient's age with PTA and the significantly higher proportion of PTA among renal recipients of 50 years or older than younger recipients are in agreement with previous studies (7, 21). The increase in PTA prevalence with age could be attributed to multiple factors such as iron and vitamin B12 deficiencies, occult blood loss or chronic infections. However, several previous studies reported no statistically significant association between recipient's age and PTA (4, 6, 12, 14, 22). On the other hand, the significant association between the delayed graft function PTA among renal transplant recipients in the present study is in agreement with those reported from Egypt, where delayed graft function was found to be a risk factor for PTA (15, 23). Therefore, poor graft function could be a reason for developing PTA. In contrast, Banjeglav and Zibar (24) found no statistically significant association between delayed graft function and PTA among Croatian renal transplant recipients.

The lack of association between PTA and the gender of Yemeni renal transplant recipients is consistent with the findings of previous studies elsewhere (4, 6, 22). In contrast, other studies reported that the female gender as a risk factor forthe development of PTA, which was explained by menstruation regain after the improvement of renal function (15, 24, 25). In another context, Yorgin et al. (26) showed that male American renal transplant recipients are more likely to have PTA than females (26). In the present study, the significant correlation between PTA and acute rejection episodes could be attributed to the kidney damage as a result of the inflammatory process. Similarly, acute rejection episodes were found to be associated with PTA among Egyptian renal transplant recipients (15, 25). In contrast, a European multicenter study did not find acute rejection to be a risk factor for PTA, although patients who experienced more episodes of treated acute rejection had lower mean Hb levels (4). In contrast, Jalalzadeh et al. (27) reported that acute rejection episodes had no adverse effects on long-term renal graft function of Iranian renal transplant recipients after successful treatment. Moreover, some previous studies found no significant correlation between PTA and acute rejection (12, 14). On the other hand, the lack of association between PTA and EPO non-use prior to transplantation in the present study is contradictory to the findings of previous studies among Sudanese and Turkish renal transplant recipients (6, 14).

In the Kidney Center of AMGH, the most frequently used calcineurin inhibitor is CsA followed by Tac, and all patients also receive MMF and prednisone. However, no significant association was found between PTA and the use of either drug. This finding is consistent with those reported by several previous studies (14, 15, 22, 28). In contrast, this finding is in disagreement with those reported from European countries, where PTA was found to be associated with immunosuppressive treatments (4, 9, 29). Kolonko et al. (9) attributed the association between PTA and immunosuppression with CsA to the greater doses of MMF compared to those prescribed with Tac-based immunosuppressive treatment. On the other hand, the common treatment with ACEIs or ARBs among about two-thirds of renal transplant recipients in the present study was not

significantly associated with PTA. This finding is compatible with the findings in several previous studies reporting the lack of association between PTA and treatment with ACEIs and ARBs (6, 12, 14, 15, 19, 22, 28, 30).

The present study reveals that the majority of renal transplants (77.9%) were donated by living related donors, with absence of cadaveric donors. This finding is in agreement with those reported from Sudan and Turkey (6, 14). This is, however, dissimilar to those reported from the developed countries, where deceased donors are the major donor type in renal transplantation (11, 12). Like Sudanese and Turkish reports (6, 14), no association was found between PTA among Yemeni renal transplant recipients and the source of grafts.

5. Conclusions

PTA is a common complication after kidney transplantation among Yemeni recipients with functioning grafts. Age of 50 years or older, history of acute rejection and delayed graft function are risk factors for PTA among renal transplant recipients. Moreover, history of acute rejection and delayed graft function represent independent predictors of PTA among Yemeni patients undergoing renal transplantation. Therefore, it is recommendedthat physicians involved in renal transplantation consider the investigation and follow-up of transplant recipients for PTA andadopt appropriate preventive and therapeutic measures.

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Authors' contributions

All authors contributed equally to the design, implementation, statistical analysis and manuscript drafting. They also read and approved the final version of the submitted manuscript.

Competing interests

The authors declare that they have no competing interests associated with this article.

Ethical approval

The protocol of the present study was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Sana'a University. Written informed consent was obtained from all participants in the study.

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