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Prevalence of Erythrocytosis and Associated Clinical Manifestations in Renal Transplant Recipients

Summra Siddiq, Adil Manzoor, Warda Riaz, Huma Ashraf, and Hamza Attiq

ABSTRACT

Erythrocytosis, also known as polycythemia is commonly defined as increase in red blood cells (RBCs) or hemoglobin concentration in the body. Polycythemia can cause blood clots and increases the risk of life threatening thromboembolic complications such as, pulmonary embolism, stroke, deep vein thrombosis (DVT), and heart attack. PTE is frequently seen among renal transplant recipients with an incidence of 10-15%, however, higher prevalence has been recorded in other communities worldwide. Risk factors associated with PTE development include male gender, renal artery stenosis, retained native kidney, hypertension, hydronephrosis, and diabetes. Role of sex hormones, smoking, polycystic kidney disease, inhibition of renin -angiotensin aldosterone system, and excessive use of immunosuppressive medications, mainly containing mycophenolic acid derivate, have been well documented. Onset of erythrocytosis is usually seen by 8 to 24 months in well- functioning grafts. In some patients it resolves spontaneously, whereas in others, can persist for more than two years. Common clinical symptoms associated with PTE are headache, vision problem, lethargy, dizziness, plethora, and increased risk of thromboembolic phenomena, including deep venous thrombosis (DVT), stroke, myocardial infarction (MI), though some patients remained asymptomatic. To study this a retrospective single-center study was conducted at Pakistan Kidney and Liver Institute & Research Centre. Our study showed that out of a total population of 80 recipients, 31.2% of patients (n=25) developed PTE while 68.8% of patients (n=55) did not develop PTE. We also found that in 60% of the patients (n=15), polycythemia resolved within 6 months. It was also found that male gender was at increased risk of erythrocytosis, indicating strong association (p=0.02). Our study did not show any co-relationship between PTE and other predisposing factors as previously reported. A larger trial with prospective analysis is needed to find any significant association.

Keywords: Erythrocytosis, erythropoietin, kidney transplant, post transplant erythrocytosis.

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I. Introduction

Erythrocytosis, also known as polycythemia is commonly defined as increase in red blood cells (RBCs) or hemoglobin concentration in the body [1]. This rise in red blood cell count increases the viscosity, which makes the blood flow sluggish through the blood vessels and organs. Polycythemia can cause blood clots and increases the risk of life threatening thromboembolic complications [2], [3] such as, pulmonary embolism, stroke, deep vein thrombosis (DVT), and heart attack. It could be primary, due to bone marrow defect or secondary, where other underlying causes produce more "erythropoietin, a hormone responsible for bone marrow stimulation to produce red blood cells [4]. PTE is frequently seen among renal transplant recipients with an incidence of 10-15% [2]-[4] however, higher prevalence has been recorded in other communities worldwide [5]-[9]. This wide variation in occurrence of PTE is multifactorial. There is a lack of consensus on values used to define erythrocytosis. Some studies have used hematocrit (50-54 percentage points) or hemoglobin (16.5 to 18 g/d) [2]-[4], whereas other have used gender related separate cut off points [10]-[11]. True erythrocytosis is defined as 'persistently elevated hemoglobin (Hb) more than 17g/dl or

hematocrit (hct) greater than 51% or both as per KDIGO 2009 criteria [12]. Other risk factors associated with PTE development are male gender [13]-[15] renal artery stenosis [16], retained native kidney [17], hypertension [4], hydronephrosis, and diabetes. Role of sex hormones [18]-[20], smoking [21]-[23], polycystic kidney disease [24]-[26], inhibition of renin -angiotensin aldosterone system [27], and excessive use of immunosuppressive medications, mainly containing mycophenolic acid derivate [28], [29], have been well documented.

Onset of erythrocytosis is usually seen by 8 to 24 months in well- functioning grafts [2], [3]. In some patients it resolves spontaneously, whereas in others, can persist for more than two years. Common clinical symptoms associated with PTE are headache, vision problem, lethargy, dizziness, plethora [13], and increased risk of thromboembolic phenomena [13], [30], [31], including deep venous thrombosis (DVT), stroke, myocardial infarction (MI), though some patients remained asymptomatic. However, it has been observed over recent years that PTE is not associated with increased risk of thromboembolic complications [32].

In high risk population, with thromboembolic risk, phlebotomy is proven therapy for immediate treatment [13]. Several therapeutic agents have promising affects in reversing this condition mainly, ACE-I and ARBS, due to RAAS inhibition [33]-[35], and withdrawal of ACE-I inhibitors leads to recurrence of erythrocytosis in some cases [36]. Other treatment options include agents containing Theophylline [37], which have been tried but not frequently used due to their associated side effects.

II. Materials and Methods

A retrospective single-center study was conducted, after ethical approval from the Institutional Review Board of Pakistan Kidney and Liver Institute & Research Center (PKLI & RC). The study followed the ethical guidelines as laid down in Helsinki declaration. This study determines the prevalence of erythrocytosis among renal transplant recipients in Pakistani population and also compares the difference in prevalence among various communities. Also, the time of onset of post-transplant erythrocytosis, its clinical manifestations and the need for phlebotomy were reviewed using non-probability sampling technique. Baseline demographic variables like age, gender, comorbidities including diabetes, hypertension, smoking, autosomal polycystic kidney disease, pre-transplant hemoglobin, duration of dialysis, were analyzed. Patients were divided into two groups based on set criteria of hematocrit into PTE group and non-PTE group and their characteristic differences were evaluated.

The study includes all age group living donor renal transplant recipients with well-functioning grafts, as indicated by serum creatinine <1.5mg/dl which is close to the normal creatinine range as per KDIGO guideline and local hospital policy. All consecutive transplant recipients between May 2018 and March 2020 were included in the study. Recipients with impaired graft functions, as indicated by the inability to reach a set minimum serum creatinine value, and those with a history of rejection within one month of transplant, were excluded from the study. Patients who received a blood transfusion during the last three months were also excluded. Secondary causes of erythrocytosis like chronic obstructive airway disease, obstructive sleep apnea, malignancy was ruled out. A total of 80 recipients were enrolled in the study. All data collection was done through electronic medical records. Monthly follow up laboratory results were reviewed over 18 to 33 months.

Data analysis was done using SPSS 2.0 Statistical software (Statistical Package for the Social Sciences). Continuous data were summarized as mean and standard deviation. Categorical data were summarized as frequency and percentage. A significant correlation between risk factors was assessed using Chi-square test. Graphically the data was presented by pie chart, graph, and bar chart. A p-value of <0.05 was taken as statistically significant.

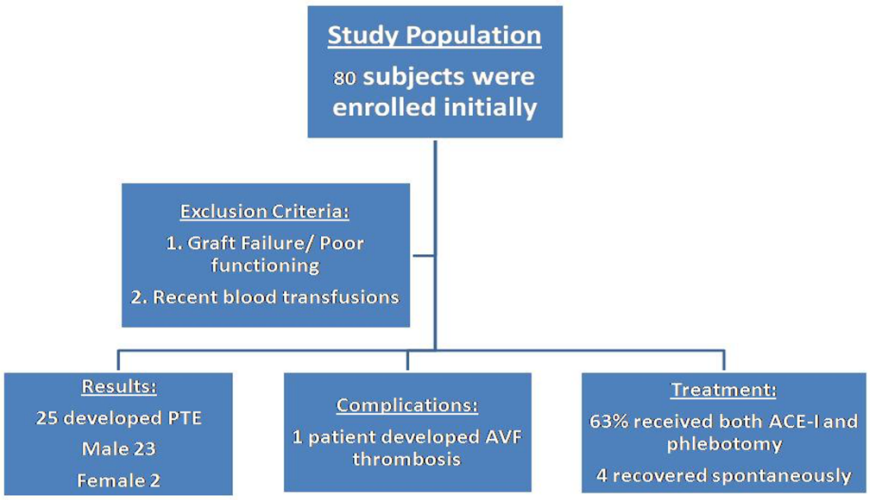

Fig. 1. Flowchart showing enrollment of patients in study and associated outcomes.

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TABLE II: BASIC DEMOGRAPHIC CHARACTERISTICS OF PTE AND NON-PTE GROUP

Variables		Total no. of patients n=80 (Percentage%)	PTE Group n=25 (Percentage%)	NON-PTE Group n=55 (Percentage%)	Chi-square test P<0.05
Age (Years) Mean +/- SD		35.47+/- 10.1	35.6 +/- 7.9	35.41+/- 11.39	
Gender	Male	73 (91.25%)	23 (91.2%)	50 (90.9%)	0.02
	Female	7 (8.75%)	2 (8.8)	5 (9.09%)	
Smoker	Yes	10 (12.5%)	4 (16%)	6 (10.9%)	0.52
	No	70 (87.5%)	21 (84%)	49 (89.1%)	
Diabetes	Yes	7 (8.75%)	3 (12%)	4 (7.3%)	0.48
	No	73 (91.25%)	22 (88%)	51 (92.7%)	
Hypertension	Yes	73 (91.3%)	25 (100%)	48 (87.3%)	0.06
	No	7 (8.7%)	0 (0%)	7 (12.7%)	
ADPKD	Yes	4 (5%)	0 (0%)	4 (7.3%)	1.67
	No	76 (95%)	25 (100%)	51 (93.7%)	
On Dialysis	Yes	65 (81.25%)	23 (92%)	42 (76.4%)	-
	No	15 (18.75%)	2 (8%)	13 (23.6%)	
Immuno-suppression therapy	Tac/MMF/PRED	77 (96.3%)	25 (100%)	52 (94.54%)	4.0
	Ever/MMF/PRED	1 (1.3%)		1 (1.82%)	
	Cyclo/AZA/PRED	1 (1.3%)		1 (1.82%)	
	Tac/AZA/PRED	1 (1.3%)		1 (1.82%)	

III. RESULTS

Our study showed that out of a total population of 80 recipients, 31.2% of patients (n=25) developed PTE while 68.8% of patients (n=55) did not develop PTE as shown in Table I.

TABLE I: PERCENTAGE OF POPULATION DEVELOPING PTE IN RENAL TRANSPLANT RECIPIENTS

Groups	Number of Patients	Percentage %
PTE group	25	31.2
Non PTE group	55	68.8

Most of them the patients with PTE were males, 91.2% (n=23), indicating a significant relationship between male gender and PTE development (p=0.02) as shown in Table II. Among other risk factors, hypertension was found in all recipients 100% (n=25), even though no significant relationship was identified as the p-value is > 0.05 (p=0.06). Also, diabetes (p=0.48), smoking (0.52), and ADPKD (p=1.67) did not show any significant relationship (Table II). Also, the immunosuppressive medications used for the PTE group and non-PTE group did not show any associated increased risk for erythrocytosis (p= 4.0).

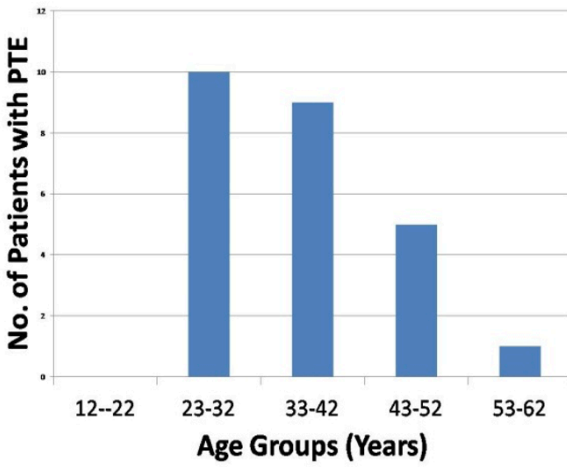

Fig. 2. Younger age at maximum risk for PTE development.

TABLE III: PREVALENCE OF PTE AMONG DIFFERENT AGE GROUPS

No	Age Groups [years]	No. of patients with PTE	Percentage [%]
1.	12-22	0	0%
2.	23-32	10	40%
3.	33-42	9	36%
4.	43-52	5	20%
5.	53-62	1	4%

The study also observed peak age of onset of PTE, with 40% (n=10) of the renal transplant recipients who developed erythrocytosis aged 23-32 years, followed by 36 % (n=9) of patients ranging between 33-42 years. Table III and Fig. 2 show that younger patients were at an increased risk of developing erythrocytosis.

The PTE group developed a hematocrit value of 53.8% +/- 2.2 at the time of diagnosis with a mean hemoglobin level 17 +/- 0.56g/dL. The highest hematocrit seen among the PTE group is 60.3%, with hemoglobin of 19.2g/dL at nine months of PTE onset (Table IV).

The study results also showed that the serum creatinine values did not rise significantly from baseline creatinine of (1.02 +/- 0.36 g/dl), reaching maximum value of (1.12 +/- 0.23 g/dl), again indicating no significant correlation between PTE and creatinine levels (p= 0.66) Table IV.

TABLE IV: HEMATOCRIT LEVELS DURING POST-TRANSPLANT PERIOD AMONG PTE GROUP

	Maximum Hematocrit (Hct) %	Maximum Hemoglobin g/dl	Serum Creatinine mg/dl	Pearson Correlation P=0.05
Baseline values (pre-transplant)	32.95 +/- 5.9	10.7 +/- 2.0	1.0 +/- 0.36	
At diagnosis (Peak)	53.8+/-2.2	17.10+/- 0.56	1.11+/- 0.23	0.66
3 months	55.5 +/-1.3	18.30 +/- 3.2		
6th month	60.2+/- 2.4	19.00+/- 2.6		
9th month	60.3 +/- 1.8	19.20 +/- 1.2		
12 month	57.2 +/- 1.6	17.60 +/- 0.2		
15 month	55.8 +/- 2.1	17.2 +/- 0.8		
18 months	51.3 +/- 2.6	15.6 +/- 1.1		
24 months	47.2 +/- 2.0	16.1 +/- 0.6		

However, the non-PTE group showed hemoglobin 10.7

+/- 1.74g/dL, and hematocrit of 33.06 +/- 1.2% post-transplantation, (Table V), reaching maximum hematocrit of 47.2%, (Fig. 3) and hemoglobin of 14.5 g/dL (Table V).

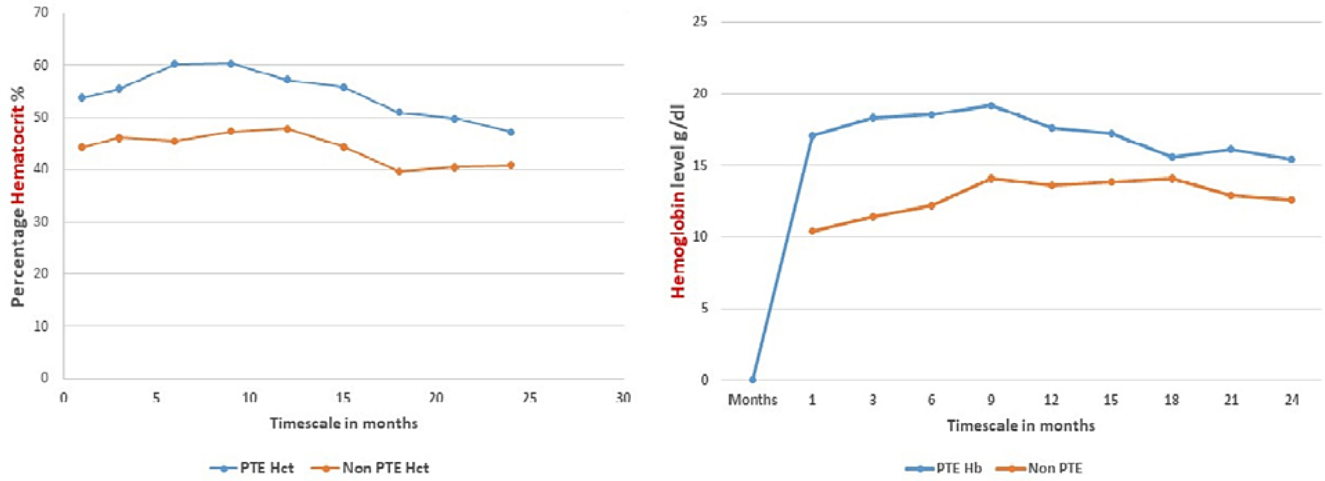

Fig. 3. Hemoglobin g/dl and hematocrit % variation between PTE and Non PTE group.

TABLE V: COMPARISON OF HEMATOCRIT % AND HEMOGLOBIN G/DL AMONG PTE AND NON PTE POPULATION

Parameters	Minimum value %	Maximum value %	Mean +/- SD
PTE group. HCT%	50%	60.3 +/- 1.8%	53.18 +/- 2.3
PTE group Hb g/dl	16.10	18.40	17.19 +/- 0.56
Non-PTE HCT %	20%	47.2%	33.06 +/- 5.5
Non-PTE Hb g/dl	6.50	14.5	10.7 +/- 1.74

Average time of onset of erythrocytosis observed is 10.12 months +/- 6.5 as shown in Fig. 4.

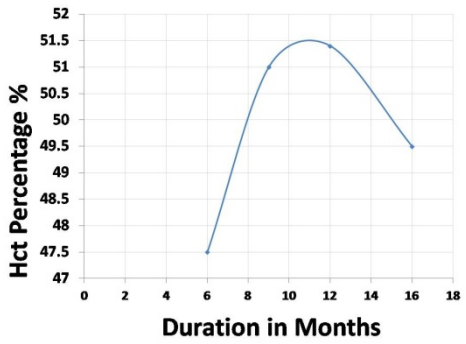

Fig. 4. Relationship between HCT % rise and PTE onset.

It was also observed that in 60% of the patients (n=15), polycythemia resolved within 6 months, 20% (n=5) required more than 6 months, and in 12 % (n=3) of recipients it took more than one year for erythrocytosis to resolve, whereas only 8% (n=2) require more than 2 years for complete recovery (Table VI).

TABLE VI: TIME PERIOD REQUIRED FOR ERYTHROCYTOSIS TO RESOLVE AMONG PTE- GROUP

Time in Months	Number of Patients	Percentage %
< 6 months	15	60
> 6months	5	20
>12 months	3	12
>24 months	2	8
TOTAL	25	100%

Despite developing PTE, only four patients (n=4) 16% manifest symptoms of headache, fatigue, blurring of vision, pruritus, whereas rest of 84% recipients (n=21), remained asymptomatic (Table VII). Only one patient (n=1)4%, had thrombosis of arteriovenous fistula (AVF), as complication of PTE.

TABLE VII: CLINICAL MANIFESTATIONS OF ERYTHROCYTOSIS AMONG PTE GROUP

	Clinical Features	Number of patients (Percentage%)
1	Headache	1 (4%)
2	Blurring of Vision	1 (4%)
3	Dizziness	0
4	Pruritus	1 (4%)
5	Fatigue	1 (4%)
6	Stroke/ MI	0

It is observed that 68% (n=17) require treatment both with angiotensive-converting enzyme inhibitors (ACE-I), and therapeutic phlebotomies, whereas 12% (n=3) respond to ACE-I therapy only, whereas 20% (n=5) recovered spontaneously.

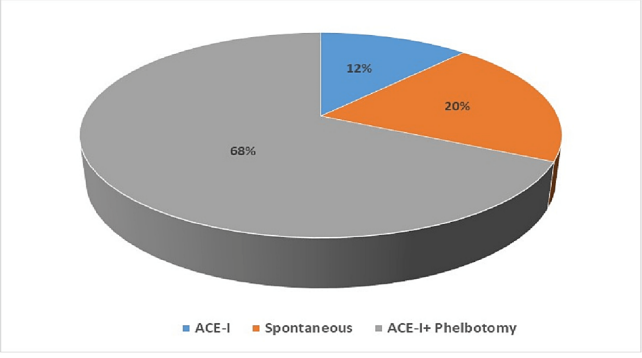

Fig. 5. The percentage of PTE group receiving different treatments.

IV. DISCUSSION

Renal transplant recipients are at increased risk of developing erythrocytosis. Wide variation is seen in the incidence of PTE worldwide, with an average incidence of 10-15% in most European communities [2]-[3] whereas a higher prevalence is reported in some of the Asian

populations [5]-[9]. Studies done in Saudi Arabia have reported an incidence of 21.6% [4], and 19% [6], whereas in the Indian population 15.5% [7], and in the Pakistani community, an even higher prevalence is seen, reaching up to 20% [8], and 28.4% [9]. This study also reports a higher prevalence of erythrocytosis estimated to be 31.2%. Multiple assumptions have been made related to prevalence rates, including the use of different cutoff values by different authors. Some studies have used gender-specific hemoglobin values 16-18g/dl for men and 12-14g/dl in women [9]-[10] whereas others have used the same reference for both sexes [5]-[6]. In this study, we have used KDIGO 2009 guidelines, as the standard reference value, to identify recipients with raised hematocrit or hemoglobin.

Apart from a lack of consensus on hemoglobin or hematocrit values, other factors that contribute to a higher prevalence of erythrocytosis are the increased use of ACE-I and ARBs for control of hypertension [3], as inhibition of RAAS leads to accelerated erythropoiesis. It is observed that erythrocytosis mostly affects males as compared to females. Androgens seem to play an important role in male predominance [2]-[4], for developing polycythemia. Studies have shown that androgens affect renal microvasculature by causing vasoconstriction, leading to hypoxia which triggers increased erythropoietin secretion and ultimately erythropoiesis [18]-[20]. Endogenous androgens have a direct effect on erythroid precursors and act directly by increasing their sensitivity to erythropoietin stimulation. Similar results were seen in our study, with the male population at an increased risk for erythrocytosis, constituting 91.2% (n=23), of the PTE population. In Pakistani community, male population have more access to medical facilities, as compared to female, due to cultural norms, which is an important factor for their higher prevalence. Similarly, non- preemptive transplant is considered as an important factor for PTE development, as in most cases hemoglobin has already been stabilized either by transfusions or recombinant EPO injection,

It is also observed that young recipients are at increased risk of developing PTE, secondary to healthy marrow undergoing effective RBC production, as seen from study results with mean age of (35.6 +/- 7.9), indicating strong association between risk of polycythemia and age (p=0.02), (Fig. 2).

Apart from age, certain other predisposing factors have been associated with erythrocytosis development. These include smoking, ADPKD, diabetes, hypertension, renal artery stenosis, pre-transplant adequate hemoglobin, retained native kidneys [14]-[17]. Though we have not found any significant co-relation in this study, as previously observed by other authors. [21]-[24], likely due to small sample size or ethnicity differences. It is observed that erythrocytosis usually develops between 8 to 24 months, post transplantation [2]-[3], though different studies report different time frames [6]-[8]. This study showed that average time of onset of PTE is (10.12 +/- 6.5) months, with most of the patients showing recovery within six months from onset (60%), and up to 20% of the individuals needing more than six months. Only about 8% require longer than two years to recover.

However, it is established that even when erythrocytosis persists, most of the patients are usually asymptomatic. Common clinical symptoms associated with PTE are headache, fatigue, lethargy, dizziness, plethora, and visual disturbance [29]-[31], due to sluggish blood flow and increased blood viscosity. Here, we came across only 16% of patients with symptomatic erythrocytosis, whereas 84% remained asymptomatic. Recent studies have shown no increased thromboembolic risk with erythrocytosis [3], while in previous studies was estimated at 18.9% leading to both arterial and venous thrombosis, myocardial infarction and an increased risk of stroke [31]. In this study, only one recipient suffered from thrombosis of arteriovenous fistula due to increased blood viscosity.

Early diagnosis and effective treatment have led to a reduction in complication rate. Over recent years, different medications have been tried, but ACE-Inhibitors and ARBs have remained the most effective treatment for reversing this condition [33]-[35], and their withdrawal is associated with increased relapse [36]. However, phlebotomy still remained the main choice for rescue therapy in life threatening situations, to avoid thromboembolic risk. We have observed in this study that most of the patients have received both phlebotomy and drugs (Fig. 5), to reduce hematocrit count to safe limits and to avoid complications. Phlebotomy, acts as bridging therapy to reduce the risk of thrombosis, and allows time for ACE-inhibitors or ARBs to produce their maximum beneficial effects. Theophylline's, have also been accepted for treatment of erythrocytosis, but their use is not common due to the side effects associated with it.

V. Conclusions

In conclusion, PTE was observed in 31.2% of transplant recipients and an average time of onset of 35.6 +/- 7.9 months post-transplantation. Male gender is at increased risk of erythrocytosis, indicating strong association (p=0.02). PTE showed a strong predilection for the younger age groups affecting younger populations the most, 40% (23-32years). Our study did not show any co-relationship between PTE and other predisposing factors as previously reported. A larger trial with prospective analysis is needed to find any significant association and role of immunosuppressive medication in causing erythrocytosis in Asian population.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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