Incidence and Associated Factors of Post-Transplant Erythrocytosis Following Kidney Transplantation

Thanachai Siriphotjanakun, Korntip Phonphok

Division of Nephrology, Department of Internal Medicine, Rajavithi Hospital, Bangkok, Thailand

Abstract

Background: Post-transplant erythrocytosis (PTE) is a persistent increase in red blood cell count following kidney transplantation. Patients with PTE face an increased thrombotic risk, which leads to higher morbidity and mortality. This retrospective cohort study aimed to identify the incidence and risk factors of PTE in kidney transplant recipients.

Methods: A total of 286 kidney transplant recipients from 1998 to 2022 were included in the study. The diagnosis of PTE was based on hemoglobin levels >17 g/dL and/or hematocrit >51%. Baseline factors associated with PTE were analyzed using the Cox proportional hazards regression model.

Results: PTE occurred in 26 (9.1%) patients, with a median onset of 7.1 months (4-41.6 months) post-transplantation. Male sex, a history of smoking, higher body mass index, higher pretransplant hematocrit, and absence of pretransplant renin-angiotensin-aldosterone system (RAAS) blockade were associated with the development of PTE. In multivariate analysis, only male sex and higher body mass index were independent predictors of PTE. Most patients responded well to RAAS blockade, with 7 (27%) patients experiencing spontaneous recovery, and 7 (27%) undergoing phlebotomy. Transplant renal artery stenosis was diagnosed in 3 (11%) patients.

Conclusions: Nine percent of kidney transplant recipients developed PTE approximately seven months post-transplantation. Male sex and higher body mass index were identified as independent predictors of PTE. Most patients responded well to RAAS blockade, with a quarter experiencing spontaneous recovery.

Keywords: renal transplant; renal transplantation; RAAS blockade; kidney allograft; sex; BMI

Corresponding author: *Korntip Phonphok*
Email: *korntip_p@rajavithi.go.th*

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อุบัติการณ์และปัจจัยที่สัมพันธ์กับภาวะการสร้างเม็ดเลือดแดงมากขึ้นหลังการปลูกถ่ายไต

ธนชัย ศิริพจนากุล และ กรทิพย์ ผลโภค

งานโรคไต กลุ่มงานอายุรศาสตร์ โรงพยาบาลราชวิถี

บทคัดย่อ

บทนำ: ภาวะการสร้างเม็ดเลือดแดงมากขึ้นหลังการปลูกถ่ายไตสามารถเพิ่มโอกาสการเกิดภาวะลิ่มเลือดอุดตัน อาจทำให้เกิดภาวะแทรกซ้อนและส่งผลต่ออัตราการอยู่รอดของผู้ป่วยที่ได้รับการปลูกถ่ายไต การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาอุบัติการณ์ของภาวะการสร้างเม็ดเลือดแดงมากขึ้นหลังการปลูกถ่ายไต และปัจจัยที่มีความสัมพันธ์กับการเกิดโรค

ระเบียบวิธีวิจัย: การศึกษานี้เป็นการศึกษาย้อนหลังในผู้ป่วยที่ได้รับการปลูกถ่ายไต ระหว่างปี พ.ศ.2541 ถึงปี พ.ศ.2565 จำนวนทั้งสิ้น 286 ราย ภาวะการสร้างเม็ดเลือดแดงมากขึ้นหลังการปลูกถ่ายไต หมายถึง การมีระดับของฮีโมโกลบินสูงกว่า 17 กรัมต่อเดซิลิตร และ/หรือ มีระดับฮีมาโทคริตสูงกว่าร้อยละ 51 หลังได้รับการปลูกถ่ายไต มีการวิเคราะห์ปัจจัยพื้นฐานที่สัมพันธ์กับการเกิดภาวะการสร้างเม็ดเลือดแดงมากขึ้นหลังการปลูกถ่ายไตด้วยวิธี Cox-proportional hazard regression model

ผลการวิจัย: จากการศึกษาพบอุบัติการณ์ของการเกิดภาวะการสร้างเม็ดเลือดแดงมากขึ้นหลังการปลูกถ่ายไตในผู้ป่วย 26 ราย (ร้อยละ 9.1) โดยมีระยะเวลาเกิดโรคที่ค่ามัธยฐาน 7.1 (4-41.6) เดือนหลังการปลูกถ่ายไต ปัจจัยพื้นฐานที่พบว่ามีความสัมพันธ์ต่อการเกิดโรค ได้แก่ เพศชาย ประวัติการสูบบุหรี่ ค่าดัชนีมวลกายที่สูงขึ้น ระดับของฮีมาโทคริตก่อนการปลูกถ่ายไตที่สูง และ การไม่เคยได้รับยาในกลุ่ม renin-angiotensin-aldosterone system (RAAS) blockade การวิเคราะห์แบบพหุตัวแปรพบว่าปัจจัยที่มีความสัมพันธ์ต่อการเกิดภาวะนี้ คือ เพศชาย และค่าดัชนีมวลกายที่สูงขึ้น ผู้ป่วยส่วนใหญ่ตอบสนองต่อการรักษาด้วยยาในกลุ่ม RAAS blockade มีผู้ป่วยจำนวน 7 ราย (ร้อยละ 27) ที่อาการดีขึ้นเองโดยไม่ได้รับการรักษา และผู้ป่วยอีก 7 ราย (ร้อยละ 27) ที่ได้รับการเจาะเส้นเลือดดำเพื่อถ่ายเลือดออกจากร่างกาย (phlebotomy) มีผู้ป่วยจำนวน 3 ราย (ร้อยละ 11.5) ที่ได้รับการวินิจฉัยว่ามีภาวะหลอดเลือดแดงที่ไปเลี้ยงไตตีบ (transplant renal artery stenosis)

สรุป: พบอุบัติการณ์ของการเกิดภาวะการสร้างเม็ดเลือดแดงมากขึ้นหลังการปลูกถ่ายไตอยู่ที่ร้อยละ 9 และเกิดขึ้นประมาณ 7 เดือนหลังได้รับการปลูกถ่ายไต ปัจจัยพื้นฐานที่พบว่าสัมพันธ์กับการเกิดภาวะนี้ คือ เพศชาย และดัชนีมวลกายที่เพิ่มขึ้น ผู้ป่วยส่วนใหญ่ตอบสนองต่อการรักษาด้วยยาในกลุ่ม RAAS blockade และมีผู้ป่วยจำนวนหนึ่งในสี่ที่หายเองโดยไม่ต้องรักษา

คำสำคัญ: เลือดข้น; เปลี่ยนไต; ปลูกไต; บำบัดทดแทนไต

Introduction

Post-transplant erythrocytosis (PTE) is a common complication following kidney transplantation, characterized by persistently elevated hemoglobin levels (> 17 g/dL) or hematocrit levels (> 51%)[1]. Its incidence varies between 5% to 26%[2-6], as reported in different studies. Some studies have even reported rates as high as 31.2%[7]. Established risk factors for PTE include male gender, a history of smoking, underlying polycystic kidney disease, and receiving a kidney from a deceased donor[5]. While patients with PTE often experience mild symptoms such as malaise, headache, or fatigue, it's crucial to note

ผู้ประพันธ์บรรณกิจ: *กรทิพย์ ผลโภค*
อีเมล: *korntip_p@rajavithi.go.th*

รับบทความ: 18 ธันวาคม 2567; ปรับปรุงแก้ไข: 20 มกราคม 2568; รับตีพิมพ์: 27 มกราคม 2568

that thromboembolic events have been reported in some cases, with an incidence ranging from 10% to 30%[5]. These events can lead to cardiovascular complications in the future, underscoring the importance of monitoring and managing PTE in kidney transplant recipients. The primary objective of this study was to investigate the incidence and risk factors associated with PTE among kidney transplant recipients.

Material and Methods

Study design and population

The present study was a retrospective single-center cohort study of end-stage kidney disease (ESKD) patients who underwent solitary kidney transplantation between January 1, 1998, and December 31, 2022, at Rajavithi Hospital, Bangkok, Thailand. The inclusion criteria were age ≥ 18 years and receiving solitary kidney transplantation from either a living or deceased donor. Patients with multiple organ transplants, malignancy, graft loss within one year, pre-existing erythrocytosis, and incomplete medical records were excluded. The study flow diagram is shown in **Figure 1**. The study was approved by the ethics committee at Rajavithi Hospital (No. 055/2567). Informed consent was not required.

Definition

PTE was defined as persistently elevated hemoglobin levels (>17 g/dL) or hematocrit levels (>51%) regardless of the duration after kidney transplantation[1].

Data collection

Baseline characteristics and laboratory data were collected from the electronic medical records database. This included sex, age, weight, height, the underlying cause of ESKD, dialysis modalities, duration of dialysis, smoking history, and the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) before kidney transplantation. Data on allograft function and immunosuppressive drugs were also collected.

Sample size calculation

The sample size was calculated based on the cumulative incidence of post-transplant erythrocytosis, as reported by Kurella et al., which was observed to be 0.26[4]. A p-value of 0.05 was considered statistically significant. We estimated the margin of error to be 20%. The sample size for this study was calculated to be 330 subjects.

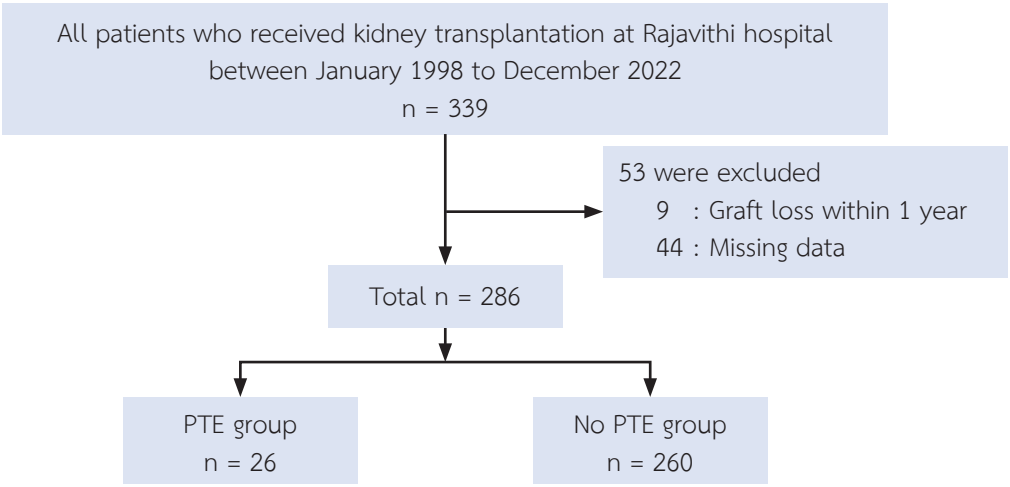

Figure 1. Study flow diagram
PTE; post-transplant erythrocytosis

Statistical analysis

Statistical Analysis

Data were presented as mean ± standard deviation, median (interquartile range), or number (percent). Differences between categorical variables were analyzed using the Chi-square test, Fisher's exact test, or McNemar test. Differences between continuous variables were analyzed using the Student's t-test or

the Mann-Whitney U-test. The incidence of PTE was analyzed using Kaplan-Meier analysis. Baseline factors associated with PTE were analyzed using univariate and multivariate Cox proportional hazards regression analyses. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using STATA version 17.0.

Results

A total of 339 patients received solitary kidney transplantation between January 1, 1998, and December 31, 2022. Fifty-three patients were excluded due to graft loss within one year (n=9) and missing data (n=44). Two hundred eighty-six patients were included in the final analysis. Baseline characteristics according to the presence or absence of PTE are shown in **Table 1**.

Table 1 Baseline characteristics and laboratory data of all patients

Parameters	PTE Group (n=26)	Non-PTE Group (n=260)	P-value
Male sex (n/%)	24 (92.3)	139 (53.5)	<0.001
Age at KT (years)	38 ± 8.3	41.7 ± 10.7	0.087
Previous smoking (n/%)	9 (34.6)	26 (10)	<0.001
Body mass index (kg/m^2)	25.5 ± 4.9	22.6 ± 3.9	0.001
Cause of end-stage kidney disease (n/%)			0.93
Diabetic nephropathy	1 (3.8)	19 (7.3)	
Glomerulonephritis	8 (30.8)	68 (26.2)	
Hypertensive nephrosclerosis	2 (7.7)	13 (5)	
Polycystic kidney disease	1 (3.8)	10 (3.8)	
Obstructive uropathy	0 (0)	4 (1.5)	
Unknown	14 (53.8)	146 (56.2)	
Pretransplant diabetes mellites (n/%)	4 (15.4)	34 (13.1)	0.741
Pretransplant hypertension (n/%)	23 (88.5)	250 (96.2)	0.073
Pretransplant ACEI or ARB use (n/%)	3 (11.5)	88 (33.8)	0.02
Hematocrit on the day of transplantation	35.4 ± 5.3	32.2 ± 4.6	0.001
Mode of dialysis (n/%)			0.693
Peritoneal dialysis	2 (7.7)	15 (5.8)	
Hemodialysis	24 (92.3)	245 (94.2)	
Dialysis vintage (months)	53 ± 39.6	62.4 ± 47.2	0.327
Donor type (n/%)			0.154
Deceased donor	14 (53.8)	176 (67.7)	
Living donor	12 (46.2)	84 (32.3)	
Graft function (n/%)			0.400
Immediate graft function	17 (65.4)	147 (56.5)	
Slow graft function	6 (23.1)	53 (20.4)	
Delayed graft function	3 (11.5)	60 (23.1)	

Table 1 Baseline characteristics and laboratory data of all patients (continued)

Parameters	PTE Group (n=26)	Non-PTE Group (n=260)	P-value
Serum creatinine after KT (mg/dL)			
At 3 months	1.74 ± 0.81	1.44 ± 0.57	0.012
At 6 months	1.69 ± 0.55	1.48 ± 0.59	0.080
At 12 months	1.6 ± 0.41	1.46 ± 0.63	0.279
Immunosuppressive drugs (n/%)			
Tacrolimus	15 (57.7)	164 (63.1)	0.589
Cyclosporin	11 (42.3)	96 (36.96)	0.589
Mycophenolate mofetil	25 (96.2)	249 (95.8)	0.926
Azathioprine	1 (3.8)	11 (4.2)	0.926
Corticosteroid	26 (100)	260 (100)	

PTE, post-transplant erythrocytosis; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; KT, kidney transplantation.

There was a significantly higher proportion of male patients in the PTE group compared to the non-PTE group (92.3% vs. 53.5%, p<0.001). The mean age was comparable between the two groups. A higher percentage of patients in the PTE group had a history of smoking (34.6% vs. 10%, p<0.001). The body mass index (BMI) was also higher in the PTE group (25.5±4.9 vs. 22.6±3.9, p=0.001). Pretransplant hematocrit was higher in the PTE group compared to the non-PTE group (35.4±5.3 vs. 32.2±4.6, p<0.001). The use of ACEI/ARB before transplantation was less frequent in the PTE group (11.5% vs. 33.8%, p=0.02). Serum creatinine was significantly higher in the PTE group (1.74±0.81 vs. 1.44±0.57, p=0.012) at 3 months post-transplantation. However, serum creatinine levels were comparable between the two groups at 6 and 12 months post-transplantation. There were no statistically significant differences regarding the underlying causes of ESKD, history of diabetes mellitus and hypertension before transplantation, dialysis modalities, dialysis vintage, post-transplant allograft function, or the types of maintenance immunosuppressive medications between the two groups.

PTE was diagnosed in 26 patients during the study period, resulting in a cumulative incidence of 9.09% **(Figure 2a)**. Kaplan-Meier analysis focusing on the time to PTE development revealed a median onset time of 7.13 (4-41.6) months, as depicted in **Figure 2b**. Subgroup analyses focusing on three factors, including sex, pre-transplant ACEI/ARB use, and history of smoking, are shown in **Figure 3**.

Cox multivariate regression analysis was conducted to identify risk factors associated with PTE **(Table 2)**. In the univariate model, male sex (HR 9.57, 95% CI 2.26-40.48), history of smoking (HR 3.98, 95% CI 1.77-8.93), higher BMI (HR 1.15, 95% CI 1.06-1.25), higher pretransplant hematocrit (HR 1.15, 95% CI 1.06-1.25), and history of ACEI/ARB use before transplantation (HR 3.68, 95% CI 1.1-12.24) were associated with PTE. After adjusting for covariates, male sex (HR 5.33, 95% CI 1.19-23.77) and higher BMI (HR 1.1, 95% CI 1.01-1.2) were independent predictors of PTE.

Baseline characteristics and laboratory data of patients diagnosed with PTE are shown in **Table 3.** The average hematocrit level at the time of diagnosis was 54.38% ± 2.38. Seven (27%) patients experienced spontaneous recovery over an average follow-up period of 7.5 months. Half of the patients were treated with ACEI/ARB and experienced favorable responses—only one patient did not respond to ACEI and subsequently required

phlebotomy. Those patients who received phlebotomy typically showed mild symptoms such as dizziness and headache. Four patients received JAK-2 mutation testing, all yielding negative results. Transplant renal artery stenosis (TRAS) was diagnosed in three patients at least one year after the initial diagnosis of PTE. There were no reports of thromboembolic events in any of the patients.

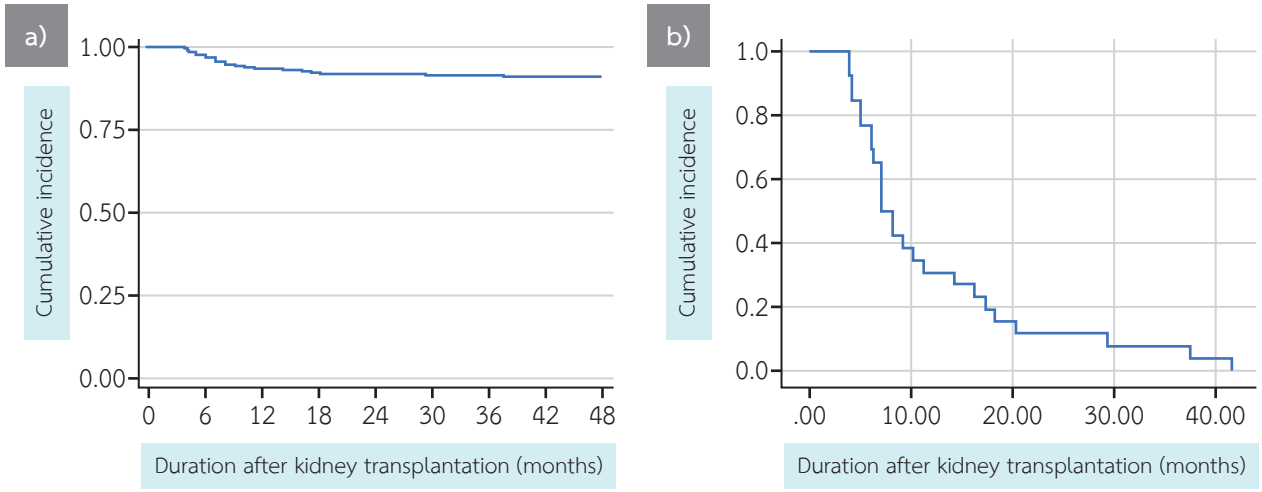

Figure 2 Kaplan-Meier analysis of the cumulative survival of post-transplant erythrocytosis
a) cumulative survival of all patients; b) time to development of post-transplant erythrocytosis

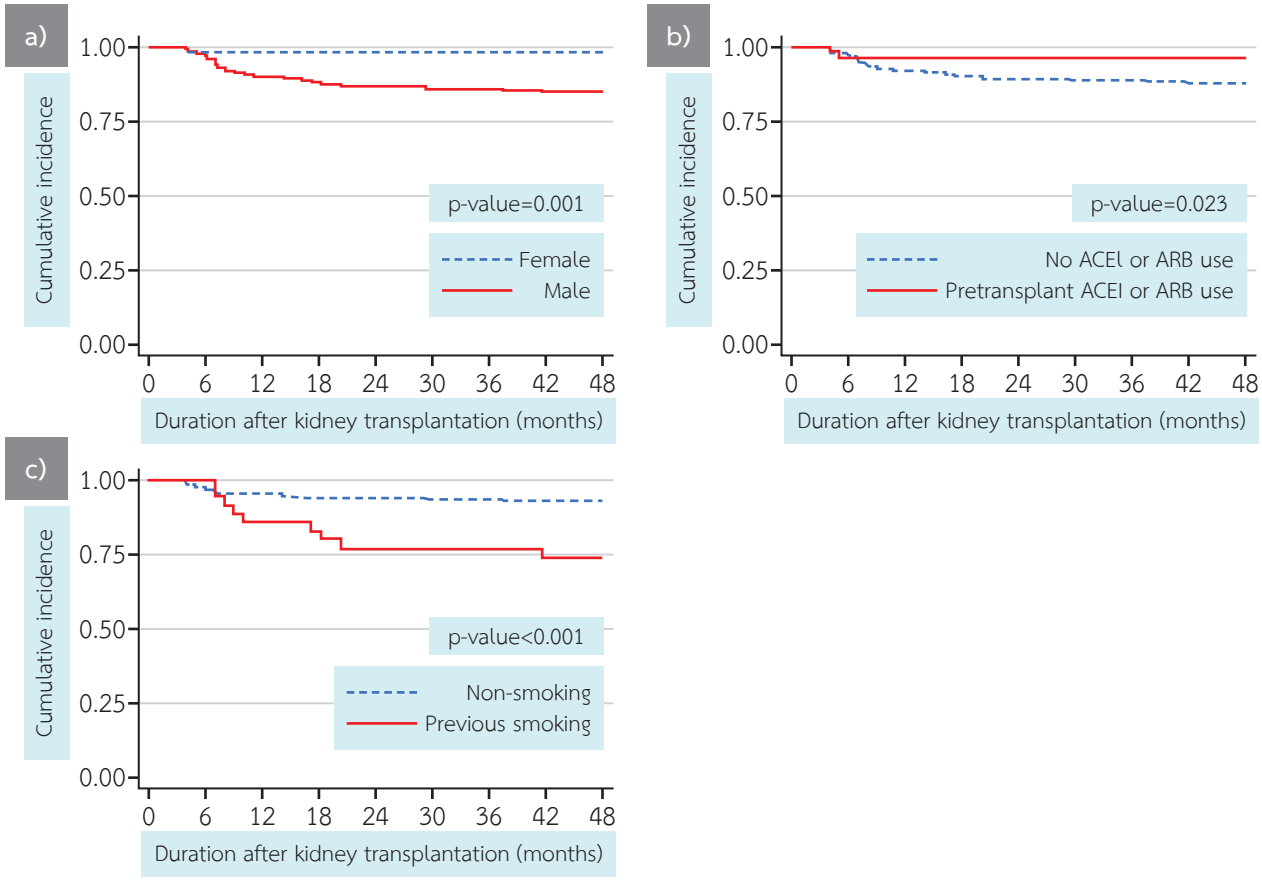

Figure 3 Kaplan-Meier analysis demonstrated the cumulative survival of post-transplant erythrocytosis according to a) sex, b) pretransplant ACEI/ARB use, c) history of smoking
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table 2 Cox-proportional hazard regression analysis of baseline factors associated with post-transplant erythrocytosis

Factors	Univariate model		Multivariate model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	9.57 (2.26,40.48)	0.002	5.33 (1.19,23.77)	0.028
Age at kidney transplantation	0.97 (0.93,1)	0.085	-	-
Previous smoking	3.98 (1.77,8.93)	0.001	2.28 (0.94,5.5)	0.067
Body mass index	1.15 (1.06,1.25)	0.001	1.1 (1.01,1.2)	0.031
Pretransplant diabetes mellites	1.18 (0.41,3.41)	0.766	-	-
Pretransplant hypertension	0.33 (0.1,1.12)	0.075	-	-
Dialysis vintage	0.99 (0.99,1)	0.318	-	-
Pretransplant hematocrit	1.15 (1.06,1.25)	0.001	1.03 (0.81, 1.31)	0.816
No history of ACEI or ARB use before transplantation	3.68 (1.1,12.24)	0.034	2.92 (0.86,9.93)	0.087
Graft function				
Delayed graft function	Reference	1	-	-
Slow graft function	2.21 (0.55,8.82)	0.263	-	-
Immediate graft function	2.29 (0.67,7.81)	0.186	-	-
Maintenance immunosuppressive drugs				
Tacrolimus	0.851 (0.37,1.77)	0.599	-	-
Cyclosporin	1.23 (0.57,2.68)	0.599	-	-
Mycophenolate	1.09 (0.15,8.04)	0.933	-	-
Azathioprine	0.92 (0.12,6.78)	0.933	-	-

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; CI, confidence interval

Table 3 Characteristics and laboratory data of the patients with post-transplant erythrocytosis

Factors			Mean ± SD / N (%)
Serum creatinine at diagnosis (mg/dL)			1.69 ± 0.39
Hematocrit at diagnosis (%)			54.38 ± 2.38
Transplant renal artery stenosis			3 (11)
Management of post-transplant erythrocytosis (n/%)			
ACEI or ARB	ACEI or ARB + Phlebotomy	Phlebotomy	No intervention
12 (46.1)	1 (3.8)	6 (23.0)	7 (26.9)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation

Discussion

The main findings of the present study include a cumulative incidence of post-transplant erythrocytosis (PTE) of 9.1%. PTE developed at a median interval of 7.1 months post-transplantation. In univariate analysis, male sex, previous smoking, higher BMI, higher hematocrit, and no prior use of ACEIs or ARBs at baseline were associated with the development of PTE. However, in multivariate analysis, only male sex and higher BMI emerged as independent predictors of PTE. Most patients responded well to RAAS blockade, with 27% experiencing spontaneous recovery.

The incidence of PTE in this study aligns with previously reported rates, ranging from 5% to 31.2%.[2-7]. The multivariate analysis confirmed that male sex was independently associated with PTE development, likely due to higher levels of endogenous androgens in males, which stimulate erythroid progenitor activation. The link between a history of smoking and PTE is possibly due to smoking's effects on gaseous exchange mechanisms, leading to hypoxemia and subsequent stimulation of red blood cell production[8].

The subgroup of patients who had received ACEIs or ARBs before transplantation showed a lower tendency to develop PTE compared to those who had not. This is likely due to ACEIs increasing levels of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SKDP), an inhibitor of erythroid progenitors. ARBs, by blocking the AT1 receptor and reducing angiotensin II levels, also inhibit erythroid progenitor activation[8]. However, conflicting data exist regarding the relationship between ACEI/ARB use and PTE risk, with some studies indicating lower risk and others indicating higher risk[9,10]. A recent meta-analysis found no significant association between pretransplant ACEI or ARB use and PTE[5].

In this study, the PTE group exhibited higher serum creatinine levels at 3 months but not at 6 or 12 months post-transplantation compared to the non-PTE group, contrasting with findings from previous studies[11]. Various factors such as muscle mass, age, and dietary intake may influence serum creatinine levels.

The association between BMI and PTE, though previously unreported, was significant in this study[5, 10]. There is evidence suggesting that overweight and obese populations have higher hemoglobin and hematocrit levels, potentially due to higher intake of iron-rich diets[12]. Further studies are warranted to confirm this observation. TRAS was identified as a risk factor for PTE[5]. Similar to previous reports, TRAS was diagnosed in 11.5% of patients with PTE in this study. The association between TRAS and PTE is primarily driven by impaired renal perfusion and subsequent compensatory mechanisms that increase erythropoietin production, leading to erythrocytosis.

Study Strengths and Limitations

The study's strengths include a well-defined cohort and comprehensive analysis of potential risk factors for PTE. However, limitations include a relatively small sample size and potential confounding factors that may not have been fully accounted for. The observational nature of the study also limits the ability to establish causal relationships.

Conclusion

Nine percent of kidney transplant recipients developed PTE approximately seven months post-transplantation. Male sex and higher BMI were identified as independent predictors of PTE. Most patients responded well to RAAS blockade, with 27% experiencing spontaneous recovery.

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