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# Incidence, Risk Factors, and Outcomes of Posttransplant Erythrocytosis Among Simultaneous Pancreas-Kidney Transplant Recipients

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**Background.** Posttransplant erythrocytosis (PTE) is a well-known complication of kidney transplantation. However, the risk and outcomes of PTE among simultaneous pancreas-kidney transplant (SPKT) recipients are poorly described. **Methods.** We analyzed all SPKT recipients at our center between 1998 and 2021. PTE was defined as at least 2 consecutive hematocrit levels of >51% within the first 2 y of transplant. Controls were selected at a ratio of 3:1 at the time of PTE occurrence using event density sampling. Risk factors for PTE and post-PTE graft survival were identified. **Results.** Of 887 SPKT recipients, 108 (12%) developed PTE at a median of 273 d (interquartile range, 160–393) after transplantation. The incidence rate of PTE was 7.5 per 100 person-years. Multivariate analysis found pretransplant dialysis (hazard ratio [HR]: 3.15; 95% confidence interval [CI], 1.67-5.92; $P < 0.001$), non-White donor (HR: 2.14; 95% CI, 1.25-3.66; $P = 0.01$), female donor (HR: 1.50; 95% CI, 1.0-2.26; $P = 0.05$), and male recipient (HR: 2.33; 95% CI, 1.43-3.70; $P = 0.001$) to be associated with increased risk. The 108 cases of PTE were compared with 324 controls. PTE was not associated with subsequent pancreas graft failure (HR: 1.36; 95% CI, 0.51-3.68; $P = 0.53$) or kidney graft failure (HR: 1.16; 95% CI, 0.40-3.42; $P = 0.78$). **Conclusions.** PTE is a common complication among SPKT recipients, even in the modern era of immunosuppression. PTE among SPKT recipients was not associated with adverse graft outcomes, likely due to appropriate management.

(*Transplantation Direct* 2024;10: e1607; doi: 10.1097/TXD.0000000000001607.)

Posttransplant erythrocytosis (PTE) is a well-known complication of kidney transplantation, typically occurring within 2 y of transplantation.[1-3] Past studies show that the incidence of PTE among kidney transplant recipients varies between 8% and 15%, with a few studies reporting an incidence as low as 2.5% or as high as 22%.[4,5] The disparity likely arises from inconsistencies in PTE definitions. For example, some studies defined PTE as having hemoglobin >16 to 18 g/dL or hematocrit concentration >50% to 52%, whereas others used gender-specific hematocrit thresholds (53%–55% for men; 48%–51% for women). Another measure used by researchers is the duration of elevated hemoglobin or hematocrit.[3,4,6-10] To address these discrepancies, the Kidney Disease Improving Global Outcomes organization formed a workgroup in 2009 that defined PTE as hemoglobin >17 g/dL or hematocrit >51%, regardless of gender or duration.[4] The consensus provides clarity and consistency for research, which serves as the guiding force for improving the care and outcomes of patients with PTE.

In recent decades, there has been a decline in the incidence of PTE among kidney transplant recipients. For instance, a study that defined PTE as hemoglobin >17 g/L reported an incidence of 18.7% among those transplanted between 1993 and 1996, which significantly decreased to 8.1% among recipients transplanted between 1997 and 2005.[3] A more recent study by Alzoubi et al[11] defined PTE as hematocrit >51% and found the incidence rate of PTE among recipients who had kidney transplants between 2001 and 2016 to be 5%. Diabetes has been shown to increase the risk of PTE in some,

*Received 26 December 2023.*
*Accepted 30 January 2024.*

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*The authors declare no conflicts of interest.*
*D.M. received research funds from the Virginia Lee Cook Foundation.*
*The data that support the findings of this study are available from the corresponding author (S.P.) on reasonable request.*
*M.L.G. participated in data collection, design, analysis, and article preparation. B.C.A. participated in design, analysis, and editing. J.O. and D.M. participated in design and editing. S.P. participated in concept, data collection, analysis, article preparation, and editing.*



*ISSN: 2373-8731*
*DOI: 10.1097/TXD.0000000000001607*

but not all, studies.[3,5,12] Additionally, 1 single-center, retrospective study has suggested that PTE may be more common among SPKT recipients compared with kidney transplants alone.[13] Given this evolving landscape in kidney transplantation, we embarked on a comprehensive study focusing on PTE among SPKT recipients. In this study, we sought to investigate the incidence of PTE, identify risk factors for PTE, and assess pancreas and kidney graft failure following PTE among SPKT recipients in a larger and more recent cohort in the era of modern immunosuppression.

## MATERIALS AND METHODS

### Population Selection and Study Design

We evaluated all adult SPKT recipients who underwent transplants between January 1, 1998, and December 31, 2021, at the University of Wisconsin. The exclusion criteria consisted of patients who were younger than 18 y at the time of the transplant and any other solid organ transplant recipients besides SPKT. We examined the incidence, management, and resolution of PTE, risk factors for the development of PTE, risk factors for pancreas graft failure, and risk factors for kidney graft failure. We also analyzed the demographics of those who had PTE and those who did not have PTE. Additionally, we compared the incidence rate of PTE between 1998 and 2009 with that of PTE between 2010 and 2021.

Following the identification of patients with PTE, control subjects were selected using event density sampling at a ratio of 3:1 at the time of PTE occurrence. Specifically, for every instance of PTE diagnosis, we selected 3 control cases without PTE, matched on the basis of the posttransplant interval. This study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin (protocol number: 2014-1072). This study was in adherence to the Declaration of Helsinki. The clinical and research activities being reported were consistent with the Principles of the Declaration of Istanbul as outlined in "The Declaration of Istanbul on Organ Trafficking and Transplant Tourism." Due to the nature of the study, informed consent from study patients pertinent to this study was not obtained.

### Definitions and Variables

Following the Kidney Disease Improving Global Outcome definition of PTE, we defined PTE as having a hematocrit concentration >51% and the resolution of PTE as having a hematocrit concentration ≤51% after the initial development of PTE.[4] To mitigate potential laboratory errors, all included patients had at least 2 consecutive hematocrit concentrations >51%. Similarly, the resolution of PTE required at least 2 consecutive hematocrit concentrations ≤51%. This study focused exclusively on SPKT recipients who were diagnosed with PTE within 2 y posttransplant because the majority of PTE cases manifest during this initial posttransplant period.[2]

The data gathered comprised basic demographic information of recipients and donors. Potential risk factors for PTE were based on the commonly established risk factors for PTE development, including age, gender, race, previous transplant, pretransplant dialysis, type of diabetes, HLA mismatch, and the use of depleting induction. Characteristics of donors assessed included age, gender, race, BMI, Kidney Donor Profile Index (KDPI), and donation after circulatory death. Kidney death-censored graft failure (DCGF) was defined as a return to dialysis or a need for retransplantation of the kidney. Pancreas DCGF was defined on the basis of the current United Network for Organ Sharing criteria for pancreas graft failure, which include removal of the pancreas graft, re-registration for a pancreas transplant, registration for an islet transplant after receiving pancreas, or an insulin requirement that is ≥0.5 units/kg/d for 90 consecutive days.[14]

### Induction and Maintenance Immunosuppressive Medications

Based on immunologic risk factors, patients undergoing SPKT received either induction immunosuppression with a depleting agent (antithymocyte globulin or alemtuzumab) or a nondepleting agent (basiliximab). Most patients were on 3 immunosuppressive medications, including a calcineurin inhibitor (predominantly tacrolimus), an antiproliferative agent (mycophenolate mofetil or mycophenolic acid), and steroids. Some recipients had early steroid withdrawal. The dosages and drug levels were tailored to each patient's clinical condition, such as infection, malignancy, and rejection, with adjustments made at the physician's discretion as described before.[15]

### Laboratory Monitoring and Management of PTE

During the initial 6 wk posttransplant, SPKT recipients received blood tests, including assessments of hemoglobin and hematocrit levels twice per week. From 6 wk to 3 mo, patients underwent blood tests once per week and then transitioned to blood tests every other week from the third to sixth month posttransplant. After 6 mo, laboratory tests were drawn once per month. However, the frequency of blood tests for some patients varied from the standard protocol depending on their clinical trajectory and the discretion of the physician. At our institution, there is no established protocol for PTE management. However, based on the patient's clinical course and physician discretion, PTE may have been managed through observation, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARBs), or phlebotomy. Usually, recipients with persistent hematocrit of >51% on multiple occasions were likely to be started on ACE-I/ARBs, and those with persistent hematocrit concentration of >55% were likely to get phlebotomy. Recipients with transient hematocrit concentrations of >51% or hematocrit concentrations just above 51% were likely to be observed without acute intervention.

### Statistical Analyses

All baseline categorical comparisons were made using the chi-square tests or Fisher exact tests. Continuous values were summarized as mean plus SD or median plus interquartile range and compared using analysis of variance or Kruskal-Wallis for nonnormally distributed data. Risk factors associated with incident PTE were identified in competing risk survival analysis models using the methods of Fine and Gray with graft failure as the competing event in addition to standard censoring.[16] Bivariate models identified unadjusted associations. Multivariate models were then built including variables based on the statistical significance of bivariate associations ($P < 0.05$).

We separately used Kaplan-Meier survival curves and log-rank tests for bivariate associations with kidney graft and

pancreas graft DCGF. Multivariate models used robust variance estimates to account for within-group clustering. All *P* values of ≤0.05 were considered statistically significant. We used Stata version 16 SE to conduct all statistical analyses (StataCorp. 2019, Stata Statistical Software: Release 16, StataCorp LLC, College Station, TX).

## RESULTS

### Incidence and Risk Factors for PTE

Of the 887 SPKT recipients during the study period, 108 (12%) were diagnosed with PTE at a median of 273 d (interquartile range, 159.5–393) after transplantation. The incidence rate of PTE was 7.5 per 100 person-years. Of the 108 recipients who developed PTE, 33 (31%) were treated with ACE-I or ARBs only, 39 (36%) needed phlebotomy (usually in addition to ACE-I/ARBs), and the remaining 36 (33%) were managed by observation. Of the 39 recipients treated with phlebotomy, 12 were treated exclusively with phlebotomy because of intolerance or documented allergic reaction to the ACE-I/ARBs. In the remaining 27 recipients, ACE-I/ARB was initiated first, followed by phlebotomy because of the inadequate response. The mean interval from the diagnosis to resolution of PTE among the entire cohort was 7.0 ± 9.3 mo. The mean interval for the resolution of PTE among those managed just with observation was 6.1 ± 9.9 mo, with ACE-I/ARB ± phlebotomy was 7.9 ± 9.6 mo, and for those treated exclusively with phlebotomy was 7.9 ± 5.5 mo. These mean intervals were not statistically different ($P = 0.65$).

The incidence rate of PTE development observed during the era 1998–2009 (6.41 per 100 person-years) was similar to the rate observed during the era 2010–2021 (9.26 per 100 person-years; $P = 0.06$).

A higher incidence of PTE was observed among male recipients, those with a history of pretransplant dialysis, and non-White donors (Table 1). Factors associated with a lower incidence of PTE development were older donor age and a donor with a higher KDPI. After adjustment for multiple variables, risk factors for increased risk of PTE were history of pretransplant dialysis (hazard ratio [HR]: 3.27; 95% confidence interval [CI], 1.75-6.10; $P < 0.001$), non-White donor (HR: 2.32; 95% CI, 1.40-3.87; $P = 0.001$), and male recipient (HR: 2.31; 95% CI, 1.46-3.67; $P < 0.001$). Older donor age was associated with lower risk for PTE (HR: 0.98, 95% CI, 0.96-1.0; $P = 0.04$). No significant association was observed for KDPI in the multivariate analysis.

### Comparison With Control

The 108 cases of PTE were compared with 324 control recipients without PTE. Recipients were followed for a median of 8.2 y following PTE/selection as a control. The comparison of various baseline characteristics between SPKT recipients who developed PTE and the control is presented in Table 2. The mean hematocrit at the time of PTE diagnosis was 53.0% ± 1.7%. Recipients in the PTE group were more likely to be men ($P = 0.001$) and have had nonpreemptive transplants ($P < 0.001$) compared with their controls. Additionally, the donors in the PTE group were more likely to be younger ($P = 0.005$) and non-White ($P < 0.001$). At the time of the diagnosis, the mean serum creatinine level was 1.24 ± 0.28 mg/dL for the PTE group compared with1.35 ± 0.50 mg/dL for the controls group ($P = 0.02$). The estimated glomerular filtration rate (eGFR) was 72.9 ± 16.8 mL/min for the PTE group and 67.2 ± 20.7 mL/min for the control ($P = 0.006$). All other baseline characteristics of the groups were not significantly different.

**TABLE 1.**

**Risk factors for PTE**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| **Covariate** | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** | ***P*** |
| Recipient age (per year) | 1.01 | 0.98-1.02 | 0.87 | | | |
| Male recipient | 2.38 | 1.49-3.85 | <0.001 | 2.31 | 1.46-3.67 | <0.001 |
| Non-White recipient | 1.21 | 0.70-2.09 | 0.49 | | | |
| Previous transplant | 0.32 | 0.07-1.31 | 0.11 | | | |
| On dialysis before the transplant | 3.57 | 1.91-6.67 | <0.001 | 3.27 | 1.75-6.10 | <0.001 |
| HLA mismatch (per) | 1.14 | 0.97-1.35 | 0.11 | | | |
| Types of diabetes | | | | | | |
| Type I | Ref | Ref | Ref | Ref | Ref | Ref |
| Type II | 2.02 | 1.24-3.30 | 0.004 | 1.48 | 0.82-2.66 | 0.18 |
| Other/unknown | – | – | – | – | – | – |
| Depleting induction | 1.37 | 0.93-2.0 | 0.11 | | | |
| Donor age (per year) | 0.97 | 0.96-0.99 | 0.004 | 0.98 | 0.96-1.0 | 0.04 |
| Donor female | 1.21 | 0.83-1.77 | 0.32 | | | |
| Donor non-White | 2.46 | 1.51-4.01 | <0.001 | 2.32 | 1.40-3.87 | 0.001 |
| Donor BMI (per kg/m$^2$) | 0.97 | 0.92-1.01 | 0.18 | | | |
| Donation after circulatory death | 0.84 | 0.49-1.45 | 0.53 | | | |
| Kidney Donor Profile Index (per %) | 0.98 | 0.97-1.0 | 0.03 | 0.99 | 0.98-1.01 | 0.14 |
| Kidney delayed graft function | 1.19 | 0.65-2.18 | 0.56 | | | |
| CMV high risk: $D^+/R^-$ | 0.99 | 0.65-1.50 | 0.94 | | | |

BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio; PTE, posttransplant erythrocytosis; Ref, reference.

**TABLE 2.**

**Baseline characteristics comparing SPK transplant recipients who developed PTE and those who did not (controls)**

| Characteristics | PTE (N = 108) | Control (N = 324) | *P* |
|---|---|---|---|
| Age at transplant, y | 42.4 ± 8.5 | 41.4 ± 8.5 | 0.32 |
| Male % | 85 (79) | 185 (57) | 0.001 |
| Non-White, % | 15 (14) | 45 (14) | 1.0 |
| Previous transplant, % | 2 (2) | 16 (5) | 0.19 |
| Nonpreemptive transplant | 97 (90) | 231 (71) | <0.001 |
| Mean HLA mismatch (of 6) | 4.6 ± 1.1 | 4.4 ± 1.2 | 0.18 |
| Types of diabetes | | | |
| Type 1 | 88 (81) | 376 (87) | 0.07 |
| Type 2 | 20 (19) | 53 (12) | |
| Unknown/other | 0 | 3 (1) | |
| Depleting induction | 61 (56) | 154 (48) | 0.13 |
| Donor age | 25.3 ± 11.7 | 29.0 ± 12.4 | 0.005 |
| Donor female | 47 (44) | 131 (40) | 0.58 |
| Donor non-White | 20 (19) | 24 (7) | <0.001 |
| Donor's BMI | 23.3 ± 4.1 | 24.3 ± 4.5 | 0.06 |
| Donation after circulatory death | 15 (14) | 48 (15) | 0.82 |
| Mean KDPI | 17.7 ± 16.4 | 21.2 ± 17.2 | 0.08 |
| Kidney delayed graft function | 12 (11) | 33 (10) | 0.78 |
| Mean hematocrit at the time of transplant | 31.1 ± 3.9 | 30.8 ± 4.2 | 0.48 |
| Mean hematocrit at the time of PTE/control | 53.0 (1.7) | 36.7 (7.0) | <0.001 |
| Range | (51.1-64) | (22-50.6) | |
| Mean serum creatinine at the time of PTE/control | 1.24 ± 0.28 | 1.35 ± 0.50 | 0.02 |
| Mean eGFR at the time of PTE/control | 72.9 ± 16.8 | 67.2 ± 20.7 | 0.006 |
| Mean interval from transplant to PTE/control, d | 299.7 ± 167.8 | 299.7 ± 167.3 | 0.99 |

BMI, body mass index; eGFR, estimated glomerular filtration rate; KDPI, Kidney Donor Profile Index; PTE, posttransplant erythrocytosis; SPK, simultaneous pancreas-kidney.

**TABLE 3.**

**Competing risk of pancreas graft failure**

| | Multivariate analyses | | |
|---|---|---|---|
| **Covariate** | **HR** | **95% CI** | ***P*** |
| Posttransplant erythrocytosis | 1.36 | 0.51-3.68 | 0.53 |
| Recipients' age (per year) | 0.92 | 0.89-0.95 | <0.001 |
| Male recipient | 1.31 | 0.78-1.61 | 0.21 |
| Non-White recipient | 1.86 | 0.88-3.96 | 0.11 |
| Previous transplant | 0.78 | 0.13-4.45 | 0.79 |
| On dialysis before the transplant | 1.26 | 0.64-2.49 | 0.50 |
| HLA mismatch (per) | 1.02 | 0.78-1.33 | 0.85 |
| Types of diabetes | | | |
| Type I | Ref | Ref | Ref |
| Type II | 0.22 | 0.02-1.76 | 0.15 |
| Other/unknown | 2.94 | 0.46-18.86 | 0.25 |
| Depleting induction | 1.12 | 0.65-1.94 | 0.67 |
| Donor age (per) | 1.02 | 0.99-1.06 | 0.09 |
| Donor female | 1.05 | 0.57-.94 | 0.86 |
| Donor non-White | 1.83 | 0.82-4.09 | 0.14 |
| Donor BMI (per kg/m$^2$) | 0.98 | 0.91-1.06 | 0.65 |
| Donation after circulatory death | 0.62 | 0.25-1.52 | 0.30 |
| Kidney Donor Profile Index (per %) | 0.99 | 0.96-1.01 | 0.41 |
| Kidney delayed graft function | 1.41 | 0.54-3.67 | 0.48 |
| Hematocrit at the time of PTE (per g%) | 0.98 | 0.93-1.03 | 0.41 |
| eGFR at time of PTE (per mL/m$^2$) | 0.99 | 0.98-1.01 | 0.79 |

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PTE, posttransplant erythrocytosis; Ref, reference.

## Competing Risk of Pancreas and Kidney Graft Failure

In the multivariate analysis of competing risks of pancreas graft failure, we identified 89 cases of pancreas DCGF and 83 deaths (Table 3). No factors were associated with an increased risk of pancreas graft failure, including PTE (HR: 1.36; 95% CI, 0.51-3.68; $P = 0.53$). This was further confirmed with the Kaplan-Meier survival analysis curve (Figure 1). A factor

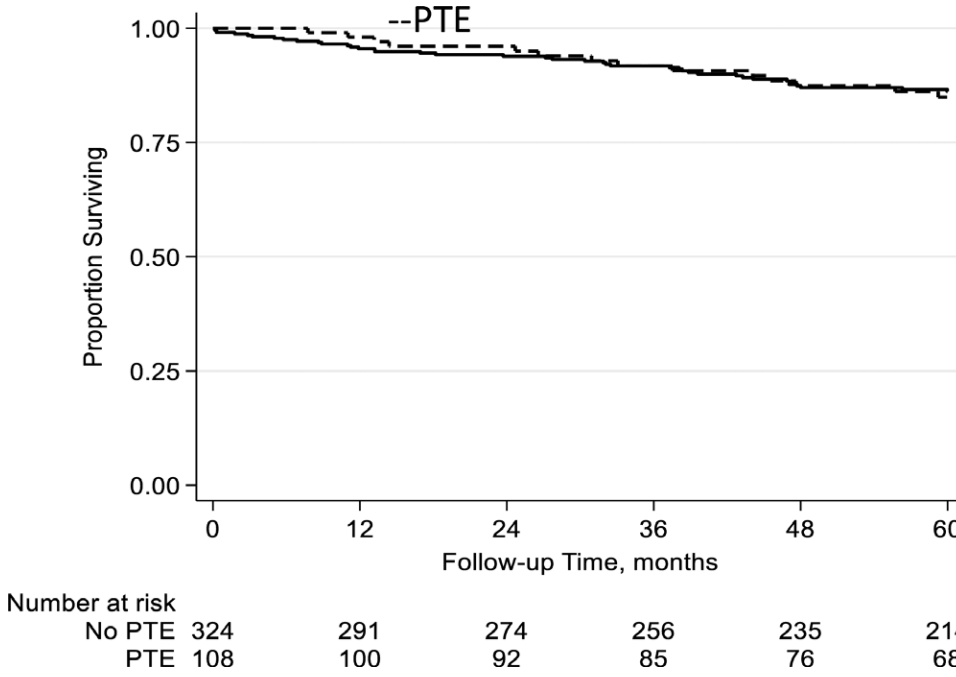


**FIGURE 1.** No significant difference in pancreas graft failure between PTE and control. PTE, posttransplant erythrocytosis.

associated with a lower risk of pancreas graft failure was older donor age (HR: 0.92; 95% CI, 0.89-0.95; $P < 0.001$). Similar outcomes of PTE not associated with increased or decreased risk of pancreas graft failure were observed when looking at the different eras of 1998–2009 and 2010–2021 (data not shown).

The multivariate analysis of competing risks of kidney graft failure had 72 cases of kidney DCGF and 61 deaths (Table 4). Non-White recipients were more likely to experience kidney graft failure (HR: 2.36; 95% CI, 1.07-5.16; $P = 0.03$). A greater risk of kidney graft failure was also more likely in recipients with kidney delayed graft function (HR: 2.17; 95% CI, 1.04-4.54; $P = 0.04$). Older recipients were less likely to experience kidney graft failure (HR: 0.95; 95% CI, 0.91-0.98; $P = 0.007$). Higher eGFR levels decreased the likelihood of kidney graft failure (HR: 0.97;

**TABLE 4.**

**Competing risk of kidney graft failure**

| | Multivariate analyses | | |
|---|---|---|---|
| **Covariate** | **HR** | **95% CI** | ***P*** |
| Posttransplant erythrocytosis | 1.16 | 0.40-3.42 | 0.78 |
| Recipients' age (per year) | 0.95 | 0.91-0.98 | 0.007 |
| Male recipient | 1.05 | 0.34-1.45 | 0.88 |
| Non-White recipient | 2.36 | 1.07-5.16 | 0.03 |
| Previous transplant | 0.47 | 0.10-2.31 | 0.35 |
| On dialysis before the transplant | 0.89 | 0.48-1.64 | 0.71 |
| HLA mismatch (per) | 0.87 | 0.68-1.11 | 0.27 |
| Types of diabetes | | | |
| Type I | Ref | Ref | Ref |
| Type II | 0.22 | 0.04-1.13 | 0.07 |
| Other/unknown | 5.03 | 1.88-13.48 | 0.001 |
| Depleting induction | 1.06 | 0.60-1.90 | 0.82 |
| Donor age (per) | 1.02 | 0.99-1.06 | 0.06 |
| Donor female | 0.78 | 0.44-1.41 | 0.42 |
| Donor non-White | 1.38 | 0.63-3.03 | 0.41 |
| Donor BMI (per kg/m$^2$) | 0.97 | 0.91-1.03 | 0.34 |
| Donation after circulatory death | 0.90 | 0.39-2.04 | 0.80 |
| Kidney Donor Profile Index (per %) | 0.99 | 0.98-1.02 | 0.87 |
| Kidney delayed graft function | 2.17 | 1.04-4.54 | 0.04 |
| Hematocrit at the time of PTE (per g%) | 0.98 | 0.93-1.04 | 0.66 |
| eGFR at the time of PTE (per mL/m$^2$) | 0.97 | 0.96-0.99 | 0.002 |

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PTE, posttransplant erythrocytosis; Ref, reference.

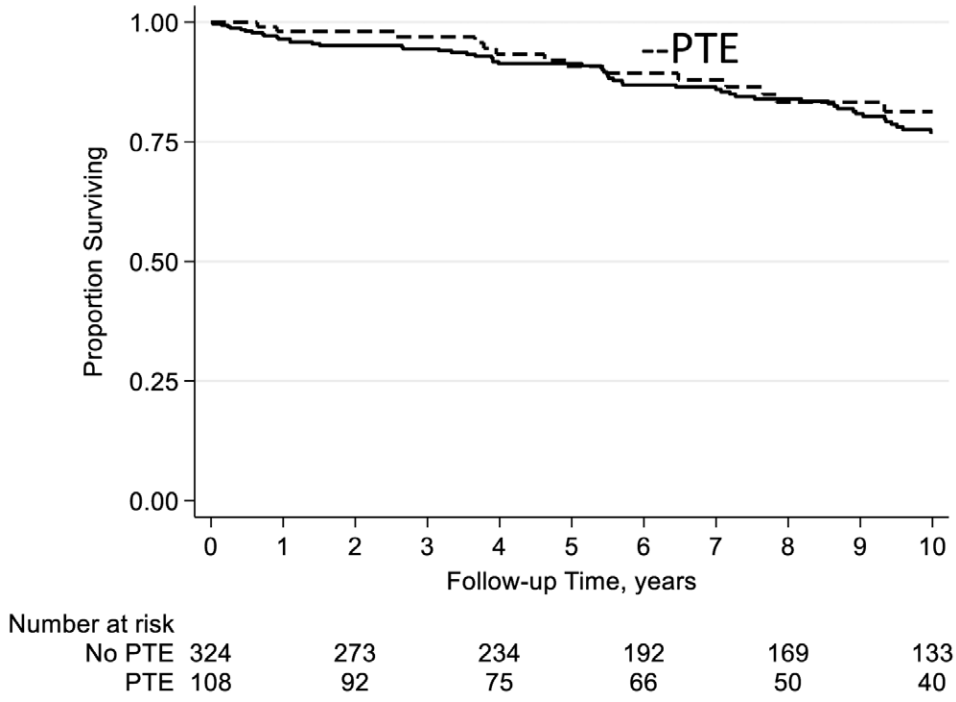


**FIGURE 2.** No significant difference in kidney graft failure between PTE and control. PTE, posttransplant erythrocytosis.

95% CI, 0.96-0.99; $P = 0.002$). PTE was not associated with an increased risk of kidney graft failure (HR: 1.16; 95% CI, 0.40-3.42; $P = 0.78$). This was further confirmed with the Kaplan-Meier survival analysis curve (Figure 2). Similar outcomes of PTE not associated with increased or decreased risk of pancreas graft failure were observed when looking at the different eras of 1998–2009 and 2010–2021 (data not shown).

There was only 1 case of deep vein thrombosis in the PTE group during the study period, and no group member had stroke. For this reason, various other complications associated with PTE including vascular thrombotic events were not studied.

## DISCUSSION

In this analysis spanning 23 y and encompassing 887 SPKT recipients, we observed an incidence of PTE at 12%. Notably, we found that male recipients were over twice as likely to develop PTE, and recipients with a history of pretransplant dialysis faced a 3-fold increased risk of PTE. Donor characteristics were also statistically significant: recipients with non-White donors were more likely to develop PTE, whereas recipients with older donors were less likely to develop PTE. When comparing the baseline characteristics between SPKT recipients who developed PTE and those who did not develop PTE, recipients in the PTE group were more likely to be male and have had nonpreemptive transplants. Additionally, the donors in the PTE group were more likely to be younger and non-White. Importantly, despite these risk factors and the occurrence of PTE, our analysis found that PTE was not associated with graft survival for either kidney or pancreas transplantation.

Our finding of a 12% PTE incidence rate prompts intriguing comparisons, as previous studies have reported different incidence rates.[13,17] For instance, a study by Guerra et al[13] that compared the incidence of 94 recipients of SPKT, 174 living donor kidney transplants, and 53 type I diabetic recipients of kidney-only transplants from 2000 to 2005 found the incidence of PTE among SPKT recipients to be 16%. A study by Reis et al[17] that compared the incidence of PTE among 65 SPKT recipients and 65 same-donor single kidney transplant recipients between January 1, 2005, and December 31, 2019, found that the incidence of PTE among SPKT recipients to be 38.5%. A possible explanation for these differences may be the diagnostic criteria of PTE. While we defined PTE as a hematocrit >51% within 24 mo posttransplant, Guerra et al[13] defined PTE as having a hematocrit >50% or the necessity for phlebotomies within 16.4 mo posttransplant and Reis et al[17] defined PTE as a hematocrit >51% between 6 and 18 mo posttransplant. Additionally, our larger sample size of 887 SPKT recipients compared with 94 SPKT recipients in the study by Guerra et al and 64 SPKT recipients in the study by Reis et al could account for the variability. Other factors to consider include characteristics of the study populations, transplant protocols, and PTE management of each study center.

Recognized risk factors of PTE include male gender, retention of native kidney erythropoietin production, renal artery stenosis, and preserved GFR.[1,3,5,7,10-13,18-21] Smoking history, pretransplant dialysis, and diabetes are associated with PTE in some studies.[1,12,21,22] Our study reaffirms male gender as a risk factor for the development of PTE. Additionally, our analysis supports previous findings that SPKT recipients with a history of pretransplant dialysis are at an increased risk of developing PTE.

Interestingly, our study challenges previous notions regarding the impact of recipient or donor age on PTE development. Although earlier studies suggested a correlation between younger age and increased PTE risk, our analysis revealed no significant effect of age. It is worth noting that prior investigations

emphasizing the role of age as a risk factor for PTE development primarily focused on kidney transplantation.[2,3] In contrast, our study focuses on SPKT, which typically involves younger donors resulting in better renal function.[13,16] This contextual difference may contribute to the outcome we observed. Moreover, we found that recipients with non-White donors were at a higher risk of developing PTE and recipients with older donors were at lower risk. Several studies have reported no such correlation, and our study is the only one connecting non-White or female donors to the development of PTE.[1,2,13] Further research is needed to fully understand the role of donor characteristics including race and gender in PTE occurrence.

Recent research indicates a reassuring trend: PTE does not negatively affect kidney graft survival among kidney transplant recipients.[2,11,20] Our analysis extends this trend to SPKT recipients showing no association between PTE and pancreas or kidney graft failure. However, we found that SPKT recipients who were non-White were over twice as likely to experience kidney graft failure. Other studies comparing graft outcomes between White and non-White or African American SPKT recipients demonstrated similar disparities.[15,23]

Numerous studies highlight the multifactorial nature of PTE and propose mechanisms involving hormonal systems and growth factors. These include erythropoietin overproduction, renin–angiotensin system activation, endogenous androgen excess, and insulin-like growth factor-1.[10,19,24-30] A potential contributor of PTE development within the context of SPKT is hyperinsulinemia, which has been associated with erythrocytosis. Notably, systemic venous drainage in SPKT as used in our study has been reported to result in relative hyperinsulinemia compared with portal venous drainage.[24,31] Sawada et al[32] conducted a bench study revealing that physiological levels of insulin and insulin-like growth factor-1 can directly stimulate erythropoiesis in the presence of erythropoietin. Future studies are warranted to explore the hormonal systems and growth factors associated with PTE to provide deeper insights into the mechanisms underlying its development and identify targeted interventions for improved patient outcomes.

Our study has several limitations. As an observational study, we could not establish a clear cause-and-effect relationship. We did not investigate potential pathophysiological variables of PTE, such as erythropoietin, endogenous androgen, insulin-like growth factor 1, or insulin levels. Furthermore, as a single-center study, our findings likely have limited generalizability because of our specific population and clinical approach. However, our analysis benefits from both its substantial population size of 887 SPKT recipients and its duration spanning from January 1998 to December 2021. Notably, it is one of the few studies to specifically examine PTE within the context of SPKT recipients.

In conclusion, our study has provided valuable insights into the incidence, risk factors, and outcomes of PTE among SPKT recipients within the modern era of immunosuppression. PTE continues to be a common complication among SPKT recipients. Likely due to proper management, PTE among SPKT recipients was not associated with adverse graft outcomes. There is still much to unravel in terms of its underlying pathophysiology. Future investigations should be directed toward shedding light on these intricate mechanisms, as understanding them can pave the way for more effective therapeutic approaches and refine management strategies for PTE.

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