Title
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CHAPTER 5

Kidney Failure Requiring Kidney Transplantation after Pancreas Transplant Alone

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INTRODUCTION

Pancreas transplant alone (PTA) is usually reserved for uncontrolled metabolic complications in type 1 diabetic patients with relatively preserved renal function (1-5). One of the major concerns about PTA is the development of renal failure following transplantation (6-10). Multiple factors affecting post-transplantation kidney failure include: kidney function at the time of transplantation, presence of co-morbid conditions (particularly diabetes, hypertension, and hepatitis C virus infection), older age, type of organ transplanted, and surgical issues. Specific immunosuppressive regimens, especially calcineurin inhibitor (CNI) therapy, have also been implicated as a principal cause of post-PTA kidney failure (11-14). The histopathologic characteristics of CNI nephrotoxicity include vascular obliteration, focal hyalinosis of small renal arteries and arterioles, global or segmental glomerulosclerosis, tubular atrophy, and striped interstitial fibrosis (15, 16). The overall incidence of chronic kidney disease (CKD) and kidney transplant in non-renal solid organ transplantation varies from 7 to 21 percent with 36 months of follow-up (17). There is limited data on kidney failure after PTA in type 1 diabetic patients. We conducted a cohort study of PTA recipients in the United States to examine the cumulative incidence and risk factors for kidney failure requiring kidney transplantation (KF/KT) after PTA.

METHODS

Source of data and study population

A retrospective cohort study was conducted using the Organ Procurement Transplant Network/ United Network for Organ Sharing (OPTN/UNOS) registry. The study population included all recipients 18 years or older who received PTA as a first transplant between years 1987 and 2011. We included recipients who had a baseline estimated glomerular filtration rate (eGFR) at the time of first PTA ≥60 mL/min/1.73m^2. We used pre-transplant serum creatinine levels in order to calculate eGFR by the Modification of Diet in Renal Disease equation (18). Sixty-seven recipients (4.2%) among the initial population who did not have serum creatinine levels for calculating eGFR were excluded. We excluded patients with kidney, multi-organ transplant, pancreas after kidney, simultaneous pancreas kidney (SPK) transplant, or islet cell transplants preceding the first PTA. Recipients who received pretransplant dialysis, either via an affirmative answer with regard to pretransplant dialysis or record of dialysis date, as well as those with unknown pretransplant status were excluded. Patients who were listed for kidney transplant or SPK prior to first PTA were excluded. The final population in the analysis included 1085 adult patients who met the eGFR criteria and received a first PTA during the study period.

Statistical analysis

The study end point was the cumulative incidence of KF/KT [defined as wait-listing for or receiving a kidney alone (KA) or SPK transplant], which was calculated using Nelson-Aalen estimation. Recipients' baseline characteristics were described using mean with standard deviation (SD), median with inter-quartile ranges or frequencies where appropriate. Continuous variables were compared using Kruskall-Wallis test. The chi-square test was used to compare categorical variables. Univariate and multivariate Cox regression models were used to analyze the relation between variables and KF/KT after PTA. Covariates included age, sex, race, body mass index (BMI), eGFR, hypertension, induction therapy, maintenance immunosuppressive drug, and year of first PTA. The results were presented as hazard ratios (HR) with 95% confidence interval (CI) and associated p-values. All p-values were two tailed and p-values less than 0.05 were considered statistically significant. STATA (StataCorp, College Station, TX) software version 10 was used for all statistic analyses.

RESULTS

Patients

One thousand eight hundred ninety-two PTA recipients in the United States from 1987 to 2011 were included. After excluding those with previous transplantation and history of dialysis, there were 1621 adult first PTA recipients. Serum creatinine level at the time of first PTA was available in 1519 recipients. Among these, 1085 adult first PTA patients met the eGFR criteria (≥60 mL/min/1.73m^2). Of these, 965 recipients had a functioning kidney with a median follow-up time of 1185 days (105 subsequently died). Ten years post PTA transplant, 120 (11.1%) recipients developed KF/KT after PTA (defined as wait-listing for, or receiving a KA or SPK transplant. There were 108 (10%) recipients who were listed for KA/SPK after their first PTAs (58 recipients subsequently received KA/SPK transplants, while 50 recipients did not receive kidney transplants after being listed). Twelve recipients received a KA transplant without being listed. Seventy PTA recipients received either a KA or SPK transplant (KA=56 recipients; SPK=14 recipients) and 50 recipients were waitlisted but did not receive a KA/SPK (Fig. 1).

Baseline characteristics

The baseline characteristics of first PTA recipients are described in Table 1. The average age at the time of first PTA was 40 years old. More than 90% of recipients were white. The mean eGFR (±SD) at the time of first PTA was 99±34 mL/min/1.73m^2. The mean BMI was 24.9 kg/m^2. The proportion of PTA recipients with drug-treated hypertension prior to transplantation was 18.3%. Most PTA recipients received antibody induction therapy (74.1% of patients) and were maintained on CNI for maintenance immunosuppression (90.4%). PTA recipients with KF/KT were significantly younger and had a lower BMI and eGFR compared to those without KF/KT. There were fewer males and a lower percentage of recipients receiving tacrolimus and Thymoglobulin in the KF/KT group compared to those not developing kidney failure.

Cumulative incidences of kidney failure requiring kidney transplantation after pancreas transplant alone

The median duration of follow-up from the time of first PTA was 1185 days (25 and 75%: 524 and 2183). At 1, 2, 3, 4, and 5 years after PTA, the cumulative incidence of KF/KT was 0.3, 1.2, 2.5, 5.6, and 9.7%, respectively (Table 2). The five-year cumulative incidence of being listed for KA/SPK transplant after PTA was 8.6% and of receiving KA/SPK after PTA was 5.2%.

Risk factors associated with kidney failure requiring kidney transplantation after pancreas transplant alone

A multivariate Cox regression analysis was performed to adjust for a number of factors associated with KF/KT after PTA. These factors

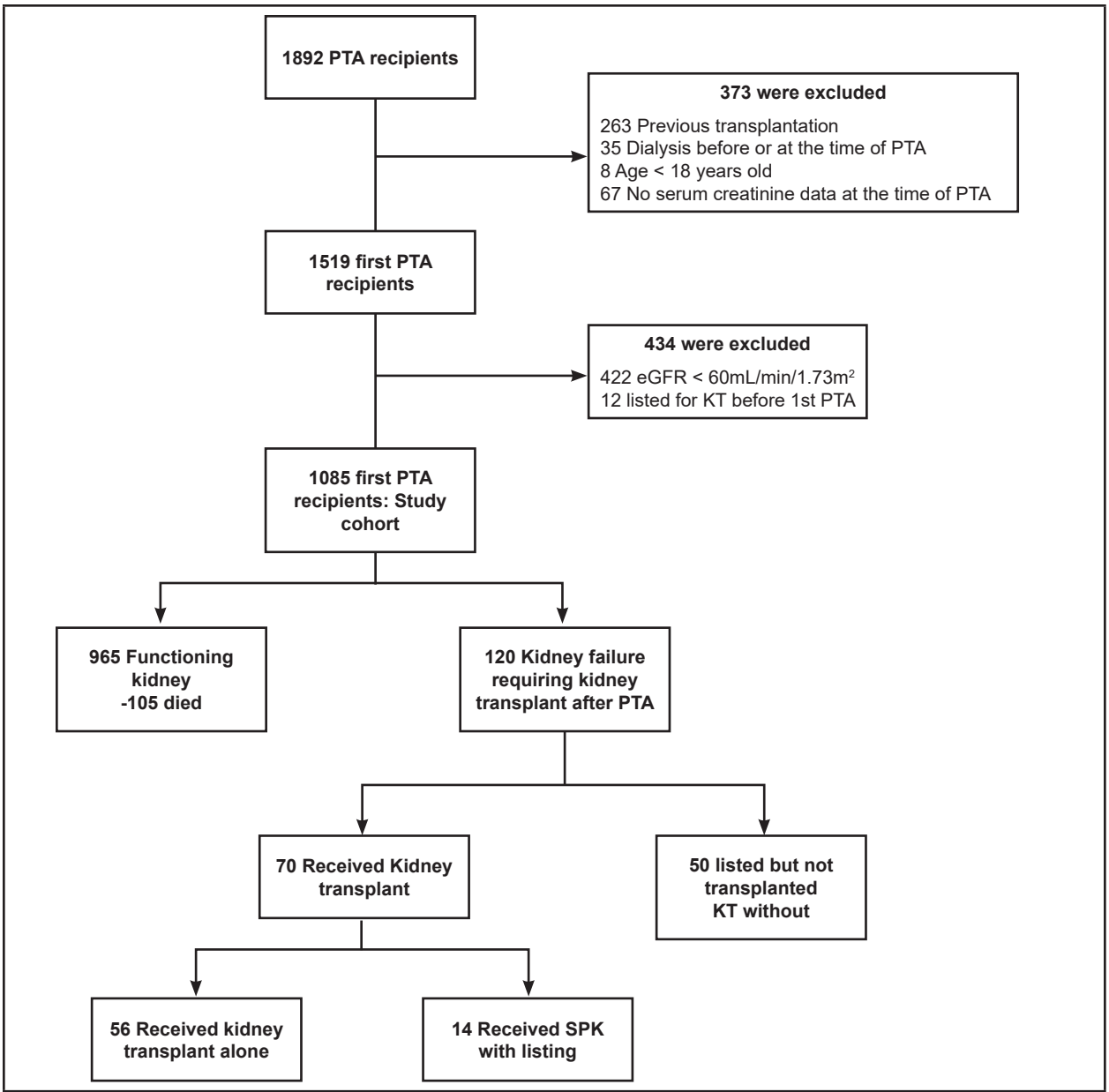

Figure 1. Enrollment and outcomes. One thousand eighty-five of first pancreas transplant alone (PTA) were analyzed. Of these, 965 had functioning kidneys (105 died) and 120 recipients had kidney failure requiring kidney transplantation (KF/KT), (70 subsequently received kidney alone (KA) or simultaneous pancreas kidney (SPK) transplant after PTA and 50 were listed without receiving transplant). Among recipients who received transplant after SPK; 56 received KA and 14 received SPK.

included recipients' age, sex, race, BMI, eGFR, the presence or absence of pre-PTA hypertension, CNI for maintenance immunosuppressive drug, and induction therapy (Table 3). Lower eGFR (60-89 mL/min/1.73m^2 versus >90 mL/min/1.73m^2) was associated with increased risk of KF/KT after PTA (adjusted HR): 1.94; 95% CI: 1.26-2.98; p<0.05). The risk of developing KF/KT was higher in those recipients who were younger than 40 years (adjusted HR: 1.65, 95% CI: 1.06-2.57; p<0.05) compared to those older than 40 years. Compared to those receiving no induction therapy, Thymoglobulin induction was associated with an increased risk of KF/KT after PTA [adjusted HR: 1.96 (95% CI: 1.04-3.69); p<0.05] (Table 3).

Table 1. Baseline characteristics.

	First PTA recipients (n=1,085)	No KF/KT after PTA (n=965)	KF/KT after PTA (n=120)	p-value
Age (years±SD)	40±10	40±10	36±8[a]	0.005
Male, n (%)	373 (34.4%)	346 (35.9)	27 (22.5)[a]	0.004
Race, n (%)				
White	1038 (95.7)	922 (95.5)	116 (96.7)	0.57
Black	23 (2.1)	22 (2.3)	1 (0.8)	0.30
Hispanic	17 (1.6)	15 (1.6)	2 (1.7)	0.93
Other	7 (0.6)	6 (0.6)	1 (0.8)	0.79
BMI (mean±SD)	24.9±4.5	25.0±4.5	24.3±4.4[a]	0.02
eGFR (mL/min/1.73m^2), n(%)				
≥90 mL/min/1.73m^2	535 (49.3)	491 (50.9)	44 (36.7)[a]	0.003
60-89 mL/min/1.73m^2	550 (50.7)	474 (49.1)	76 (63.3)[a]	0.003
Mean eGFR (mean±SD, mL/min/1.73m^2)	98.7±34.4	99.9±35.0	89.2±27.5[a]	<0.001
Serum creatinine (mean±SD; mg/dl)	0.85±0.19	0.84±0.19	0.94±0.21[a]	<0.001
Hypertension, n (%)	199 (18.3)	175 (18.1)	24 (20)	0.62
Maintenance immunosuppression, n (%)				
Tacrolimus	846 (78.0)	763 (79.1)	83(69.2)[a]	0.01
Cyclosporine	135 (12.4)	106 (11.0)	29(24.2)[a]	<0.001
Mycophenolic acid	694 (64.0)	622 (64.5)	72 (60.0)	0.34
Azathioprine	124(11.4)	101 (10.5)	23 (19.2)[a]	0.005
Sirolimus	69 (6.4)	60 (6.2)	9 (7.5)	0.59
Corticosteroid	887(81.8)	790 (81.9)	97 (80.8)	0.78
Antibody induction therapy, n (%)				
None	256 (23.6)	222 (23.0)	34 (28.3)	0.20
Antithymocyte globulin	377 (34.7)	342 (35.4)	35 (29.2)	0.17
IL-2RA	83 (7.7)	74 (7.7)	9 (7.5)	0.95
Alemtuzumab	104 (9.6)	95 (9.8)	9 (7.5)	0.41
Multiple/OKT3/ALG	240 (22.1)	208 (21.6)	32 (26.7)	0.20
Missing	25 (2.3)	24 (2.5)	1 (0.8)	0.26
Year of first PTA, n (%)				
1987-2000	295 (27.2)	223 (23.1)	72 (60.0)[a]	<0.001
2001-2005	432 (39.8)	391 (40.5)	41 (34.2)	0.18
2006-2011	358 (33.0)	351 (36.4)	7 (5.8)[a]	<0.001

[a] Statistically significant difference between kidney failure and no kidney failure requiring kidney transplant after PTA group. ALG – anti lymphocyte globulin; BMI – body mass index; eGFR – estimated glomerular filtration rate; KF/KT – kidney failure requiring kidney transplantation; PTA – pancreas transplant alone; RA – receptor antibody; SD – standard deviation.

Table 2. Cumulative incidences of KF/KT, listed for KA/SPK or receiving KA/SPK after PTA.

Outcome	Cumulative incidence (Percentage ± SD)				
	1 year	2 years	3 years	4 years	5 years
KF/KT after PTA	0.3±0.2	1.2±0.4	2.5±0.6	5.6±0.9	9.7±1.3
Listed for KA/SPK after PTA	0.3±0.2	0.9±0.3	1.9±0.5	4.8±0.8	8.6±1.2
Received KA/SPK after PTA	0.2±0.1	0.6±0.3	1.3±0.4	2.7±0.6	5.2±1.0

KA – kidney alone; KF/KT – kidney failure requiring kidney transplantation (defined by wait-listing for or receiving a KA or SPK); PTA – pancreas transplant alone; SD – standard deviation; SPK – simultaneous pancreas kidney.

DISCUSSION

The majority of first PTA recipients in the United States transplanted from 1987 to 2011 have preserved renal function before transplant. In our study, 71% of recipients for whom a pre-transplant creatinine was available had a baseline eGFR >60 mL/min/1.73m^2. Among these patients, KF/KT at 5 years post-PTA was fairly common, occurring in 9.7% of patients. Those with a lower baseline eGFR at study entry (60-89 mL/min/1.73m^2) were at greater risk for KF/KT compared to those with higher eGFR (14% versus 8% among recipients with eGFR ≥ 90 mL/min/1.73m^2).

Prior reports have described the association of kidney failure with PTA, but the incidence of kidney failure may have been inflated due to the inclusion of recipients with advanced pre-transplant kidney disease. In one of the largest series of PTA recipients, 15% of PTA recipients developed kidney failure at 5 years. One of the strongest risk factors for kidney failure was a pre-transplant serum creatinine ≥1.5 mg/dl (HR: 12.55 versus <1.5 mg/dl; 95% CI: 5.75-27.4, p<0.0001) (9). Smail et al. reported that the cumulative incidence of end-stage renal disease (ESRD) in 43 PTA recipients was 22.4%. Of the recipients who had a baseline eGFR <60 mL/min/1.73 m^2 (21% of the study population), the cumulative incidence of ESRD was 61.9% at 5 years after transplant (19). Scalea et al. reported in a single-center retrospective study that 32.1% of PTA recipients developed renal dysfunction (reduction in eGFR of ≥40 mL/min/1.73m^2) and that 9.9% required a kidney transplant (8).

The strength of our study is its description of kidney outcomes in what is to our knowledge the largest set of PTA recipients to date. In the United States, all kidney transplant recipients must be registered through UNOS, and therefore, we believe we have comprehensively captured all PTA recipients who have subsequently required and received a kidney transplant. Our study has reported a rate of KF/KT after PTA of 9.7% at 5 years. Although our study has reported a fairly high rate of ESRD following PTA, we believe that the actual incidence of kidney failure following PTA could be even higher than what we have reported in this study. First, this study only included recipients with a pre-transplant eGFR ≥60 mL/min/1.73m^2 and the incidence of KF/KT of all PTA recipients would likely be higher if we had included recipients with a pre-transplant eGFR <60 mL/min/1.73m^2. Second, our observed incidence of kidney failure underestimates the true rate of ESRD, as we did not have information on those who developed

Table 3. Risk factors associated with KF/KT after PTA.

		KF/KT after PTA	
Covariates	Reference	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Age <40 (years)	≥40	1.77 (1.17-2.68)	1.65 (1.06-2.57)
Male	Female	0.47 (0.29-0.77)	0.44 (0.27-0.74)
Race	White		
Black		0.96 (0.13-6.95)	0.80 (0.11-5.86)
Hispanic		1.71 (0.42-6.96)	1.59 (0.38-6.64)
Other		2.06 (0.28-14.8)	2.65 (0.36-19.4)
BMI	<25		
25-29.9		0.57 (0.37-0.91)	0.73 (0.46-1.19)
≥30		0.51 (0.23-1.11)	o.59 (0.27-1.31)
eGFR at 1st PTA			
60-89 mL/min/1.73m^2	≥90	1.57 (1.05-2.34)	1.94 (1.26-2.98)
Hypertension	No	1.04 (0.66-1.64)	1.28 (0.78-2.09)
Cyclosporine	No CNI	1.18 (0.71-1.95)	0.82 (0.44-1.54)
Tacrolimus	No CNI	1.22 (0.49-3.02)	1.43 (0.56-3.65)
Sirolimus	No Sirolimus	1.51 (0.76-2.99)	1.63 (0.77-3.45)
Induction therapy	No induction		
Thymoglobulin		1.50 (0.89-2.52)	1.96 (1.04-3.69)
IL-2RA		0.77 (0.32-1.86)	1.04 (0.41-2.68)
Alemtuzumab		1.26 (0.58-2.70)	1.55 (0.62-3.90)
Multiple/OKT3/ALG		0.96 (0.56-1.63)	1.06 (0.58-1.94)

[a] Hazard ratios were calculated with multivariate Cox proportion regression models. Adjusted HRs were controlled for all variables listed in the table. ALG - anti lymphocyte globulin; BMI – body mass index; CI – confidence interval; CNI – calcineurin inhibitor; eGFR – estimated glomerular filtration rate; HR – hazard ratio; KF/KT – kidney failure requiring kidney transplantation; PTA – pancreas transplant alone; RA – receptor antibody.

kidney failure but were not registered for kidney transplantation.

There may be various reasons as to why PTA recipients are at greater risk for kidney failure than the general type 1 diabetic population. First, PTA recipients might be suffering from more advanced or poorly controlled diabetes than non-pancreas transplant patients. We were unable to assess this possibility as UNOS does not collect information on pre-transplant diabetic co-morbidities, microalbuminuria or proteinuria, and hemoglobin A1C levels. Second, it is likely that chronic exposure to CNIs may place non-renal solid organ transplant recipients at greater risk for kidney disease. Histological changes associated with chronic CNI nephrotoxicity have been well-described and include arteriolar hyalinosis, glomerulosclerosis, and interstitial fibrosis and tubular atrophy (15). In a cohort of heart, lung, liver, and intestinal transplant recipients from the Scientific Registry of Transplant Recipients, most of whom were maintained on a CNI, the cumulative incidence of chronic renal failure, defined as eGFR $\leq$ 29 mL/min/1.73 m^2, was 17% and ESRD occurred at a rate of 1.0-1.5% per year among recipients of a non-renal solid organ transplant (17).

Independent risk factors associated with KF/KT in our study included age >40 years, female gender, and Thymoglobulin induction. Lower calculated eGFR at the time of first PTA (60-89 mL/min/1.73 m^2) was the strongest risk factor for KF/KT after PTA (HR: 1.94; 95% CI: 1.26-2.98).

Potential PTA candidates should be cautioned about the risks of subsequent kidney failure. However, this is not to necessarily say that PTA should be avoided altogether, as the decision on whether to proceed with PTA is complex and the potential benefit of a functioning pancreas allograft should be weighed against the risks of complications. In type 1 diabetic patients with life-threatening hypoglycemic unawareness, PTA or islet transplant may be the only viable option. Nevertheless, when mortality following PTA was previously compared to that of waitlisted PTA candidates, there was an increased risk of death associated with PTA (20). In light of these risks, one should consider whether there is any clear benefit to PTA before recommending it for a prospective type 1 diabetic candidate. Our recommendation is that all type 1 diabetic candidates for PTA should be carefully evaluated for kidney function before and after transplant and counseled about the risk of developing KF/KT after PTA.

Our study has several limitations. First, we did not have post-PTA creatinine values on the majority of our patients, as UNOS did not collect the data on serum creatinine level during the follow-up until 2007 and there was limited data on serum creatinine after 2008. Therefore, the effect of PTA on the development of CKD could not be assessed. Second, we did not have data on returning to dialysis after PTA, and our observed incidence of ESRD is likely underestimated. Last, as our study only included first PTA recipients who had eGFR $\geq$ 60 mL/min/1.73m^2, our results are not applicable to patients with eGFR <60 mL/min/1.73m^2 or repeat transplant recipients.

In conclusion, the majority of PTA recipients had preserved renal function at the time of transplant. Despite this, KF/KT at five years post-PTA was relatively common, occurring in 9.7% of first PTA recipients in our study. This data suggests that there is a considerable risk of KF/KT after PTA and patients who are being recommended for PTA should be aware of this risk.

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SUMMARY

Pancreas transplant alone (PTA) is usually performed in type 1 diabetic patients with preserved renal function to correct severe metabolic complications. One of the major concerns is renal failure after PTA. Here, we reported the cumulative incidence of kidney failure requiring kidney transplantation (KF/KT) among PTA recipients in the United States. Using the Organ Procurement Transplant Network/ United Network for Organ Sharing database, all primary adult PTA recipients with estimated baseline glomerular filtration rate (by the Modification of Diet in Renal Disease equation) $\geq$60 mL/min/1.73m^2 were selected (n=1085). KF/KT after PTA was defined as: wait-listing for or receiving a kidney alone (KA) or simultaneous pancreas kidney (SPK) transplant. The median follow-up time was 1185 days (25-75%: 524-2183). Ten years post PTA, 120 (11.1%) patients developed KF/KT; of those, 70 (6.5%) subsequently received a KA/SPK transplant (56 received KA and 14 received SPK) and 50 (4.6%) recipients were listed without receiving a transplant. The cumulative incidence of KF/KT after PTA at 1, 3, and 5 years after PTA was 0.3, 2.5, and 9.7%, respectively. In conclusion, KF/KT after PTA was not uncommon (9.7% at 5 years), and prospective PTA recipients should be aware of the risks of kidney failure after transplantation.

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