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The time interval between kidney and pancreas transplantation and the clinical outcomes of pancreas after kidney transplantation

Luan FL, Kommareddi M, Cibrik DM, Samaniego M, Ojo AO. The time interval between kidney and pancreas transplantation and the clinical outcomes of pancreas after kidney transplantation.

Abstract: Pancreas after kidney (PAK) transplantation is one of the accepted pancreas transplant modalities. We studied the impact of time interval between kidney and pancreas transplantation on the outcomes of PAK transplantation. Using OPTN/SRTR data, we included 1853 PAK transplants performed between 1996 and 2005 with follow-up until November 1, 2008. Kaplan–Meier survival and multivariate Cox regression analyses were performed using the time interval between kidney and pancreas transplantation either as a categorical (less than one yr, between one and less than three yr, and greater than or equal to three yr) or as a continuous variable (months) to assess kidney graft and patient survival. Patients who received a pancreas transplant three yr or later after kidney transplantation had higher risk of death-censored kidney graft loss (HR 1.56, 95% CI 1.04, 2.32, p = 0.03). Each month beyond three yr between kidney and pancreas transplantation incurred 1% higher risk of subsequent death-censored kidney graft loss (HR 1.01, 95% CI 1.001, 1.02, p = 0.03). In conclusion, time interval between pancreas and kidney transplantation is an independent risk factor of kidney graft loss following pancreas transplantation. Shortening the time interval between pancreas and kidney transplantation to less than three yr may reduce the risk of kidney graft loss in qualified PAK transplant candidates.

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Key words: death-censored kidney graft failure – pancreas after kidney transplantation – time interval

Abbreviations: aMDRD, abbreviated Modification of Diet in Renal Disease; ANOVA, analysis of variance; ATG, anti-thymocyte globulin; BMI, body mass index; CI, confidence interval; CNIs, calcineurin inhibitors; DCD, donor after cardiac death; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigens; HR, hazard ratio; HRSA, Health Resources and Services Administration; IL2, interleukin 2; IRB, institutional review board; OPTN/SRTR, Organ Procurement and Transplantation Network/ Scientific Registry of Transplant Recipients; PAK, pancreas after kidney; PRA, panel reactive antibodies; SCD, standard criteria donor.

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Pancreas after kidney (PAK) transplantation is one of the accepted pancreas transplant modalities (1, 2). PAK transplantation allows uremic type 1 diabetic patients to receive a life-saving kidney transplant first and then a subsequent pancreas transplant to correct hyperglycemia (3). Historically, PAK transplants have a lower pancreas graft survival rate compared with simultaneous pancreas

and kidney transplants although lately some single-center studies have reported comparable results (3–5). Furthermore, one study has suggested that PAK transplant recipients had inferior patient survival compared with wait-listed PAK candidates treated with conventional insulin therapy (6).

Several investigators over the years have examined the potential risk factors associated with poor PAK outcome, including the timing elapsed between pancreas and kidney transplantation (7, 8). The number of patients included in these studies was limited. One recent study, however, did show that timing of pancreas transplantation has an impact on the clinical outcome as the time interval between kidney and pancreas transplantation longer than one yr was associated with inferior uncensored kidney graft survival post-pancreas transplantation (8).

We hypothesized that the longer time interval between kidney and pancreas transplantation could predispose kidney transplant to the development of chronic injuries, immunologic or not, and thus negatively impact kidney graft and/or patient survival after pancreas transplantation. We undertook a retrospective analysis of national registry data to determine the effect of time interval on pancreas and kidney graft survival and mortality risk among PAK transplant patients.

Materials and methods

We included all adult primary PAK transplants performed between January 1, 1996 and December 31, 2005 in the United States with follow-up until November 1, 2008. Data were collected and provided by the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the OPTN, and has been described elsewhere (9). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. The study was approved by the Institutional Review Board (IRB).

We identified the date of kidney and pancreas transplantation and calculated the time interval elapsed between kidney and pancreas transplantation. This time interval was then utilized either as a categorical variable separating all PAK transplant recipients into three groups (less than one yr, one to less than three yr, and greater than or equal to three yr) or as a continuous variable (months) and incorporated into multivariate analyses separately. As Group 3 included a larger proportion of kidney transplant patients from 1995 or earlier, to account for the possible influence of era in transplant care, we created era 1995 or earlier and era after 1995 as an indicator variable. This era covariate was incorporated into all multivariate analyses. In addition, baseline recipient- and donor-related characteristics were examined and used in multivariate analyses as well. Other important variables considered in the multivariate analyses included the baseline renal allograft function post-kidney transplant and at the time of pancreas transplantation, expressed as estimated glomerular filtration rate (eGFR) and calculated using the abbreviated Modification of Diet in Renal Disease (aMDRD) prediction equation, surgical modality in exocrine pancreas drainage (bladder vs. enteric), the use of various immunosuppressive agents at the time of kidney and pancreas transplantation, induction and maintenance, and center volume of pancreas transplants performed at a given year.

Demographic and baseline characteristics from the time of pancreas transplantation were compared using ANOVA and chi-square test among the three groups of PAK patients. The time at risk of the outcomes of interest, death and death-censored kidney graft loss, started at the time of pancreas transplantation as both outcomes could not happen prior to pancreas transplantation by the nature of study design. Kaplan–Meier survival analyses were carried out for composite event-free survival, for death-censored pancreas and kidney transplants survival, and patient survival. Several sets of multivariate Cox proportional hazards regression models using a backward selection approach were performed to assess the effects of time interval and to identify other independent risk factors on death-censored pancreas and kidney graft loss and death. Analyses were performed using SAS 9.1, (Cary, NC, USA) and statistical significance was set at $p \leq 0.05$.

Results

We identified a total of 1853 PAK transplant recipients during the study period with complete information on the date of both organ transplants and clinical follow-up. The mean and median time between kidney and pancreas transplant was 31.7 ($\pm$35.8) and 17.1 (0.1, 200.7) months, respectively. The mean age was 41.5 ($\pm$7.6) yr. African American patients accounted for 7.3% of PAK patients. The majority of kidney transplants were from a living donor (70.9%). The mean eGFR at the time of pancreas transplant was 60.4 ($\pm$17.8) mL/min.

PAK transplant recipients were separated into three groups according to the time interval between kidney and pancreas transplantation: Group 1 with less than one yr, Group 2 from one to less than three yr, and Group 3 with three or more years between the two transplant events. PAK transplant recipients from the three groups differed in several demographic and baseline characteristics (Table 1). PAK transplant recipients from Group 3 were older (42.9 yr vs. 40.9 and 41.1 yr in Group 1 and 2, respectively, $p < 0.001$) and had shorter duration of diabetes at kidney transplant (24.8 yr vs. 26.2 and 25.0 yr in Group 1 and 2, respectively, $p = 0.002$). They received less often a preemptive kidney transplant (16.3% vs. 32.1% and 26.7% in Group 1 and 2, respectively, $p < 0.001$) and had fewer living donor kidney transplants (60.6% vs. 77.3% and 72.3% in Group 1 and 2, respectively, $p < 0.001$), although the kidney donor age was younger for Group 3 PAK transplant recipients (34.9 yr vs. 40.1 and 38.5 yr in Group 1 and 2, respectively, $p < 0.001$). Bladder drainage of pancreas transplant was more frequently utilized among patients from Group 3 (48.4% vs. 38.3% and 30.4% in Group 1 and 2, respectively, $p < 0.001$). There were also significant differences in immunosuppression regimens at the time of kidney transplantation as PAK transplant recipients from Group 3 often received no induction (71.8% vs. 44.5% and 49.7% in Group 1 and 2, respectively, $p < 0.001$), more frequently used cyclosporine (81.7% vs. 36.1% and 47.2% in Group 1 and 2, respectively, $p < 0.001$) and less frequently mycophenolates (32.2% vs. 73.7% and 73.3% in Group 1 and 2, respectively, $p < 0.001$). However, at the time of pancreas transplantation, the difference in immunosuppression regimens was much less striking (Table 1). While baseline renal function post-kidney transplant was comparable, the renal function at the time of pancreas transplantation was significantly lower for PAK transplant recipients in Group 3 (57.2 vs. 61.4 and 61.6 mL/min in Group 1 and 2, respectively, $p < 0.001$).

Following pancreas transplantation, PAK transplant recipients from Group 3 displayed overall inferior clinical outcome (Fig. 1A, log-rank $p = 0.01$). This was mainly related to reduced death-censored kidney graft survival as well as patient survival (Fig. 1B and C, log-rank $p < 0.0001$ and $p < 0.001$, respectively). Pancreas allograft survival, early (within 90 d) and during subsequent years, was not different between the three groups (data not shown). Multivariate Cox proportional hazards regression analyses demonstrated that the time interval equal to or greater than three yr between kidney and pancreas transplantation was independently and significantly associated with increased risk of death-censored kidney graft loss (HR 1.56, 95% CI 1.04, 2.32, $p = 0.03$ with era as a covariate) (Table 2). This was further confirmed in an alternate analysis using the time interval between kidney and pancreas transplantation as a continuous variable. Each month beyond three yr between kidney and pancreas transplantation incurred 1% increase in the risk of kidney graft loss (HR 1.01, 95% CI 1.001, 1.02, $p = 0.03$). As an alternative analytic approach, we performed a different set of multivariate Cox proportional hazards regression analyses using pancreas transplantation as a time-dependent covariate and with starting point at the time of kidney transplantation, and we found an even greater increase in the risk associated with longer time interval (HR 1.66, 95% CI 1.18, 2.35, $p = 0.004$ for time interval between one and less than three yr and HR 2.27, 95% CI 1.54, 3.33, $p < 0.001$ for time interval greater than or equal to three yr, respectively) although we felt that a greater bias was created because of inclusion of all patients prior to pancreas transplantation in the reference group as they were not at risk for the study outcomes (death and kidney graft loss) until after their pancreas transplantation. Other factors contributing to the risk of kidney graft loss following pancreas transplantation included older kidney donor age (HR 1.01, 95% CI 1.003, 1.03, $p = 0.011$), the use of kidneys from expanded criteria donor (ECD) and/or donor after cardiac death (DCD) (HR 2.38, 95% CI 1.63, 3.48, $p < 0.001$), and the use of alemtuzumab as an induction agent at the time of kidney transplantation (HR 3.11, 95% CI 1.24, 7.76, $p = 0.015$). On the other hand, older recipient age and higher renal function at the time of pancreas transplantation were associated with reduced risk of subsequent kidney graft loss (Table 2). The duration of diabetes exposure up to the time of kidney transplantation did not appear to negatively impact kidney graft survival post-pancreas transplantation. Furthermore, the time interval between kidney and pancreas transplantation did not appear to be associated with increased risk of death when the era effect was incorporated into the model (Table 3). Other factors that negatively affected patient survival included older recipient age at the time of pancreas transplantation (HR 1.03, 95% CI 1.01, 1.06, $p = 0.002$), previous dialysis history (HR 1.74, 95% CI 1.30, 2.33, $p < 0.001$), history of peripheral vascular disease (HR 1.58, 95% CI 1.17, 2.79, $p = 0.003$), history of coronary artery disease (HR 1.51, 95% CI 1.16, 1.97, $p = 0.002$), and African American kidney donor (HR 1.95,

Table 1. Demographic and baseline characteristics of study patient population

	Group 1	Group 2	Group 3	
	N = 726	N = 592	N = 535	p
Age, yr (SD)	40.9 (7.9)	41.1 (7.8)	42.9 (6.9)	<0.001
Gender: male (%)	416 (57.3)	354 (59.8)	308 (57.6)	0.622
Race: African American (%)	45 (6.2)	52 (8.8)	38 (7.1)	0.196
BMI, kg/m^2 (SD)	24.9 (4.1)	25.5 (4.2)	25.1 (4.2)	0.017
Duration of diabetes at kidney transplant, yr (SD)	26.2 (7.9)	25.0 (7.9)	24.8 (6.5)	0.002
Dialysis history, yes (%)	493 (67.9)	434 (73.3)	448 (83.7)	<0.001
Angina/coronary artery disease, yes (%)	129 (17.8)	103 (17.4)	81 (15.1)	0.433
History of blood transfusion, yes (%)	301 (41.5)	267 (45.1)	282 (52.7)	<0.001
Peripheral vascular disease, yes (%)	60 (8.2)	66 (11.2)	65 (12.2)	0.058
Cerebrovascular disease, yes (%)	19 (2.6)	20 (3.4)	14 (2.6)	0.657
History of hypertension, yes (%)	574 (79.1)	465 (78.6)	379 (70.8)	0.001
Kidney donor type (%)				
Living	561 (77.3)	428 (72.3)	324 (60.6)	<0.001
SCD	142 (19.6)	136 (23.0)	139 (26.0)	
ECD or DCD	23 (3.2)	28 (4.7)	72 (13.5)	
Kidney donor age, yr (SD)	40.1 (12.5)	38.5 (12.6)	34.9 (13.5)	<0.001
Pancreas donor age, yr (SD)	26.8 (10.9)	26.0 (10.4)	26.1 (11.1)	0.380
Kidney donor race: African American (%)	38 (5.2)	35 (5.9)	25 (4.7)	0.648
Kidney donor gender: male (%)	274 (46.3)	326 (44.9)	270 (50.5)	0.137
Era of kidney transplant: 1995 or earlier (%)	18 (2.5)	45 (7.6)	305 (57.0)	<0.001
eGFR 6 months post-kidney transplant, mL/min (SD)	58.8 (19.0)	60.0 (17.9)	59.4 (17.5)	0.553
eGFR at pancreas transplantation, mL/min (SD)	61.4 (17.6)	61.6 (17.6)	57.2 (18.2)	<0.001
HLA mismatches at kidney transplantation (SD)	2.78 (1.81)	2.66 (1.85)	2.42 (1.80)	0.003
HLA mismatches at pancreas transplantation (SD)	3.8 (1.4)	4.0 (1.3)	3.9 (1.5)	0.100
Peak PRA at pancreas transplantation (SD)	7.5 (18.0)	9.7 (21.2)	11.9 (23.0)	0.001
Bladder drainage of pancreas, yes (%)	278 (38.3)	180 (30.4)	359 (48.4)	<0.001
CNIs at kidney transplantation (%)				
None	38 (5.2)	30 (5.1)	14 (2.6)	<0.001
Cyclosporine	262 (36.1)	279 (47.2)	437 (81.7)	
Tacrolimus	426 (58.7)	283 (47.8)	84 (15.7)	
Anti-metabolites at kidney transplantation (%)				
None	57 (7.9)	43 (7.3)	54 (10.1)	<0.001
Mycophenolates	535 (73.7)	434 (73.3)	172 (32.2)	
Sirolimus/everolimus	70 (9.6)	42 (7.1)	22 (4.1)	
Imuran and others	64 (8.8)	73 (12.3)	287 (53.6)	
Steroids at kidney transplantation, yes (%)	678 (93.4)	577 (97.5)	528 (98.7)	<0.001
Induction at kidney transplantation (%)				
None	323 (44.5)	294 (49.7)	384 (71.8)	<0.001
ATG/Thymoglobulin	228 (31.4)	129 (21.8)	95 (17.8)	
Anti-IL2 receptor antibodies	151 (20.8)	161 (27.2)	56 (10.5)	
Alemtuzumab	24 (3.3)	8 (1.4)	0 (0)	
CNIs at pancreas transplantation (%)				
None	64 (8.8)	60 (10.1)	40 (7.5)	0.046
Cyclosporine	75 (10.3)	89 (15.0)	70 (13.1)	
Tacrolimus	587 (80.9)	443 (74.8)	425 (79.4)	
Anti-metabolites at pancreas transplantation (%)				
None	83 (11.4)	58 (9.8)	49 (9.2)	0.437
Mycophenolates	566 (78.0)	473 (79.9)	413 (77.2)	
Sirolimus/everolimus	65 (9.0)	49 (8.3)	59 (11.0)	
Imuran/others	12 (1.7)	12 (2.0)	14 (2.6)	
Steroids at pancreas transplantation, yes (%)	674 (92.8)	562 (94.9)	506 (94.6)	0.226
Induction at pancreas transplantation (%)				
None	193 (26.6)	152 (25.7)	134 (25.1)	<0.001
ATG/thymoglobulin	382 (52.6)	298 (50.4)	277 (51.7)	
Anti-IL2 receptor antibodies	83 (11.4)	104 (17.6)	100 (18.7)	
Alemtuzumab	68 (9.4)	38 (6.4)	24 (4.5)	

BMI, body mass index; HLA, human leukocyte antigens; PRA, panel reactive antibodies; SCD, standard criteria donor; ECD, expanded criteria donor; DCD, donor after cardiac death; eGFR, estimated glomerular filtration rate; ATG, anti-thymocyte globulin.

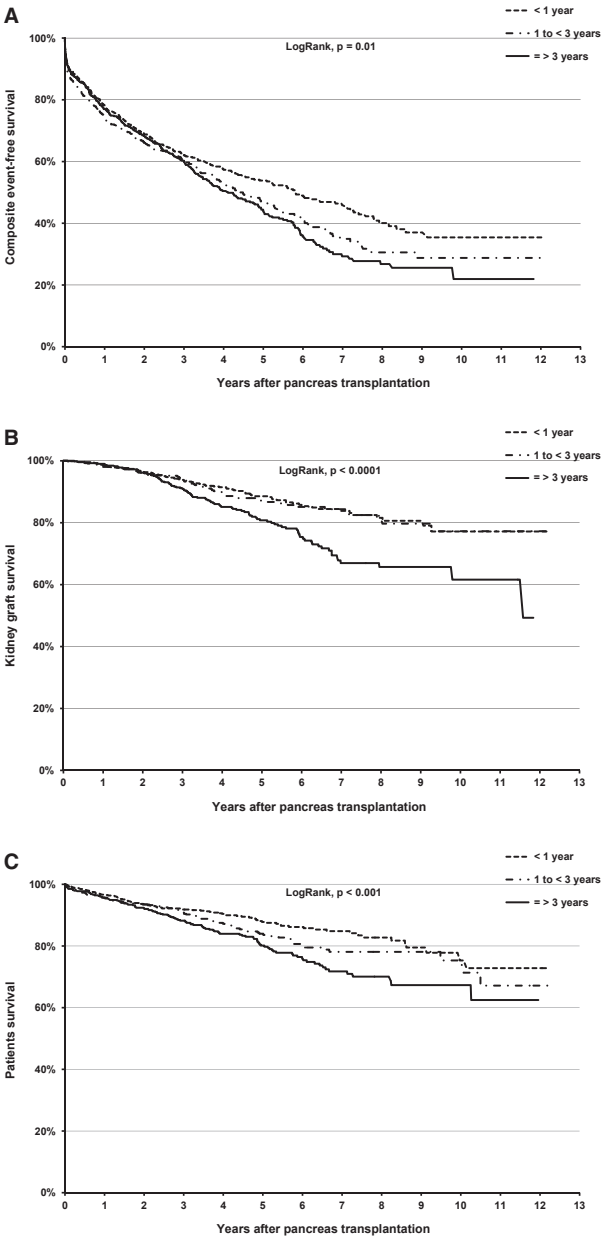

Fig. 1. Kaplan–Meier survival analyses among three groups of pancreas after kidney transplant patients: (A) composite event-free survival, (B) death-censored kidney graft survival and (C) patient survival.

95% CI 1.29, 2.94, p = 0.001). Higher body mass index and renal function at the time of pancreas transplantation were associated with lower risk of death (HR 0.95, 95% CI 0.93, 0.98, p = 0.001 and HR 0.99, 95% CI 0.98, 0.994, p < 0.001, respectively).

Although the changing in renal function over the time, expressed as the slop, was not significantly different among the three groups (0.24 ± 4.42, 0.18 ± 1.70, and −0.03 ± 0.39 for patients from Groups 1, 2, and 3, respectively, p = 0.25), eGFR at the time of pancreas transplantation was significantly lower for PAK patients from Group 3 and was independently associated with post-pancreas transplant outcomes. We further investigated the impact of actual eGFR divided according to three tertiles (Table 4). Patients in the highest tertile had eGFR equal to or >65 mL/min, those in the mid-tertile between 50 and <65 mL/min, and those in the lowest tertile <50 mL/min. Using patients in the highest tertile as a reference group, patients with eGFR in the mid- and lower tertiles had 27% and 93% higher risk of death-censored kidney graft loss (p = 0.19 and p < 0.001, respectively). Similarly, patients with eGFR in the mid- and lower tertiles had 51% and 95% higher risk of death (p = 0.005 and p < 0.001, respectively).

Discussion

This study demonstrates that the time interval between kidney and pancreas transplantation independently impacts the clinical outcome of PAK transplantation, in particular, death-censored kidney graft survival. There appears to be a threshold effect, namely, a time interval equal to or greater than three yr between the two transplant events was associated with a significant increase in the risk of death-censored kidney graft loss that was independent of kidney function at the time of pancreas transplantation. Speculation on possible mechanisms for this negative effect of longer time interval could involve the progressive development of kidney graft injuries with the time, immunologic or not such as subclinical acute rejection, calcineurin inhibitor (CNI) nephrotoxicity, and continued exposure to the diabetic environment, etc. (10–14). On the other hand, the time interval did not appear to negatively impact patient survival following pancreas transplant when the effect of era in which kidney transplantation was performed was taken into consideration. In addition, renal function at the time of pancreas transplantation played an important role in determining the clinical outcome of post-pancreas transplantation. These findings should help the transplant community to provide appropriate counseling for qualified type 1 diabetic kidney transplant patients in pursue of pancreas transplantation.

PAK transplantation is one of the pancreas transplant modalities endorsed by the American Diabetes Association for qualified patients with diabetic end-stage renal disease (ESRD) who had a successful kidney transplant (2). As the life-saving property of a kidney transplant has been firmly established (15), the major advantage of PAK transplantation is to allow patients with type 1

Table 2. Clinical correlates of kidney graft loss following pancreas transplantation

	Variables	Hazard ratio	95% CI	p
Model 1[a]	Years between transplantations			0.07
	<1 yr	Ref.	Ref.	Ref.
	1 to <3 yr	1.07	0.76, 1.49	0.71
	≥3 yr	1.56	1.04, 2.32	0.03
	Duration of diabetes at kidney transplant (yr)	0.98	0.96, 0.999	0.04
	Age at pancreas transplantation (yr)	0.96	0.95, 0.98	<0.001
	eGFR at pancreas transplantation (mL/min)	0.99	0.98, 0.995	0.003
	Kidney donor age (yr)	1.01	1.003, 1.03	0.011
	Kidney donor type			<0.001
	Living	Ref.	Ref.	Ref.
	SCD	1.07	0.77, 1.49	0.70
	ECD or DCD	2.38	1.63, 3.48	<0.001
	Induction at kidney transplant			0.07
	None	Ref.	Ref.	Ref.
	ATG/thymoglobulin	1.12	0.83, 1.53	0.46
	Anti-IL 2 receptor antibodies	0.90	0.61, 1.33	0.60
	Alemtuzumab	3.11	1.24, 7.76	0.02
Model 2[b]	Months between transplantations			
	All	1.01	1.004, 1.014	<0.001
	<1 yr	1.01	0.94, 1.08	0.89
	1 to <3 yr	1.02	0.98, 1.05	0.44
	≥3 yr	1.01	1.001, 1.02	0.03

SCD, standard criteria donor; ECD, expanded criteria donor; DCD, donor after cardiac death; eGFR, estimated glomerular filtration rate; ATG, anti-thymocyte globulin.
[a]Time interval as categorical variable.
[b]Time intervals as continuous variable.

Table 3. Clinical correlates of death following pancreas transplantation

	Variables	Hazard ratio	95% CI	p
Model 1[a]	Years between transplantations			0.24
	<1 yr	Ref.	Ref.	Ref.
	1 to <3 yr	1.22	0.92, 1.61	0.17
	≥3 yr	1.30	0.93, 1.81	0.13
	Age at pancreas transplantation (yr)	1.03	1.01, 1.06	0.002
	Recipient BMI at pancreas transplantation (kg/m^2)	0.95	0.93, 0.98	0.001
	eGFR at pancreas transplantation (mL/min)	0.99	0.98, 0.994	<0.001
	History of peripheral vascular disease, yes	1.58	1.17, 2.79	0.003
	History of coronary artery disease, yes	1.51	1.16, 1.97	0.002
	African American kidney donor, yes	1.95	1.29, 2.94	0.001
	Dialysis history, yes	1.74	1.30, 2.33	0.001
	Induction at pancreas transplantation			<0.001
	None	Ref.	Ref.	Ref.
	ATG/thymoglobulin	0.78	0.60, 1.00	0.06
	Anti-IL 2 receptor antibodies	0.54	0.38, 0.76	0.001
	Alemtuzumab	0.49	0.26, 0.92	0.03
Model 2[b]	Months between transplantations	1.002	0.998, 1.006	0.37

BMI, body mass index; eGFR, estimated glomerular filtration rate; ATG, anti-thymocyte globulin.
[a]Time interval as a categorical variable.
[b]Time intervals as continuous variable.

diabetic ESRD to receive a living donor kidney transplant as soon as this is available, while still having the possibility of receiving a pancreas transplant later on. This approach also has the potential to increase both the deceased donor kidney and pancreas pools (16). Notwithstanding this benefit, one of the main concerns of this approach is the potentially negative effect that pancreas transplantation can have on the function and the lifespan of previous kidney transplant (1, 6, 15). A few studies have addressed the question of whether the time interval elapsed between the two transplant procedures impacts the outcome of PAK transplantation (7, 8). Chronic kidney allograft injuries, in the form of interstitial fibrosis and tubular atrophy, can be detected as early as within the first year of kidney transplantation, either as a result of undetected subclinical acute rejection or CNI nephrotoxicity, and increase progressively with time (10, 13, 14, 17). Furthermore, continued diabetes exposure following kidney transplantation has also been shown to cause renal transplant injuries (11, 12). In one study, PAK transplant recipients who received a pancreas transplant with a time interval between the two transplant procedures greater than four months had no difference in outcomes when compared with those with a time interval less than four months (7). On the other hand, one recent study involving 126 PAK transplant recipients reported that a time interval greater than one yr between kidney and

Table 4. Renal function at pancreas transplant and clinical outcome

Renal function[a] (mean ± SD, mL/min)	Adjusted HR	95% CI	p
Kidney graft failure			
eGFR ≥65 (79.5 ± 15.4)	Ref.	Ref.	Ref.
eGFR 50 to <65 (56.9 ± 4.4)	1.27	0.89, 1.82	0.19
eGFR <50 (42.9 ± 5.0)	1.93	1.35, 2.77	<0.001
Death			
eGFR ≥65 (79.5 ± 15.4)	Ref.	Ref.	Ref.
eGFR 50 to <65 (56.9 ± 4.4)	1.51	1.13, 2.02	0.005
eGFR <50 (42.9 ± 5.0)	1.95	1.46, 2.62	<0.001

[a]Abbreviated Modification of Diet in Renal Disease formula.
eGFR, estimated glomerular filtration rate.

pancreas transplantation affected subsequent uncensored kidney graft loss but the impact on death-censored graft survival and patient survival was not separately addressed and the direction of such effect was not clear from their analyses (8). Thus, our study provides additional information that may be helpful in the assessment of the benefit and risk when PAK transplantation is considered.

The importance of renal function prior to PAK transplantation on the subsequent kidney graft survival has been recognized by several investigators (1, 8, 18). Our study is in full agreement with these previous observations, and in addition, we demonstrated that the levels of kidney function at the time of PAK transplantation, independent of time interval between kidney and pancreas transplantation, impact the risk of death, which is consistent with similar observation among kidney transplant patients (19). Although we did not identify a threshold of renal function levels below which PAK transplantation should not be recommended, an appropriate counseling for patients seeking a PAK transplant with emphasis on the degree of renal function should be provided.

Our study has several major limitations. First, as this is a retrospective national registry data analysis, the bias in patient selection for pancreas transplantation and post-transplant care by individual transplant centers could not be accounted for. For the same reason, the conclusion relies heavily on the accuracy of data collection from individual transplant centers reported to OPTN/SRTR. Second, separation of patients into three groups was somewhat arbitrary and without a particular rationale; thus, as a consequence, the patients from the three groups were dissimilar on many aspects. In particular, patients from Group 3 were more likely to have their kidney transplant from an early era (prior to 1995) and had more frequent use of cyclosporine as the initial CNI and less use of mycophenolates as an anti-proliferative agent. Although we adjusted for these and other variables in our multivariate analyses, this adjustment may have not eliminated the impact stemmed from the difference in care and in immunosuppressive regimens over the years. Third, the lack of detailed and important clinical information regarding clinical events such as the occurrence of biopsy proven rejection, CNI nephrotoxicity and infection, the degree of glycemia control and the presence of proteinuria prior to pancreas transplantation, etc., prevents us from pinpointing the specific mechanisms of our findings. Finally, our observations do not address the question whether having a pancreas transplant is better than not having it when the waiting time for a pancreas transplant is long and renal function is suboptimal. Thus, the time interval need not be used as a sole criteria to determine whether a qualified type 1 diabetic kidney transplant patient should receive a pancreas transplant or not. Rather, it should be considered in conjunction with many other factors such as the stability of kidney transplant and the degree of renal function as our study shows that better renal function was associated with good clinical outcome following pancreas transplantation.

In conclusion, longer time interval beyond three yr following kidney transplantation and reduced renal function were independently associated with an increased risk of kidney graft loss in PAK transplant recipients. Thus, reducing the waiting time for qualified type 1 diabetic kidney transplant patients and optimizing their renal function prior to pancreas transplantation should be emphasized.

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