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PANCREAS TRANSPLANTATION (D AXELROD AND N TURGEON, SECTION EDITORS)

The Current State of Pancreas Transplantation in the USA—A Registry Report

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Abstract

Purpose A successful pancreas transplantation is still the only method to provide long-term insulin independence and provide good metabolic control for patients with type I diabetes. Since the first pancreas transplant in 1966, the patient and graft survival after pancreas transplantation improved significantly. The aim of this report was to study the most recent outcome of pancreas transplants.

Recent Findings Between 2011 and 2016, 5159 primary deceased donor pancreas transplants in diabetic patients were performed—4342 (84%) SPK, 399 PAK (8%), and 418 (8%) PTA. One-year (3-year) SPK patient survival reached 98% (95%), PAK 97% (93%), and PTA 98% (96%). The most influential risk factor for patient survival in all three categories was a failed graft. In SPK, older recipients and being on dialysis at the time of transplant also carried an increased risk to die. SPK pancreas graft function improved to 90% at 1-year and 83% at 3-year post-transplant; 87% and 74% for PAK; and 84% and 71% for PTA. One-year (3-year) kidney graft function for the simultaneous SPK kidney was 96% (90%). The difference in outcome between SPK and solitary transplants is still significant but the gap is narrowing. A risk factor for pancreas graft failure was especially young recipient age, but a careful donor selection can improve outcome. The majority of recipients received depleting antibodies for induction followed by a maintenance protocol of Tacrolimus in combination with MMF. Steroids were used more often in SPK (70%) compared to solitary pancreas transplants.

Summary In summary, outcome after pancreas transplantation has significantly improved due to refinement in immunosuppressive protocols and better donor and recipient selection. It can be successfully performed in patients with labile diabetes and will not only improve the quality of life of the patient but also can be life extending.

Keywords Pancreas transplantation · Simultaneous pancreas kidney transplants (SPK) · Pancreas after kidney transplant (PAK) · Pancreas transplants alone (PTA) · Patient survival · Graft survival · Immunological graft loss · Technical complications

Introduction

Diabetes is a pandemic disease of the modern era around the globe. It is estimated that overall 30.3 million people in the USA have diabetes which represents 9.4% of the population. Type 1 diabetes accounts for 5–10% of those cases [1] and it is on the rise. Diabetes is the seventh leading cause of death in the USA, and it is one of the main contributing factors for cardiovascular disease, stroke, amputation, and end-stage renal disease. The DCCT trial could show that intensive insulin therapy with three or more daily insulin injections or insulin pump therapy guided by self-monitored glucose was effective compared to conventional insulin therapy. [2•] Rates of diabetic complications have improved after the publication of the study, but in many cases, it only extends the time until the diabetic complications manifest. Newer studies have shown that intensified control cannot prevent the onset of complications; it only will delay their onset. Furthermore, the early onset of type 2 diabetes is critical and leads to longer time of disease, earlier insulin dependence, and therefore to additional increase in diabetic complications.

Despite the prevalence, morbidities, and the associated financial burden, treatment options for diabetes have not changed very much since the introduction of injectable

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insulin. For patients who cannot be successfully treated with intermittent insulin therapy and who have developed brittle diabetes, one possible treatment option is pancreas transplantation. Pancreas transplantation still presents the only method to achieve long-term insulin independence and euglycemia. When transplanted before the onset of severe complications, it even can reverse or ameliorate them.

With the improvements in surgical technique and immunosuppression, pancreas transplantation is, right now, the best treatment choice for those patients with labile diabetes mellitus. The pancreas can be transplanted either alone (PTA), after a previous kidney transplant (PAK), or simultaneously together with a kidney graft (SPK). A SPK transplant is recommended as an acceptable treatment method for diabetic patients with imminent or established end-stage renal disease by the American Diabetes Association.

The number of pancreas declined significantly over the last years, and this analysis focuses on transplants performed between 2011 and 2016 and describes characteristics, risk factors, and outcome.

Methods

All patients with type 1 and type 2 diabetes mellitus who received a primary pancreas and/or pancreas and kidney transplant between 1/1/2011 and 12/31/2016 were included in this study. All patients had a follow-up time of at least 1 year post-transplant.

Pancreas graft function was defined as complete insulin independence. Partial function or dying with a functioning graft was counted as failure when not mentioned otherwise. Kidney graft failure, respectively, was defined as return to dialysis or dying with a functioning graft.

To measure the impact of risk factors on immunological failure, only technically successful transplant was analyzed. Technical failures were primarily defined as early graft thrombosis during the first 2 weeks post-transplant, or graft removal due to bleeding, anastomotic leak, pancreatitis, or infections during the first 3 months post-transplant.

The impact on center volume was measured by defining low, medium, and high volume centers. This was achieved by counting the total number of pancreas transplants per center for the period and defining the tertiles of these counts. A low volume center performed a maximum of 14 and a high volume center at least 40 transplants during a 6-year period.

A wide range of different antibody induction regimens was noted. For analyses, induction therapy was defined as the use of depleting (e.g., rabbit anti-thymocyte globulin, Alemtuzumab, ATGAM) and/or non-depleting (Daclizumab, Basiliximab) antibodies.

For maintenance therapy, a multitude of different drugs and combinations were recorded. The analyses focused on the mostly used combination of Tacrolimus in combination with mycophenolate mofetil (MMF) with or without steroids. Another category was protocols which were based on Sirolimus in combination with other drugs. All the other possible combinations of mono, duo, or CsA-based therapies which just represented a very small percentage were f combined or analyses in the category 'Other'.

Patient survival and graft function were computed using the Kaplan-Meier method. *P* values for pairwise comparisons were corrected according to Sidak. Cox proportional and non-proportional hazard models were applied to compute adjusted patient and graft survival rates and to assess the independent influence of risk factors. Time-dependent covariates were added for specific estimation of patient and graft survival. All statistics were performed using SAS 9.4 (SAS Institute, CARY, NC).

Results

A total of 6044 pancreata were transplanted between 1/1/2011 and 12/31/2016. The majority of pancreas transplants were performed in diabetic patients (93.4%). In 399 cases, the pancreas transplant was done in combination with a liver and/or intestine for non-diabetes-related reasons.

Of the 5645 transplants for diabetic reasons, the majority were primary pancreas transplants (94.4%). The rate of re-transplants was by far the highest in PAK (31.6%) when a pancreas was re-transplanted after a failed SPK (86%). PTA re-transplants were performed in 10.4%, SPK re-transplants only in 1.6%. Nineteen third and fourth rePAK transplants, 6 rePTA, and 3 reSPK were done. The majority of pancreas transplants were from deceased donors and only one living pancreas and kidney donor SPK was performed, and in six cases, a deceased donor pancreas was simultaneously transplanted with a kidney from a living donor during this time period.

This study concentrated on the remaining 5159 transplants which represented the majority of cases with primary pancreas transplants for type 1 and 2 diabetes mellitus (DM).

Recipient Characteristics

The majority of pancreas transplants were performed in combination with a simultaneous kidney graft (SPK) (Table 1). Pancreas transplants alone (PTA) and pancreas transplants after a kidney transplant (PAK) both accounted for 8% of primary transplants. Most frequently, type 1 DM was the indication for transplant but type 2 DM accounted for 12% of transplants in SPK. PTA transplants were only very rarely performed for type 2 DM.

Over the years, the recipient age at time of transplant trended towards older age. In solitary transplants, the median age of solitary transplants was 44 years compared to SPK

Table 1 Transplant recipient characteristics for primary deceased donor pancreas transplants performed between 2011 and 2016

	SPK	PAK	PTA	*p*
# Primary Tx (%)	4342 (84)	399 (8)	418 (8)	
Diabetes type				
Type 1	3838 (88)	371 (93)	412 (99)	< 0.0001
Type 2	504 (12)	28 (7)	6 (1)	
Recipient age (years)				
< 18	1 (0)	0 (0)	0 (0)	< 0.0001
18–29	72 (5)	24 (6)	45 (11)	
30–44	779 (59)	203 (51)	171 (41)	
45–59	458 (35)	160 (40)	180 (43)	
≥ 60	11 (1)	12 (3)	22 (5)	
Gender				
Male	2719 (63)	245 (61)	158 (38)	< 0.0001
Race				
White	2582 (59)	288 (72)	381 (92)	< 0.0001
Black	995 (23)	47 (12)	17 (4)	
Hispanic	594 (14)	52 (13)	18 (4)	
Asian	102 (2)	3 (1)	1 (0)	
Multi/other	69 (2)	9 (2)	1 (0)	
Body mass index				
< 18.5 (underweight)	75 (2)	12 (3)	5 (1)	< 0.0001
18.5–24.9 (normal)	2098 (480	173 (43)	162 (39)	
25–29.9 (overweight)	1663 (38)	148 (37)	179 (43)	
> 30 (obese)	506 (12)	66 (17)	72 (17)	
Recent cPRA%				
0–20	3687 (85)	322 (81)	328 (78)	< 0.0001
> 20	469 (15)	77 (19)	90 (22)	
Blood group				
A	1541 (36)	168 (42)	171 (41)	0.059
B	536 (12)	47 (12)	47 (11)	
AB	186 (4)	15 (4)	12 (3)	
O	2079 (48)	169 (42)	188 (45)	
Time to Tx (dys)				
0 < 30	424 (10)	30 (7)	71 (17)	< 0.0001
30 < 180	1413 (33)	82 (21)	165 (40)	
180 < 360	919 (21)	83 (21)	93 (22)	
≥ 360	1586 (36)	204 (51)	89 (21)	

recipients with a median age of 41 years ($p = 0.0002$). Pancreas transplants in recipients under the age of 30 were rarely performed and only one SPK transplant in a pediatric recipient was reported. The oldest recipients of a pancreas transplant were 67 years of age.

The majority of uremic and post-uremic recipients were male (> 61%) while the majority of PTA recipients were female (62%). Most of the solitary transplant recipients reported to be of White race compared to SPK transplants where the rate of Black and Hispanic recipients increased and accounted for 37% of transplants. Pancreas transplants in Asian recipients were only rarely performed. The racial distribution in the two diabetes types was significantly different. Significantly more of Black SPK than White recipients received a pancreas transplant because of type 2 DM ($P < 0.0001$).

The recipients' body weight was above 25 kg/m^2 in half of the SPK and more than half in solitary transplant recipients. A significantly higher percentage of PAK recipients (XX%) had a PRA greater than 20%. This was expected because these patients had already received a previous kidney transplant.

The time to transplant was significantly different for all three categories. While 25% of SPK and PTA recipients received their transplant after a wait time of 2–3 months, 25% of PAK waited 5 months. Median wait time for PTA was 4.7 months, for SPK 7.5 months and for PAK 12 months ($p = 0.0001$). Changes in the kidney allocation system (KAS) on 12/04/2014 effected the wait time for SPK recipients. The median wait time for patients transplanted before the introduction of KAS was 8.3 months but 6.5 months afterwards ($p < 0.0001$).

Donor Characteristics

With a decrease in the number of pancreas transplants over the last decade, the age of deceased pancreas donors declined, and now, the majority of donors were between the age of 16 and 30 years (Table 2). In SPK transplants, slightly older donors were accepted for transplantation compared to donors for solitary transplants (23 years vs. 21 years median age, $p < 0.0001$). Male donors were used preferentially because those were most likely trauma victims and of younger age. In 69% of all male and 42% of all female pancreas, donor trauma was the reported cause of death. A significant interaction of donor cause of death and gender could be found ($p < 0.0001$).

DCD (donation after cardiac death) donor organs were only rarely used for pancreas transplantation and more frequently in SPK. The body mass index of the donor was in the majority normal or slightly overweight. Only in SPK, more obese donors were accepted.

Attention to HLA matching was more often paid in PTA compared to SPK and PAK. Transplants with four or more HLA mismatches were performed in 84% in SPK, 80% in PAK, and 73% in PTA.

The use of a CMV positive donor was not different in the three transplant categories. In contrast, SPK (53%) and PAK recipients (57%) tested more often positive for CMV compared to PTA recipients (41%) ($p \leq 0.0001$).

Transplant Characteristics

The majority of pancreas transplants was performed at high volume centers (Table 3). Especially, PTA transplants were preferentially performed at high volume center ($P < 0.0001$). Over time, pancreas preservation time decreased significantly and almost all pancreas transplants were now performed with a preservation time under 24 h.

Table 2 Donor characteristics for primary deceased donor pancreas transplants performed between 2011 and 2016

	SPK	PAK	PTA	*P*
# of primary Tx (%)	4342 (84)	399 (8)	418 (8)	
Donor age [years]				
< 15	452 (10)	62 (9)	64 (15)	0.0006
16–30	2961 (68)	270 (68)	282 (68)	
31–45	837 (19)	63 (16)	62 (15)	
> 45	92 (2)	4 (1)	10 (2)	
Donor gender				
Male	3040 (70)	294 (74)	274 (66)	0.039
Donor race				
White	2671 (62)	239 (60)	275 (66)	0.59
Black	852 (20)	74 (18)	75 (18)	
Hispanic	609 (14)	66 (12)	56 (13)	
Asian	94 (2)	11 (3)	8 (2)	
Other/MultRace	116 (3)	9 (2)	4 (0)	
Donor cause of death				
Trauma	3410 (80)	304 (78)	308(76)	< 0.0001
CCV	856 (20)	86 (22)	89(22)	
CNS tumor	9 (0)	1 (0)	7(2)	
Missing	67	8	16	
DCD donor	113 (3)	1 (0)	13 (3)	0.01
Donor body mass index				
< 18.5 (underweight)	281 (6)	27 (7)	39 (9)	0.004
18.5–24.9 (normal)	2492 (58)	243 (61)	255 (61)	
25–29.9 (overweight)	1277 (29)	113 (28)	111 (27)	
> 30 (obese)	288 (7)	16 (4)	12 (3)	
Missing	4	0	1	
HLA A, B, DR mismatch				
0	16 (0)	1 (0)	4 (1)	< 0.0001
1	23 (1)	5 (1)	6 (1)	
2	128 (3)	20 (5)	30 (7)	
3	520 (12)	54 (14)	72 (17)	
4	1170 (27)	105 (26)	104 (25)	
5	1527 (35)	147 (37)	120 (29)	
6	958 (22)	67 (17)	82 (19)	
Recipient/donor CMV Status				
Negative/negative	833 (20)	66 (15)	94 (23)	0.0001
Negative/positive	1168 (27)	101 (26)	148 (36)	
Positive/negative	864 (20)	92 (24)	63 (15)	
Positive/positive	1393 (33)	199 (33)	105 (26)	
Missing	84	11	8	

Table 3 Transplant characteristics for primary deceased donor pancreas transplants performed between 2011 and 2016

Transplant year	SPK	PAK	PTA	*p*
# of primary Tx (%)	4342 (84)	399 (8)	418 (8)	
Tx center volume				
Low	274 (6)	49 (12)	22 (5)	< 0.0001
Medium	1030 (24)	114 (29)	58 (14)	
Large	2073 (70)	236 (59)	338 (81)	
Preservation time [h]				
0 < 12	2705 (65)	227 (59)	218 (54)	< 0.0001
12–23	1374 (33)	150 (40)	184 (45)	
> 24	76 (2)	2 (1)	4 (1)	
Missing	187	20	12	
Duct management				
Enteric drainage	3938 (92)	357 (91)	376 (91)	< 0.0001
Bladder drainage	322 (8)	28 (7)	35 (9)	
Duct injection	10 (0)	9 (2)	0 (0)	
Missing	72	5	7	
Venous Mgmt (EDTxs)				
Systemic drainage	3140 (80)	328 (92)	336 (90)	< 0.0001
Portal drainage	798 (20)	29 (8)	40 (10)	
Induction therapy				
None	423 (10)	38 (10)	27 (7)	0.004
Non-depleting AB	308 (7)	16 (4)	21 (5)	
Depleting AB	3405 (80)	331 (85)	346 (86)	
Both	133 (3)	4 (1)	9 (2)	
Missing	73	10	15	
Steroid maintenance				
No	1282 (30)	137 (35)	189 (47)	< 0.0001
Yes	2987 (70)	252 (65)	214 (53)	
Missing	72	10	15	
Maintenance protocol				
Tac&MMF	3904 (92)	349 (90)	326 (81)	< 0.0001
Srl based	169 (4)	18 (5)	53 (13)	
Tac	59 (1)	11 (3)	6 (1)	
MMF	45 (1)	4 (1)	6 (1)	
CsA	51 (1)	1 (0)	1 (0)	
Other	41 (1)	6 (1)	26 (6)	
Missing	73	10	15	

In most transplants, the pancreatic duct was enterically drained. Bladder drainage of the pancreatic was only used in 9% of all PTA. Duct injection was only used in very few cases. Portal drainage in enteric drained transplants accounted for 20% in SPK and 10% or less in solitary transplants.

In over 80% of transplants, recipients received induction therapy with depleting antibodies. In 68% of those cases, the therapy included anti-thymocyte globulin. Alemtuzumab was given in 15% of transplants. Compared to PTA, more SPK and PAK recipients received no induction therapy. In the majority of cases, the immunosuppressive maintenance protocol included Tacrolimus in combination with mycophenolic acid. There was a greater use of sirolimus in PTA recipients (13%). Single-drug maintenance protocols were only reported in a very small number of transplants. Maintenance steroids were more often used in SPK than in solitary transplants. Steroid-free protocols were more frequently preferred in high-volume centers ($p < 0.0001$).

Transplant Outcomes

The survival of diabetic patients on the wait list was dependent on the uremic status. Figure 1 shows the patient survival of those patients listed between 1/1/2005 and 12/31/2016. The best patient survival could be found for non-uremic patients waiting for a solitary pancreas transplant with a 1-year (5-year) patient survival of 97% (83%), followed by patients listed for a kidney transplant alone 95% (54%) and SPK 92% (45%). The survival was significantly different between the three groups

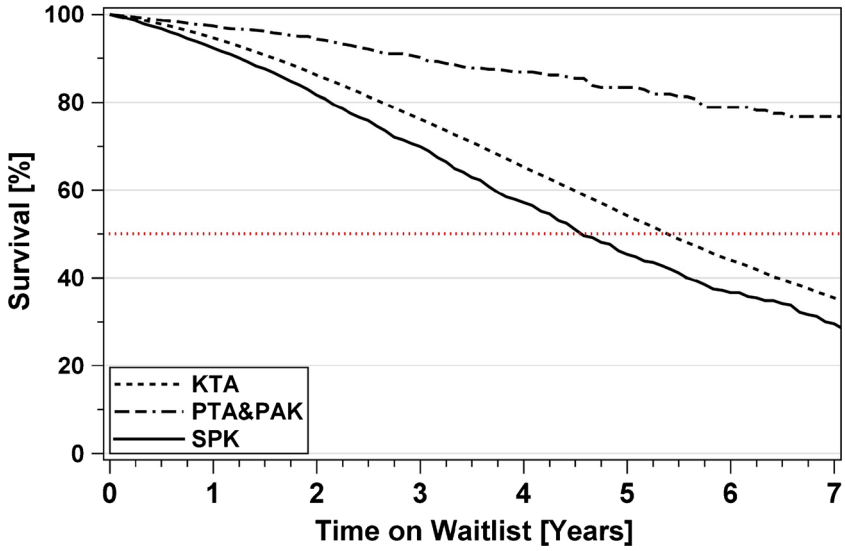

Fig. 1 Wait-list survival for diabetic patients waiting for a kidney, pancreas/kidney, or solitary pancreas transplant listed between 2000 and 2016

($p < 0.0001$). When only waitlisted patients with type 1 diabetes were compared, the 1-year (5-year) patient survival on the wait-list for solitary transplants was 97% (84%), for KTA 93% (50%), and for SPK 92% (45%) ($p < 0.0001$).

Patient survival after the transplant was not different between the three categories. Three-month patient survival was 100% for PTA, 99% for PAK and SPK (Fig. 2). Three-year post-transplant, the patient survival was 96% for PTA, 95% for SPK, and 93% for PAK ($p = 0.3$).

No significant risk factors for patient death could be found for PTA during the first 3 years post-transplant. For PAK, only a failed kidney graft (hazard ratio = 16.5) but not a failed pancreas graft carried a significant risk to die. All other risk factors proved to be non-significant. Figure 3 shows the risk factors for patient death in SPK. The highest risk to die was associated with a failed kidney or pancreas graft. Younger as well as older age was a risk factor, but only the older age category reached significance. Diabetes type had no impact on patient survival but being on dialysis pre-transplant increased the risk to die by over 70%. The pancreas transplant center volume had no effect on patient survival but the relative risk to die increased by 13% with each year on the wait-list for a transplant.

The causes of patient death were not reported in 20% of all cases overall. During the first 90 days post-transplant, the most frequent causes of patient death were cardio-cerebrovascular events (27%), infections (26%), and hemorrhages (10%). Later, infections and cardio-cerebro events remain to be the

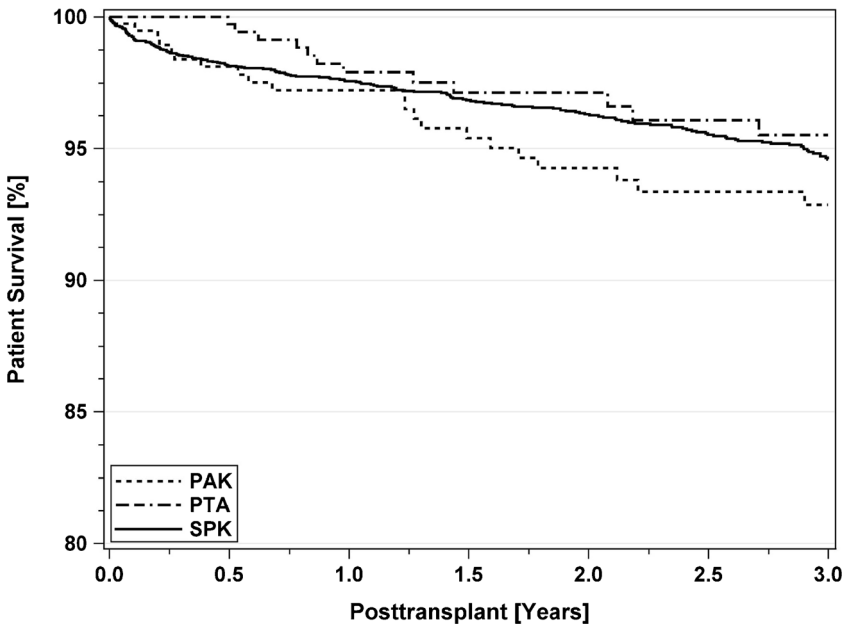

Fig. 2 Patient survival after primary deceased donor pancreas transplants for transplants performed between 2011 and 2016

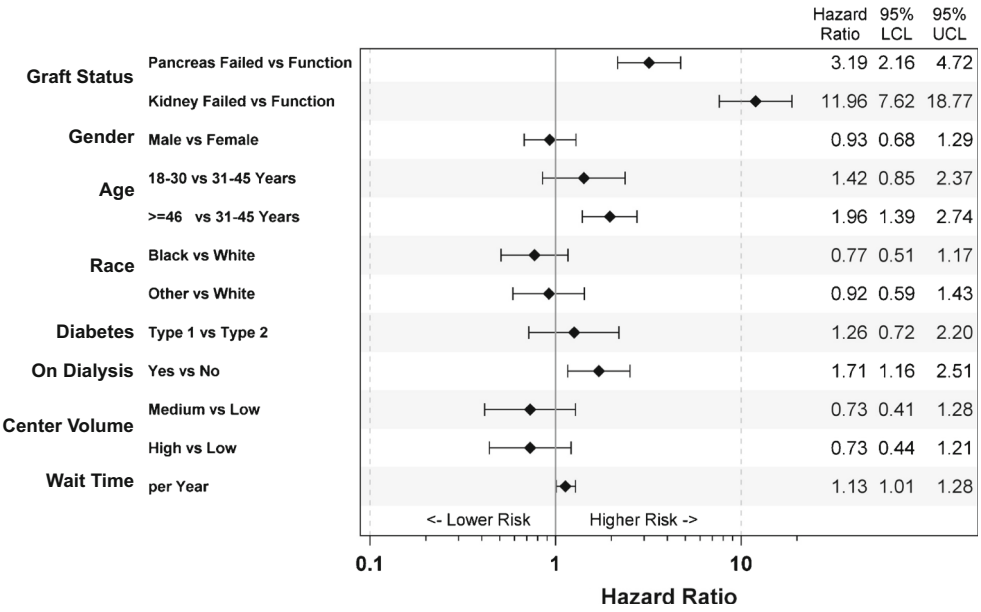

Fig. 3 Risk factor analysis for patient death after a simultaneous pancreas kidney (SPK) transplant for transplants performed between 2011 and 2016

main reasons for patient deaths. Between year 1 and year 5 post-transplant, malignancies were reported as cause of death in 6% of cases (11 cases).

Pancreas and combined pancreas/kidney graft function improved over time dramatically (Fig. 4). The 1-year (3-year) graft function of SPK pancreas was 90.0% (83.4%); SPK kidney was 95.7% (89.5%); PAK pancreas 86.5% (74.4%); and PTA 83.9% (71.4%). The difference in graft survival between SPK and the solitary pancreas transplants was significant ($p < 0.0001$). Death-censored graft failure at 1 year (3 years) increased to 91.8% (86.9%) for SPK pancreas; 97.8% (93.4%) for SPK kidney, 88.5% (78.8%) PAK pancreas, and 85.7% (74.0%) for PTA. Recipients who reached the 1-year mark with a functioning pancreas graft showed graft function at 3 years of 92.6% in SPK pancreata, 86.1% in PAK, and 85.1% in PTA.

The most influential factors for SPK pancreas graft failure were donor age over 45 years and center volume (Fig. 5a). Center with larger volume showed significantly better overall outcome. The use of depleting anti-bodies resulted in decreased pancreas loss; however, the different maintenance protocols did not reach significance. Male recipients showed a trend for better outcome and a BMI of 30 kg/m^2 was associated with higher graft failure. Recipient age, diabetes type,

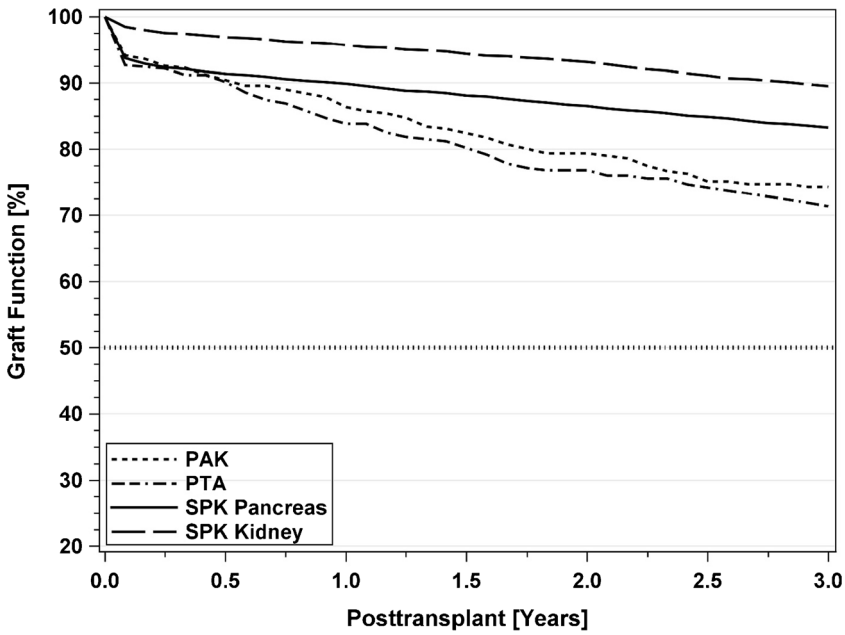

Fig. 4 Graft function after a primary deceased donor pancreas or pancreas kidney transplant for transplants performed between 2011 and 2016

race, pre-transplant, dialysis HLA mismatch, preservation time, donor body mass index, cPRA levels, and the maintenance protocols did not impact outcome.

The main risk factors for SPK kidney graft failure were low transplant center volume, being on dialysis, and being under the age of 30 at the time of transplant (Fig. 5b). Rarely used immunosuppressive regimens with only one drug or CsA-based regimens carried also an increased risk for kidney failure. The relative risk for male recipients to lose the kidney was significantly lower as well as enteric drainage of the pancreas protected significantly the simultaneous kidney graft.

The factor with the highest impact on PAK pancreas graft failure was pancreas quality including young donor and short preservation time. A previous kidney graft from a young donor showed a decreased risk of pancreas graft failure. A pancreas transplant during the first 2 months post kidney transplant carried only a slightly increased risk for graft failure. Center volume was not associated with graft failure risk.

For PTA, graft survival was associated with recipient age, a maintenance protocol beside tacrolimus/MMF/ and steroids ($P < 0.0001$) (Fig. 5c). The risk of pancreas graft loss increased with increasing donor age and decreased with increasing transplant center volume. Enteric drainage as well as cPRA levels over 20% were not associated with higher risk of graft loss. The relative risk for male recipients was again slightly lower compared to female recipients.

Technical failures were the main cause of graft loss during the first 90 days post-transplant. The failure rate ranged

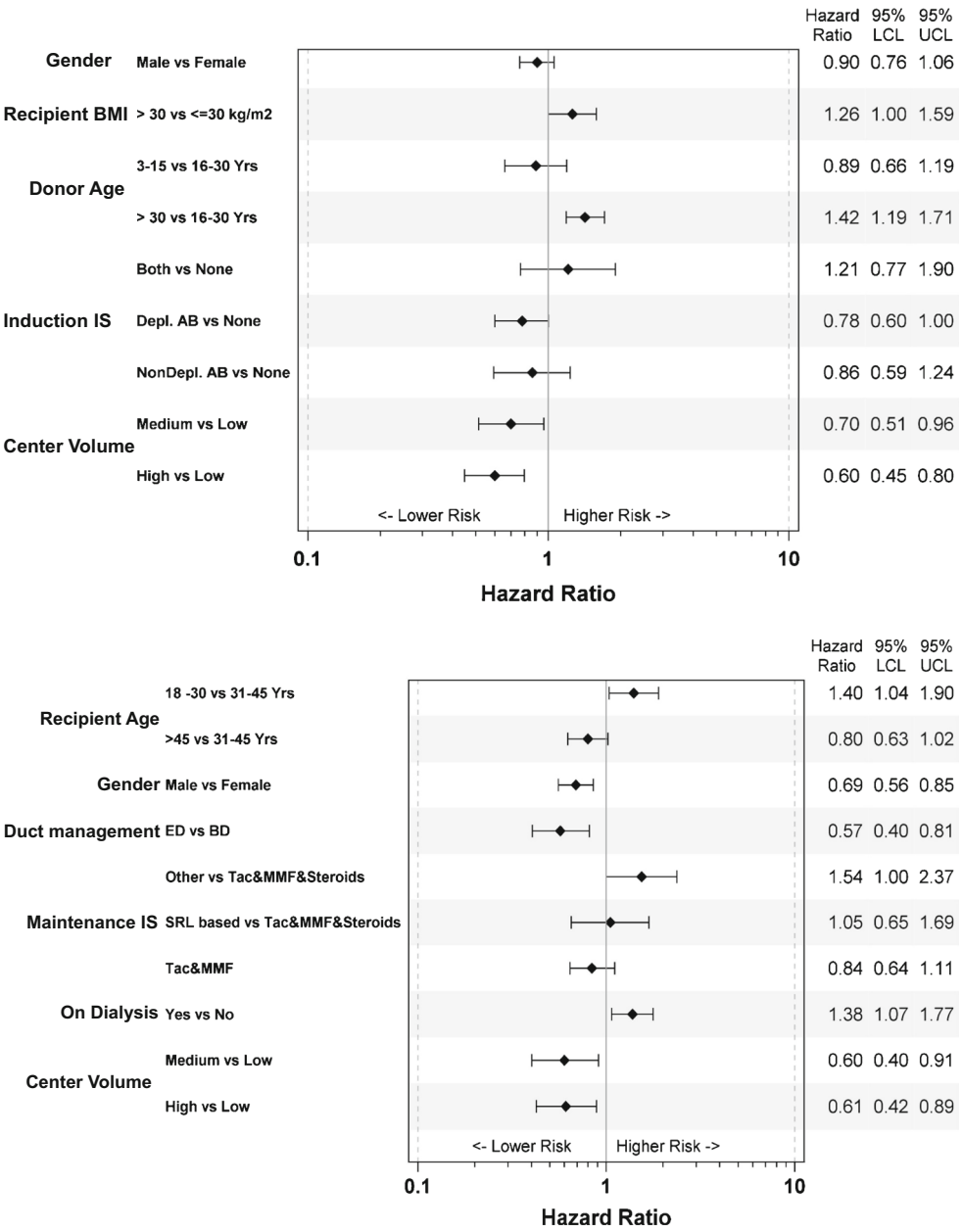

Fig. 5 Risk factor analysis for graft failure **a** SPK pancreas graft failure, **b** SPK kidney graft failure, **c** PTA pancreas graft failure for transplants performed between 2011 and 2016

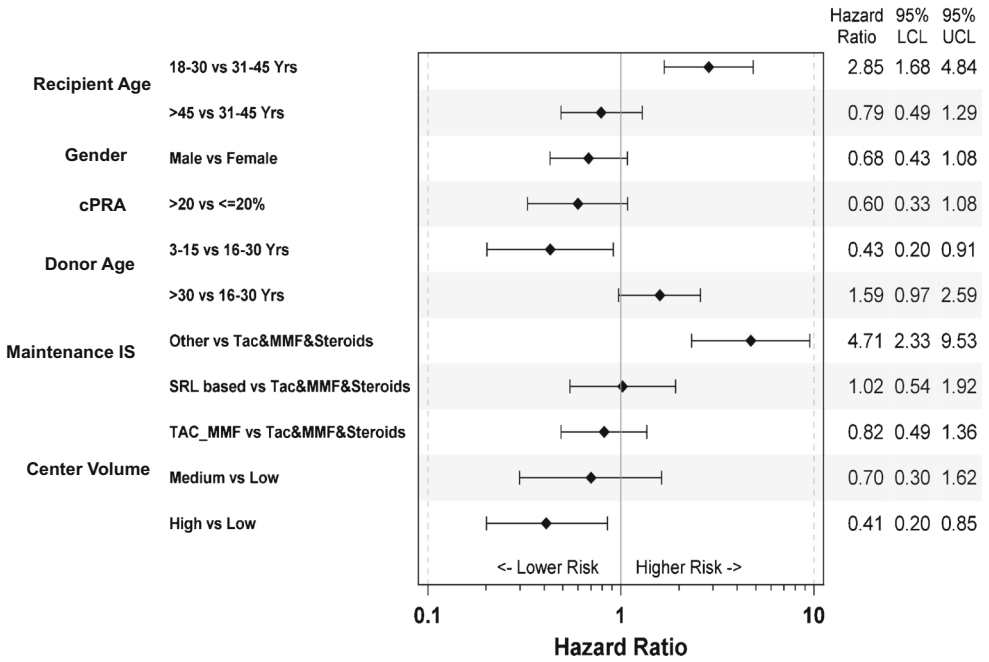

Fig. 5 (continued)

between 4.7 and 5.7% ($p = 0.74$) and did not reach significance (Table 4). The most prominent complication was 'graft thrombosis' which accounted for the majority of technical failures. PTA showed the highest rate of graft thrombosis failures which may be misdiagnosed as rejection episodes. Other complications were only rarely reported. Figure 6 shows the graft thrombosis rate for bladder and enteric drained (ED) pancreas transplants. The failure rates were slightly higher in ED transplants, but the difference did not reach significance for the different categories. The impact of the vascular management in ED drained transplants is shown in Fig. 7. The use of portal drainage resulted in slightly lower technical failure rates in SPK and PTA and in a higher rate in PAK. None of the comparisons reached significance.

Immunological graft loss in technically successful transplants is shown in Fig. 8. At 3 years post-transplant, the immunological graft loss in SPK pancreas was 3.6%, in SPK kidney 3.0%, in PAK 8.7%, and in PTA 12.9%. The differences between the three pancreas categories were significantly different.

Table 4 Technical failures in enteric and bladder drained pancreas transplants performed between 2011 and 2016

	SPK	PAK	PTA	*p*
Technical failure rate (%)	5.2	4.7	5.7	0.74
Graft thrombosis (%)	4.2	4.4	4.9	
Infection (%)	0.3	0.3	0.2	
Pancreatitis (%)	0.2	0.0	0.2	
Anastomotic leak (%)	0.4	0.0	0.2	
Bleeding (%)	0.1	0.0	0.2	

The treatment for rejection during the first year post-transplant, younger age, and no induction therapy carried the highest risk for immunological graft loss in all three transplant categories. The use of depleting antibody therapy and a maintenance protocol of Tacrolimus in combination with MMF provided also a significantly lower relative risk for immunological graft loss. The risk of immunological SPK pancreas graft loss was slightly increased for Black compared to White recipients. All remaining factors did not reach significance.

Discussion

The outcome of pancreas transplantation alone, in combination with a kidney graft, or after a previous kidney graft improved significantly over time for patients with brittle diabetes and/or end stage renal disease [3]. At this time, pancreas transplant remains the best short- and long-term treatment to achieve insulin independence, realize good metabolic control, and, potentially, avoid, ameliorate, or even reverse secondary diabetic complications [4–8]. Regardless of this progress, the number of pancreas transplants declined significantly though 2015. However, pancreas transplants started to increase in 2016 and remained stable in 2017. Especially concerning is the reduction in the number PAK during this time period [9, 10, 11••]. PAKs offer the diabetic patient the opportunity to receive a living or deceased kidney first to correct uremia as soon as possible, and subsequently a well-matched pancreas allograft from an excellent donor. The new allocation system was specifically designed to encourage PAK but removing SPK priority in organ allocation. Although outcome of PAK

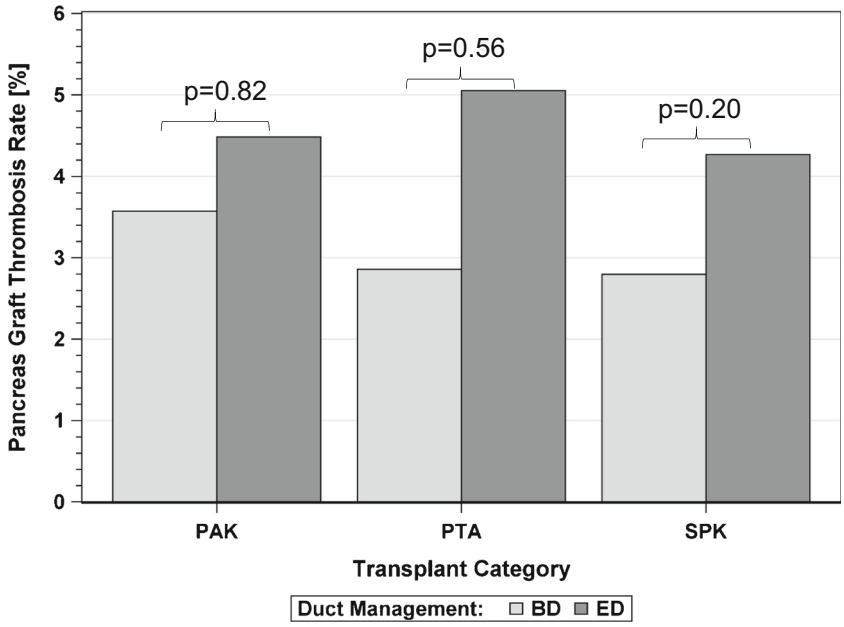

Fig. 6 Early technical failure rates for enteric and bladder drained pancreas transplants by transplant type for transplants performed between 2011 and 2016

is not quite equivalent to SPK, the gap is closing. PAK can be a life-preserving procedure because it avoids long-term dialysis and mortality on the wait-list. It provides the opportunity to find a good pancreas graft after the kidney transplant to correct the underlying diabetes and provide excellent metabolic control [12]. A kidney transplant alone only corrects only one secondary diabetic complication, does not prevent or delay recurrent diabetic nephropathy, and does nothing for disabling hypoglycemic unawareness. [13]. Nevertheless, many center stopped to perform PAK transplants and only offer kidney transplant alone or combined pancreas/kidney transplant increasing organ discard to and reducing access to this vital procedure. The number of PTA remained relatively stable during the analyzed time period. The outcome improved significantly in this population with severe brittle diabetes and preserved kidney function. The mortality risk for patients with severe brittle diabetes and hypoglycemic unawareness remains a significant risk for mortality and poor quality of life [14, 15•]. Therefore, a solitary transplant should be considered before the patient develops end-stage renal disease when alternative treatments are not successful [16, 17]. There is still a reluctance to consider pancreas transplantation without the development of more severe diabetic secondary complications because many physicians still believe that exogenous insulin

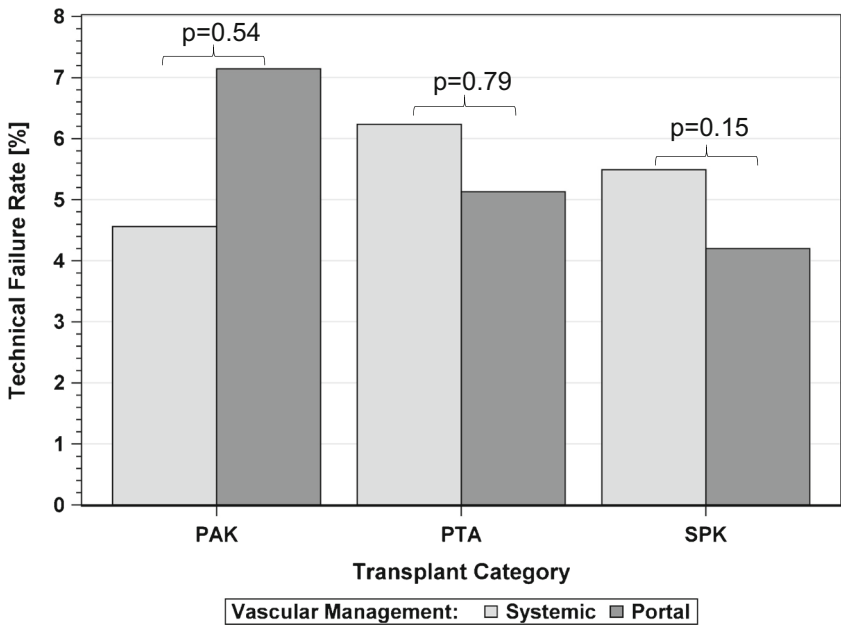

Fig. 7 Early technical failure rates for enteric pancreas transplants by vascular management and transplant type for transplants performed between 2011 and 2016

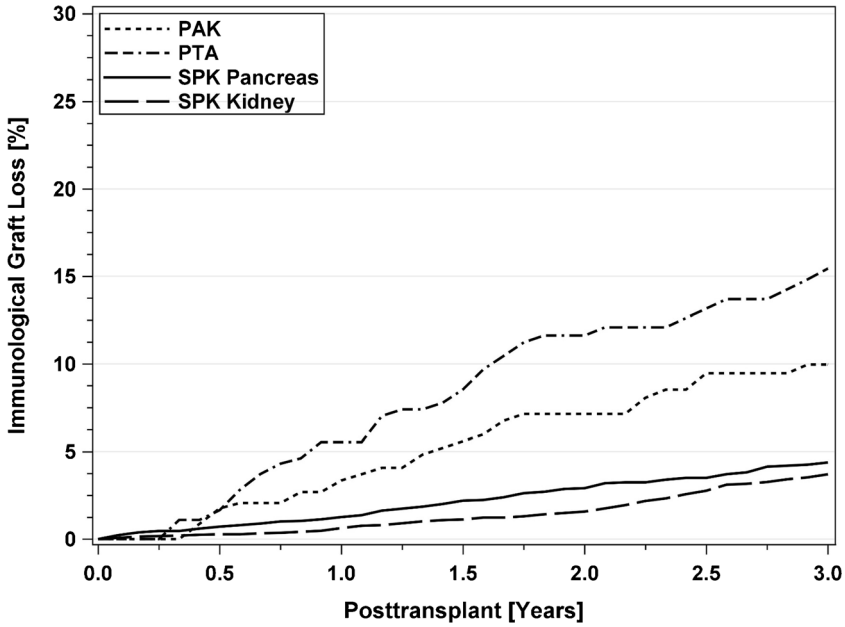

Fig. 8 Immunological graft loss for primary technically successful deceased donor pancreas transplants performed between 2011 and 2016

administration outweighs the surgical risk and the risk of long-term immunosuppression. However, this is only true for patients that are able to maintain strict glucose control, something that many patients with significant lability find difficult or impossible.

The majority of pancreas transplants were performed in combination with a kidney graft and here the outcomes improved significantly while the numbers increased in 2016 after a drastic decline [18], while the numbers were declining the characteristics of recipients and donors were changing. The median recipients' age increased as the onset of diabetic related kidney disease has been delayed with improved medical management. Similarly, the weight of patients at transplant has increased over time, reflecting societal trends, improved metabolic control with exogenous insulin, and greater use of SPK transplant in type 2 diabetics, who are more commonly African American. [19•]. Pancreas donor quality improved significantly with decreased donor age, more male donors and more often trauma reported as cause of death [20••, 21]. The pancreas preservation time also dropped significantly with the decrease in transplant numbers [22]. A standardization of pancreas transplantation technique is also apparent. Most transplants were performed with enteric drainage and the number of cases with vascular drainage through the portal vein declined [23]. Most recipient received induction therapy with depleting antibodies and a maintenance protocol of tacrolimus in combination with MMF was used in the majority of cases.

With the decline in transplants, the numbers of center remained relatively stable but the pancreas transplant volume declined significantly. Pancreas transplant volume was associated with graft outcome but not on patient survival [24–26]. Declining pancreas volume impacts also the education of future transplant surgeons. More and more centers performed only 1–2 pancreas transplants a year and transplant fellows see fewer and fewer pancreas transplants.

The changes in recipient and donor selection and refined surgical techniques and immunosuppressive appear to result in improved outcome for patient and graft survival. Those facts about pancreas transplantation should be brought out to the specialists, informing physicians about those achievements so that they feel better equipped to refer suitable patients for transplantation and manage, counsel, and support when encountering them within their own specialty [27, 28].

Compliance with Ethical Guidelines

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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