Pancreas outcomes between living and deceased kidney donor recipients in pancreas after kidney transplantation

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Abstract

Background: Pancreas outcomes in pancreas after kidney transplantation have been reported as being inferior to those from simultaneous pancreas-pancreas (SPK). The influence of kidney donor (living- vs deceased-donor) has never been previously addressed.

Methods: We retrospectively analyzed all pancreas transplants performed in a single center since 2007, and compared the outcomes from those who had previously received a living-donor kidney transplant (PAldK; n=18) or a deceased-donor kidney transplant (PAddK; n=28), using SPK (n=139) recipients as reference.

Results: Pancreas survival was similar between all groups, but inferior for PAldK when included only those with functioning graft at day 90 post-transplant (p=.004). Pancreas acute rejection was significantly increased in PAldK (67%; 1,8±1,4 episodes/graft) when compared to PAddK (25%) and SPK (32%) (p<.05). In a multivariate Cox regression model including known risk factors for pancreas rejection, PAldK was the only predictor of acute rejection (HR 6,82 95% CI 1,51-30,70, p<.05). No association was found between donor-recipient HLA mismatches and graft rejection. Repeated HLA mismatches between kidney and pancreas donors (0 vs 1-6) did not correlate with pancreas graft rejection or survival in both PAK groups (p>.05).

Conclusions: Pancreas graft outcomes are worse for PAldK when compared to PAddK and SPK.

Introduction

Pancreas after kidney transplantation (PAK) is a treatment alternative to simultaneous pancreas-kidney transplantation (SPK) which gained relevance in the beginning of the 21st century, when mortality on the waiting list was high for patients with diabetes mellitus type 1 (DM1). With a 4-year patient survival of 58,7% for those awaiting a SPK compared to 81,7% for those who received a kidney transplant prior to pancreas transplantation (1), PAK transplantation reached a yearly peak of 412 procedures performed in the US in 2004 (2).

In kidney transplantation, living-donor outcomes are better than those from standard deceased-donors (3,4). In DM1 recipients, overall patient survival for recipients from a living donor kidney transplantation (LDKT) alone is similar to those receiving a SPK in the mid-term (5). Nonetheless, several studies have demonstrated that patient survival is increased with a functioning pancreas graft (5–7). The culprit for these patients appears to be the time on waiting list. On an UNOS/OPTN/IPTR registry analysis (1), survival curves on the waiting list between SPK and pancreas after kidney (PAK) appear to diverge further from the 2nd year onwards. This has become more evident since many centers have implemented a policy of promoting LDKT prior to pancreas transplantation, particularly those with long time on the waiting list.

LDKT followed by deceased donor pancreas transplantation (PAldK) poses as an appealing alternative to SPK. In the US, the median waiting-list time to SPK is over 20 months (2). When available, LDKT could be performed preemptively, avoiding dialysis, or be performed with a short dialysis vintage, and thereafter be maintained on the waiting list for a pancreas transplant. The advantages, in addition to reducing exposure to uremia, are a potential increase of standard criteria donors to the kidney deceased donor pool, and the optimization of pancreas used for transplantation, avoiding conflicts with kidney allocation systems (8).

Results for PAK are most often analyzed from registry data and include patients from different transplant eras and immunosuppression protocols (1,6,7,9). Therefore, a possible bias might be inherent to these registry data. On the other hand there seems to be a certain decline in numbers of performed

PAldK as an alternative to SPK, which might be explained by experiences of the different centers that might somehow differ from those reflected on registries. Herein we report the outcomes of PAldK transplants from a large volume center in the current immunosuppression era.

Material and Methods

Patient Population

Kidney and pancreas transplant was indicated to type 1 diabetic patients (C-peptide < 1.0ng/mL) with end stage renal disease (ESRD) stages 4-5d (glomerular filtration rate <20m/min/1,73m^2). Pre-transplant workup included biochemical and hematological parameters, cardiologic evaluation, and CT-scan of splanchnic and iliac vessels. Immunological workup included complement dependent cytotoxicity (CDC) panel reactive antibodies (PRA) for patients with low immunological risk (absence of previous blood transfusions or solid organ transplant). Solid phase Luminex® screening was performed for those with previous sensitization episodes, and solid phase single bead antigen performed in the presence of a positive class I and/or II Luminex® screening.

From 2007 onwards, all patients evaluated for simultaneous kidney-pancreas transplant were informed about the possibility of performing LDKT followed by a deceased donor pancreas transplant. Those with a suitable donor who opted for a LDTK prior to pancreas transplantation were subsequently included on the waiting list for pancreas transplant alone (PAldK). All the remaining patients were included on the waiting list for a simultaneous kidney-pancreas transplant (SPK).

Patients with a functioning kidney graft from a previous deceased donor transplant (either kidney transplant alone or a previous SPK who had lost the pancreas graft) who received a pancreas transplant (PAddK) were also included in the analysis.

Study design

Following protocol approval by the ethics committee institutional review board, we conducted a retrospective analysis including all pancreas transplants (PTx) performed at our center from January 1st, 2007 until December 31st, 2015, including SPK, PAldK, and PAddK recipients. Two patients received a pancreas transplant alone and were excluded from the analysis. Data was collected until the December 31st, 2016, in order to obtain a minimum follow-up of 12 months.

Both donor and recipient data were included, such as demographic, clinical, biochemical and immunologic. Patient survival was defined as last day of the follow-up, death with a functioning

pancreas graft, or up to 90 days after pancreas failure. Graft loss was defined as a) pancreas: graft removal, C-peptide <1ng/mL, total daily insulin need >0,5U/Kg, or death; b) kidney: return to dialysis, retransplantation, or death.

Immunosuppression

Induction therapy was used in all patients. In SPK, anti-IL2 monoclonal antibody (basiliximab) 20 mg at D0 and D+4 was used as standard therapy until July 2013, and thereafter replaced by rabbit anti-human lymphocytes polyclonal antibodies (either Thymoglobulin® 1,25mg/Kg/day or ATG® 2,5mg/Kg/day) for 4 consecutive days. In PAK, either PAldK or PAddK, these doses were extended to 7 consecutive days.

Maintenance immunosuppression protocol was based on triple therapy with tacrolimus (TAC), mycophenolate (MMF), and steroids - methylprednisolone in the immediate post-transplant period, followed by oral prednisone. Prednisone withdrawal was attempted from post-transplant month 3 to month 12 in non-sensitized SPK transplants, in the absence of prior sensitization or previous episode of rejection (either kidney or pancreas). It maintained *ad eternum* in both PAK groups.

Acute rejection

Pancreas acute rejection was diagnosed based on a) clinical criteria: acute elevation of pancreatic enzymes in the absence of other probable cause; b) biopsy proven acute rejection (BPAR) when pancreas graft biopsy was performed. Biopsies were attempted from 2010 onwards, and classified according to the 2011 Banff criteria (10). Banff cellular rejection grade I was treated with methylprednisolone 500mg for 3 consecutive days, and grade II-III treated additionally with T-cell depleting antibodies (either thymoglobulin® 1,25mg/Kg/day or ATG® 2,5mg/Kg/day) for 7 consecutive days. Antibody mediated rejections (ABMR) were treated with two doses of anti-CD20 monoclonal antibody (Rituximab) 375 mg/m2, plasma exchange (5 sessions), and intravenous immune globulins (IVIG) 0,5mg/Kg.

Rejections diagnosed based on clinical criteria were treated with methylprednisolone 500 mg for 3 consecutive days. In the absence of improvement, corticoresistent rejection was presumed and patients treated additionally with T-cell depleting antibodies as for Banff grade II-III rejections. If ABMR rejection was suspected, treatment was performed as previously described.

Statistical analysis

For continuous variables a Kolmogorov-Smirnov test was used to determine normality. Parametric variables are described as mean ± standard deviation, and non-parametric as median [interquartile range (IQR)], and the corresponding tests used (t-test, ANOVA, Kurskal-Wallis). Kaplan-Meier was used to estimate unadjusted patient and graft survival and compared using log-rank test. A Cox proportional regression was performed to estimate grafts' hazards. A multivariate logistic regression model was designed to estimate odds ratio for acute rejection. Statistical analysis was performed using SPSS (IBM, USA) software, with all tests two-tailed and significance considered if $p<.05$.

Results

Demographics

A total of 185 pancreas transplantations were performed in 174 patients during the study period. Of these, 139 were SPK, 18 PAldK, and 28 PAddK. Both PAK groups had shorter waiting list time prior to pancreas transplantation, a shorter dialysis vintage, and a lower prevalence of patients on peritoneal dialysis (p<.05) (table 1). All other recipient and donor related demographic data, including sensitization prior to pancreas transplantation and number of HLA mismatches (table 1), were similar between the three groups.

Pancreas after living-donor kidney transplantation

Eighteen PTx were performed to 15 recipients of LDKT (2 ABOi, 1 paired kidney exchange program). Recipients were mostly from blood group O (61%) and often received a kidney transplant preemptively (33%) - the remaining were a median of only 11 months on hemodialysis (minimum 1; maximum 38). Donors were most frequently genetically related to recipients - either parents (39%) or siblings (28%). Patients were included in the waiting list for pancreas transplantation at a median time of 7 months (minimum 2.3; maximum 24.9) following kidney transplantation. Pancreas transplantation was performed on average 13.9±5.2 months after receiving a living-donor kidney transplant. Three patients received a second pancreas transplant (two had lost the first graft due to thrombosis <48h post-transplant, and a third due to chronic rejection 6.4 months post-transplant). Three patients died during follow-up (17%), one due to gastrointerstinal bleeding, other due to infection, and a third with sudden death. All cases occurred at least 4 years after transplantation. Two of which had received a pancreas re-transplantation.

Patient survival

Overall patient survival at 12, 36 and 60 months was 98% and 95%, and 92%, respectively. Fifteen patients died during follow-up, on average 26.7±19.0 months post-pancreas transplantation. Infection (47%) and cardiovascular disease (20%) were the leading causes of death.

No differences were found regarding patient survival between SPK, PAldK, or PAddK (Log Rank *p*>.05), even though there was a tendency towards an inferior survival in PAldK (OR 3.75; 95% CI 0.99-14.2; *p*=.52) when compared to SPK (Figure 1-A).

Kidney graft survival

Overall kidney graft survival (death-censured) at 12, 36, and 60 months was 98%, 97%, and 96%, with similar results between all groups (Figure 1-B). Death with functioning graft (50%) was the most frequent cause of kidney graft failure. Chronic rejection (38%), surgical complications (8%) and BK virus nephropathy (4%) were the other causes of graft failure.

Pancreas graft survival

Overall pancreas graft survival (death-censured) at 12, 36, and 60 months was 86%, 79%, and 75%, respectively. Surgical complications were the main cause of graft failure (42% of all failures). Excluding graft failure within the first 90 days, pancreas survival for the same periods was 96%, 89%, and 83%, respectively. Chronic (52%) and acute rejection (10%) were the main causes of graft failure in this group, with five patients (17%) dying with a functioning graft.

Pancreas graft survival was inferior for both PAldK and PAddK when compared to SPK (log-rank *p*=.0001 and p=.031, respectively; figure 1-C). When included only those with a functioning graft on day 90 post-transplantation (D+90), survival for PAddK was similar to SPK (log-rank *p*=.58), but inferior for PAldK (log-rank p<.000) (figure 1-D). Considering re-transplantations as a separate group, pancreas survival for PAldK and re-transplantation, but not PAddK, were inferior to SPK (log-rank p values .010, .003 and ..983, respectively; Figure S1-A). In a binary logistic regression for graft failure risk, and using SPK as reference, PAldK presented a HR of 3,58 (95% CI 1.59-8.08; *p*=.002) and PAddK a HR of 2,30 (95% CI 1.06-5.00; *p*=.035).

To identify the risk factors for pancreas graft failure we applied a multivariable Cox regression model including variables known to be associated with graft loss (table 2), regardless of their statistical value on the univariate analysis. Only recipient female gender was independentely associated with graft failure. Pancreas transplant category did not reach statistical significance (*p*=.15).

We further investigated the association between PAldK and graft failure. First, we eliminated all variables deemed insignificant (p >.20) from the previous model. Recipient female gender (HR 2.45; 95% CI 1.28-4.71; p=.007) was the only risk factor associated with graft failure (data not shown). Pancreas transplant category was not significant (p=.21). Then, and since we had identified graft survival to be inferior in PAldK even when included only those with functioning graft at day 90 following transplantation, we investigated which risk factors could predict graft failure beyond this period. To do so we used the previously described Cox model in this group (D+90). Once again, pancreas transplant category did not reach statistical significance (p=.70).

Acute rejection

Twenty-eight patients (18%) presented at least one episode of kidney acute rejection, without any differences in rejection incidence between pancreas transplant categories (p>.05).

As for pancreas, at least one episode of rejection was diagnosed in 63 allografts (34,1%; rejection-free graft survival of 43.7±42.2 months) (Table 3). Most episodes occurred during the first 12 months post-transplantation (78%; median 3.6 months). BPAR accounted for 75% of all acute rejection diagnosis in PAldK, while only up to 30% and 43% of the diagnosis of the SPK and PAddK groups, respectively.

Pancreas graft rejection was significantly increased in PAldK (67%; 1.8±1.4 episodes/graft) when compared to PAddK (25%) or SPK (32%) (Figure 2). These results were sustained even when pancreas re-transplantations were considered separately (figure S1-B). The median time to first rejection episode was 5.1 [2.3-17.6], 0.5 [0.3-2.8], and 6.2 months [1.3-10.1] for PAldK, PAddK, and SPK, respectively (p=.14).

On a multivariate logistic regression model including known risk factors for pancreas rejection, such as pre-transplant sensitization, donor age and BMI, pancreas CIT, induction immunosuppression and the mismatches between pancreas donor and recipient, PAldK (HR 6,82 95% CI 1,51-30,70, p=.012) was the only factor associated with graft rejection (table 4). No association was found between donor-recipient HLA mismatches and graft rejection, neither as a continuous variable nor as a categorical one (p>.05) (figure S2-A).

In an attempt to clarify this unexpected result, we analyzed the effect of HLA mismatches on graft rejection per transplant category. No differences were found for any group (figure S2-B-D). We then explored the possibility of repeated incompatibilities between pancreas and kidney donors as a risk factor for pancreas rejection. For this analysis, both PAIdK and PAddK were grouped into a single category (PAK) due to the small sample size. There was a tendency towards an increased incidence of rejection in those who repeated at least one HLA incompatibility between kidney and pancreas donors (0 vs 1-6; 58% vs 29%; p=.075) (Figure S3-A), though it was not associated with a worse graft survival (Figure S3-B; p>.05). Finally, we equated whether repeated HLA compatibilities between kidney donor and recipient could influence pancreas graft rejection risk, based on the assumption that increased compatibilities would decrease total alloantigen mass, possibly leading to an augmented immune response when exposed to pancreas graft alloantigens. As expected, the number of HLA compatibilities between kidney donor and recipient was superior in PAIdK recipients (3.4±1.5 vs 5.0±1.0 in PAddK; p=.001). Nonetheless, rejection risk was similar (p=.274) for those recipients sharing at least one haplotype, compared to those with 2 or less HLA compatibilities.

Discussion

In this study we evaluate the outcomes from three different pancreas transplant categories from a single center. Pancreas after living donor kidney transplantation presented similar patient survival compared to simultaneous pancreas-kidney and pancreas after deceased-donor kidney transplantation, but a worse pancreas graft survival (compared to SPK) and a significant increase in the incidence of acute rejection.

Pancreas graft survival has historically been inferior for PAK when compared to SPK (2,11). A significant improvement was observed with the introduction of T-cell depleting antibodies to induction immunosuppression protocols (12) and with the reduction in surgical complications and early graft loss (7). Despite this improvement, the most recent UNOS and IPTR registry data analysis still report an inferior 1 and 3 years pancreas survival for PAK compared to SPK (84.4 vs 89.1% and 75.4 vs 82.2%, respectively). In this report, both PAK groups (PAldK and PAddK) are analyzed together and no reference is made to differences in the outcomes between the two groups. Of relevance, 80% of all PAK included are PAldK recipients, and therefore the results most significantly represent those of this group. As for PAddK, the largest published series is also from an analysis of the UNOS database, including only recipients of pancreas re-transplantations with a functioning kidney graft, and reports a decreased graft survival compared to SPK (13). Both these reports are in accordance to those found in our cohort. Nonetheless, we have found long-term PAddK graft survival to be similar to SPK, , while PAldK presented a worse outcome. A rather high incidence of death with functioning graft in this population (18%) may only partially explain these results, and graft rejection failed to reach statistical significance on the multivariate analysis.

Incidence of pancreas graft rejection was another outcome expected to be higher in PAK compared to SPK (2,7,14). Uremia induced immunosuppression and transplant of a larger allogeneic mass in a dual transplantation have been proposed as probable factors for the better outcomes in SPK. Unexpected was the increased rejection incidence and decreased rejection-free graft survival in PAldK compared to PAddK. Baseline immunological factors were assumed as the most probable explanation and were therefore explored.

Females have been associated with an increased risk for acute rejection (15), likely due to pregnancy associated pre-transplant sensitization. Gender associated immunological risk factors could not be confirmed, since there were no differences on the incidence of immunological events between males and females.

HLA mismatching has long been recognized as a cause of increased graft rejection incidence (16,17) and generation of *de novo* donor specific antibodies (DSAs) (18,19). In an exhaustive analysis of HLA mismatches and pancreas outcomes, Mittal *et al* describe an increased acute rejection risk for those with 4-6 mismatches (18), with HLA loci B and DR being the most relevant ones. In a Portuguese cohort, Malheiro *et al* report HLA loci DR as a risk factor for *de novo* DSAs(19). Of notice, PAK transplantations were not included in any of these analyses. Also, in the UNOS/IPTR registry analysis, mismatches in DR were associated with risk for immunological graft loss in SPK, but not in PAK. In our cohort, HLA mismatches could not explain the increased incidence of AR in the PAldK group. In this group, neither the total number of HLA mismatches was superior to the other groups, nor were any differences found within the group (either total, or specific DR or B loci – data not shown) when comparing those with and without any episodes of rejection.

In kidney re-transplantation, repeating donor's HLA incompatibilities confers a poorer graft prognosis (20). In fact, some centers use repeated incompatibilities as an exclusion criterion for organ acceptance, despite the absence of pre-formed DSAs. We compared repeated incompatibilities in both PAK groups and explored its relation to graft outcomes. To the authors' knowledge, this approach has never been performed before in pancreas transplantation. Repeated HLA incompatibilities did not correlate with acute rejection or with graft survival, neither as continuous nor as a categorical variable (data not shown). This remained true for repeated incompatibilities on the DR loci between pancreas donor and recipient, either for DR*03 or DR*04 (data not shown).

Immunosuppression protocols have an influence on pancreas outcomes. Induction therapy with thymoglobulin improves pancreas graft survival (11) and reduces acute rejection incidence (21). In this analysis, only a portion of SPK recipients received induction therapy with basiliximab. All patients from both PAK groups received induction with T-cell depleting antibodies. Moreover, the cumulative dose

administered was pre-emptively decided to be higher for both PAK groups, therefore not explaining the increased incidence of AR in the PAldK group. Moreover, prednisone withdrawal, controversially associated with acute rejection, was not performed in either of PAK patients.

The authors recognize some limitations to the study. The cohort is small and only representative of a regional population, and waiting list patient survival was not included in the analysis, and conclusions as to the patients' best treatment alternatives cannot be withdrawn. It has been previously demonstrated that PAldK transplantation may present a survival advantage when compared to being maintained on the waiting list for an SPK (1), with the culprit being on the waiting list vintage prior to transplantation. Therefore, the results from this study should be interpreted with caution.

This study highlights some features associated with pancreas graft outcomes in PAldK transplant recipients. Pancreas graft survival was inferior in PAldK when compared to SPK and PAddK (in those with functioning pancreas at day 90), while presenting an increased incidence of acute rejection. These results should not discourage centers from advising this alternative, however, they should individually evaluate their median waiting-list time before proposing this treatment option to their patients. PAldK implies several advantages for patients and for the transplant community and further analysis comparing these two populations are warranted in order to clarify the cause of the inferior outcomes.

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Disclosure

The authors decline any conflict of interests regarding study design or manuscript preparation.

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Pedro Ventura-Aguiar – Data collection and manuscript preparation

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Fritz Diekmann – Manuscript revision

Mª José Ricart – Manuscript preparation and revision

FIGURE LEGENDS

Figure 1 – Kaplan-Meier estimate survivals by pancreas transplant modality for: A) patient; B) kidney graft; C) pancreas graft; D) pancreas graft (if functioning at day +90). SPK – simultaneous pancreas-kidney transplantation; PAldK – pancreas after living donor kidney transplantation; PAddK – pancreas after deceased donor kidney transplantation; PTx – pancreas transplantation

Figure 2 – Pancreas graft rejection incidence according to pancreas transplant category. SPK – simultaneous pancreas-kidney transplantation; PAldK – pancreas after living donor kidney transplantation; PAddK – pancreas after deceased donor kidney transplantation.

Figure S1 – (A) Kaplan-Meier estimate pancreas graft survival (death-censured) and (B) Cox regression proportional analysis for rejection free graft survival for each pancreas transplant modality, including re-transplantation as a separate group; SPK – simultaneous pancreas-kidney transplantation; PAldK – pancreas after living donor kidney transplantation; PAddK – pancreas after deceased donor kidney transplantation;

Figure S2 – Association between the number of HLA mismatches and cumulative incidence of pancreas rejection for A) all groups. B) SPK. C) PAldK. D) PAddK. SPK – simultaneous pancreas-kidney transplantation; PAldK – pancreas after living donor kidney transplantation; PAddK – pancreas after deceased donor kidney transplantation.

Figure S3 – Association between the number of repeated HLA mismatches between pancreas and kidney donors in PAK recipients (both PAldK and PAddK) and A) the incidence of acute rejection; B) graft survival.

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Table 1 – Donor and recipient demographic and clinical data

Demographic and clinical data				
	SPK (n= 139)	**PAldK (n= 18)**	**PAddK (n=28)**	***p***
Recipient				
Age (years)	41.6±7.1	39.5±6.0	43.5±8.9	NS
Gender (Male; %)	63.3	55.6	57.1	NS
Diabetes *vintage* (years)	27.8±8.4	24.5±6.6	30.5±9.9	NS
Dialysis modality (n;%)				.04
HD	86 (63)	12 (67)	18 (64)	
PD	42 (30)	0	6 (21)	
Pre-dialysis	11 (7)	6 (33)	4 (15)	
Dialysis *vintage* (months)	34.2±19.7	12.5±12.4	33.0±22.4	.00
Pancreas waiting list vintage (months)	19.3±12.9	5.4±2.7	3.9±4.1	.00
Re-transplantations (*n*/% of total)	1 (0.07%)	3 (17%)	21 (75%)	.00
Blood Group (%)				NS
O	39.6	61.1	28.6	
A	50.4	33.3	64.3	
B	9.4	0.0	7.1	
AB	0.7	5.6	0.0	
Donor				
Age (years)	33.4±10.3	30.5±11.2	30.0±11.4	NS
Gender (Male; %)	59.0	61.1	46.4	NS
BMI (Kg/m2)	23.8±2.9	24.3±2.9	23.7±2.9	NS
Cause of death (%)				NS
Cerebrovascular disease	43.2	29.4	38.5	
Trauma	44.6	52.9	46.2	
Anoxia post-CPR	5.8	17.6	11.5	
Other	6.5	0	3.8	
PDRI	1.28±0.38	1.27±0.46	1.00±0.21	.045
Cold ischemia time – Pancreas (hours)	10.8±3.0	11.8±3.1	11.4±2.2	NS
Donor-recipient CMV status (%)				NS
-/-	9.0	5.9	0.0	
+/-	11.9	17.6	9.5	
-/+	29.9	41.2	42.9	
+/+	49.3	35.3	47.6	

Immunological data				
	SPK (n= 139)	**PAldK (n= 18)**	**PaddK (n=28)**	***p***
HLA mismatches (pancreas; n)				
A+B	3.1±1.1	2.8±1.0	2.9±1.4	NS
DR	1.5±0.7	1.4±0.8	1.3±0.8	NS
Total	4.7±1.1	4.5±1.1	4.7±1.5	NS
HLA compatibilities between pancreas and kidney donors				
A+B				
DR		1.0±1.0	1.2±1.5	NS
Total		1.0±1.0	1.2±1.5	NS
Sensitization pre- pancreas transplant (%)*	28.1	27.8	25.0	NS
PRA pre-transplant (maximum)	6.6 ± 14.5	5.4 ± 10.6	5.0 ± 11.7	NS
Luminex I positive (%)	4.6	5.9	5.9	NS
Luminex II positive (%)	3.4	5.9	11.8	NS
Pre-formed DSA (%)	0	0	0	NS
Immunosuppression (%)				.00
Thymoglobulin	25.9	100	95.7	
Basiliximab	74.1	0	4.3	
Prednisone withdrawal (%)	30.2	0	3.6	.00
Transplant vintage at withdrawal (months)	4.9 ± 0.8	0	5.0	

*Sensitization pre-pancreas transplant – assumed as a PRA >0% and/or a Luminex class I and/or class II positive. SPK – simultaneous pancreas-kidney transplantation; PAldK – Pancreas transplantation after living-donor kidney transplantation; PAddK – pancreas transplantation after deceased-donor kidney transplantation; NS- Not significant (p value ≥0.05);

Table 2 Multivariable Cox proportional regression analysis for pancreas graft failure risk

		95% CI		
	HR	Inferior	Superior	*p*
Recipient age (years)	1.013	.936	1.097	.745
Recipient gender (female)	6.274	2.062	19.090	.001
Recipient blood group				.385
Group O	1.000	-	-	-
Group A	2.641	.773	9.021	.121
Group B	.910	.065	12.812	.945
Group AB	.000	0.000		.981
Diabetes Vintage (months)	1.045	.981	1.113	.174
Waiting list time (months)	.983	.924	1.046	.598
Previous pancreas transplants (n)	4.997	.676	36.950	.115
Transplant Category				.149
SPK (reference)	1.000	-	-	-
PAldK	2.470	.265	22.999	.427
PAddK	0.264	.017	3.994	.337
Donor/recipient CMV status				.128
-/- (reference)	1.000	-	-	-
-/+	.186	.037	.931	.041
+/-	.675	.126	3.608	.646
+/+	.374	.066	2.104	.264
Donor age (years)	1.009	.953	1.068	.755
Donor gender (female)	.890	.321	2.463	.822
Donor BMI (Kg/m^2)	1.070	.906	1.263	.428
Donor COD				.081
Cerebrovascular Disease (reference)	1.000			
Trauma	5.030	.1.454	17.404	.011
Cerebral anoxia	3.780	.482	29.629	.206
Other	.717	.056	9.106	.797

Pancreas cold ischemia time (minutes)	1.023	.859	1.217	.801
Sensitized pre-transplant (Yes)	1.148	.429	3.070	.783
HLA mismatches (*n*)	1.084	.705	1.667	.713
Induction treatment (basiliximab)	.577	.124	2.675	.482
Prednisone maintenance (yes)	1.298	.402	4.192	.663
Pancreas rejection (yes)	.438	.136	1.412	.167
Kidney rejection (Yes)	1.175	.316	4.379	.810
Year of transplantation				.487
2007	1.000			
2008	.385	.065	2.283	.29
2009	.914	.169	4.937	.92
2010	.550	.079	3.817	.55
2011	1.531	.265	8.864	.63
2012	2.036	.260	15.952	.50
2013	3.333	.452	24.555	.24
2014	.660	.062	6.989	.73
2015	.177	.011	2.898	.22

Table 3 – Demographic characteristics of patients with acute rejection

	No rejection (*n*=122)	Rejection (*n*=63)	*p*
Recipient age (years)	41.9±6.9	41.3±8.2	.57
Recipient gender (female)	45 (63.4%)	26 (36.6%)	.38
Diabetes vintage (years)	27.5±8.6	28.5±8.6	.43
Dialysis pre-transplant			.16
Pre-emptive	11 (52.4%)	10 (47.6%)	
Hemodialysis	74 (63.8%)	42 (36.2%)	
Peritoneal dialysis	36 (75.0%)	12 (25.0%)	
Dialysis vintage (months)	35.5±20.9	26.3±17.9	.006
Time on waiting list (months)	17.0±13.9	13.0±10.9	.045
Donor age	33.0±10.7	32.0±10.4	.54
Donor gender (male)	68 (64.2%)	38 (35.8%)	.72
Donor BMI (Kg/m2)	23.9±3.0	23.7±2.8	.75
Donor COD			.4
CVD	54 (72.0%)	21 (28.0%)	
Trauma	50 (60.2%)	33 (39.8%)	
Anoxia	8 (57.1%)	6 (42.9%)	
Other	7 (70.0%)	3 (30.0%)	
Donor PDRI	1.26±0.39	1.25±0.39	.70
Cold ischemia time (minutes)	10.7±2.8	11.5±3.2	.06
Sensitized pre-transplant			.3
No	91 (67.9%)	43 (32.1%)	
Yes	30 (58.8%)	21 (41.2%)	
HLA mismatches*	4.5±1.3	4.1±1.5	.32
HLA mismatches**			.78
0	1 (100%)	0 (0%)	
1	2 (100%)	0 (0%)	

2	2 (66.7%)	1 (33.3%)	
3	17 (77.3%)	5 (22.7%)	
4	27 (67.5%)	13 (32.5%)	
5	35 (62.3%)	21 (37.5%)	
6	33 (62.3%)	20 (37.7%)	
Pancreas transplant category*			.002
SPK	95 (68.3%)	36/44 (26/32%)	
PAldK	5 (27.8%)	7/13 (39/67%)	
PAddK	21 (75.0%)	7/7 (25/25%)	
Year of transplantation			.066
2007	14	9	
2008	25	9	
2009	13	11	
2010	9	13	
2011	12	4	
2012	11	1	
2013	11	7	
2014	12	3	
2015	15	6	
Induction therapy			.43
Thymoglobulin	52 (68.4%)	24 (31.6%)	
Basiliximab	65 (62.5%)	39 (37.5%)	
Prednisone withdrawal			.004
No	85 (59.9%)	57 (40.1%)	
Yes	36 (83.7%)	7 (16.3%)	

*Rejection group data represented as rejection episodes during the first 12months post-transplant/total number of rejection episodes during follow-up; SPK – simultaneous pancreas-kidney transplantation; PAldK – Pancreas transplantation after living-donor kidney transplantation; PAddK – pancreas transplantation after deceased-donor kidney transplantation;

Table 4 – Multivariable logistic regression analysis for pancreas acute rejection risk

	HR	95% CI		p
		Lower	Upper	
Sensitized pre-transplant (yes)	1.394	.616	3.156	.425
Donor age (years)	.992	.955	1.029	.657
Donor BMI (Kg/m2)	.945	.823	1.084	.418
Cold ischemia time (min)	1.037	.918	1.172	.558
HLA mismatches (n)	1.206	.874	1.665	.255
Induction immunosuppression (Basiliximab)	2.742	.979	7.682	.055
Transplant category				.041
SPK (reference)	1.000			
PAldK	6.821	1.515	30.701	.012
PAddK	1.461	.345	6.181	.606
HLA MM - A-B				.61
0	1.000			
1	.000	.0000		.999
2	.316	.033	3.004	.316
3	.506	.057	4.468	.540
4	.710	.093	5.429	.741
HLA MM - DR				.672
0	1.000			
1	1.370		6.236	.684
2	.729		3.132	.671

SPK – simultaneous pancreas-kidney transplantation; PAldK – Pancreas transplantation after living-donor kidney transplantation; PAddK – pancreas transplantation after deceased-donor kidney transplantation;

FIGURE 1

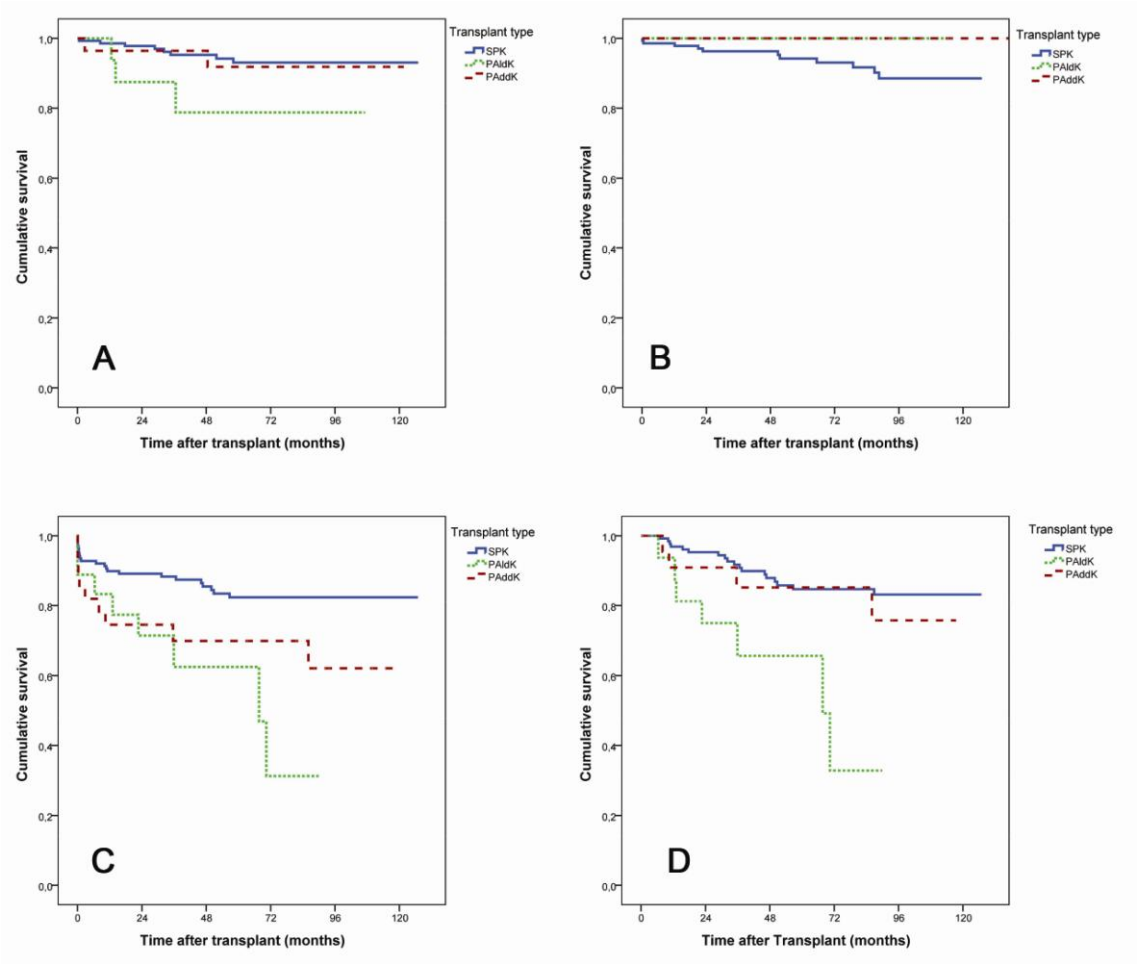

Transplant type
SPK
PAldK
PAddK
Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
Time after transplant (months)
A
B
C
D
Time after Transplant (months)

FIGURE 2

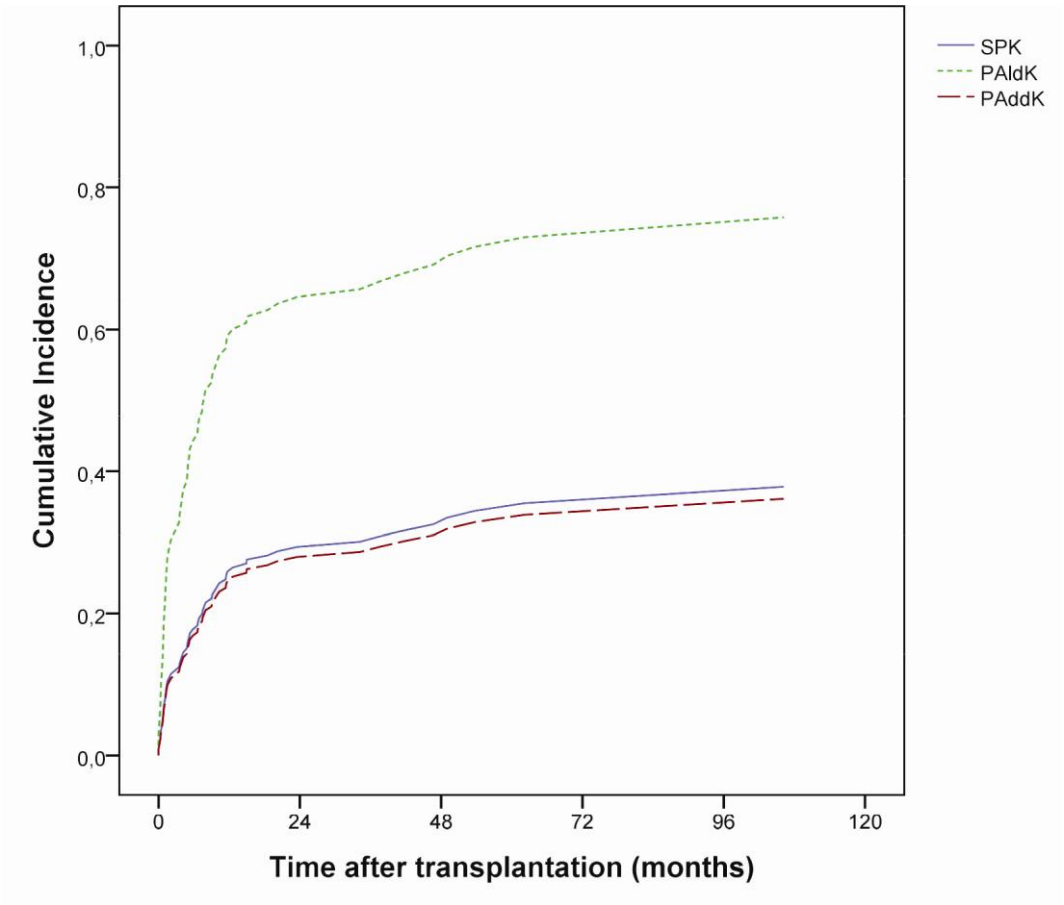

SPK
PAIdK
PAddK
Cumulative Incidence
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
Time after transplantation (months)

Figure S1

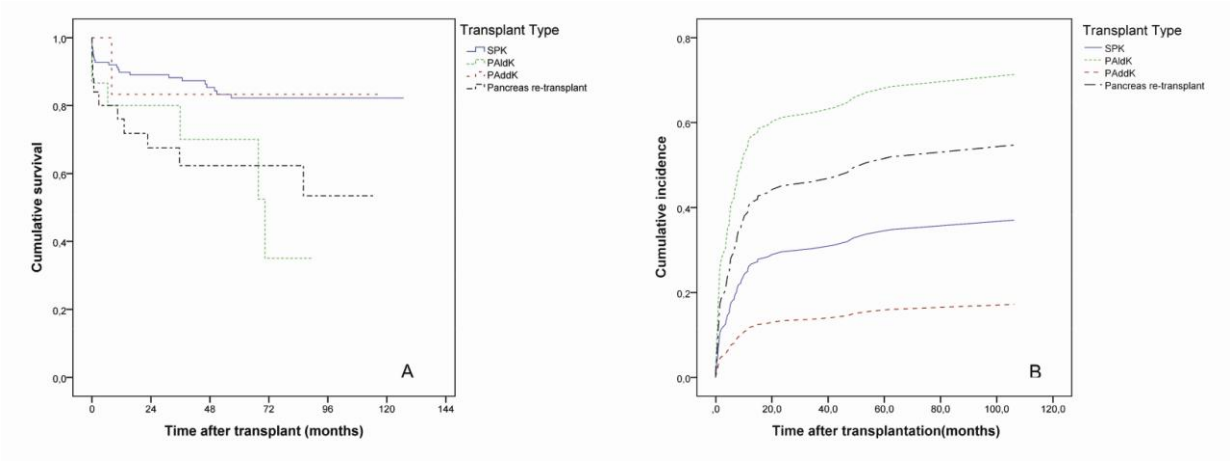

Transplant Type
SPK
PAtdK
PAddK
Pancreas re-transplant
Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
0
24
48
72
96
120
144
Time after transplant (months)
A
Cumulative incidence
0,8
0,6
0,4
0,2
0,0
,0
20,0
40,0
60,0
80,0
100,0
120,0
Time after transplantation(months)
B

FIGURE S2

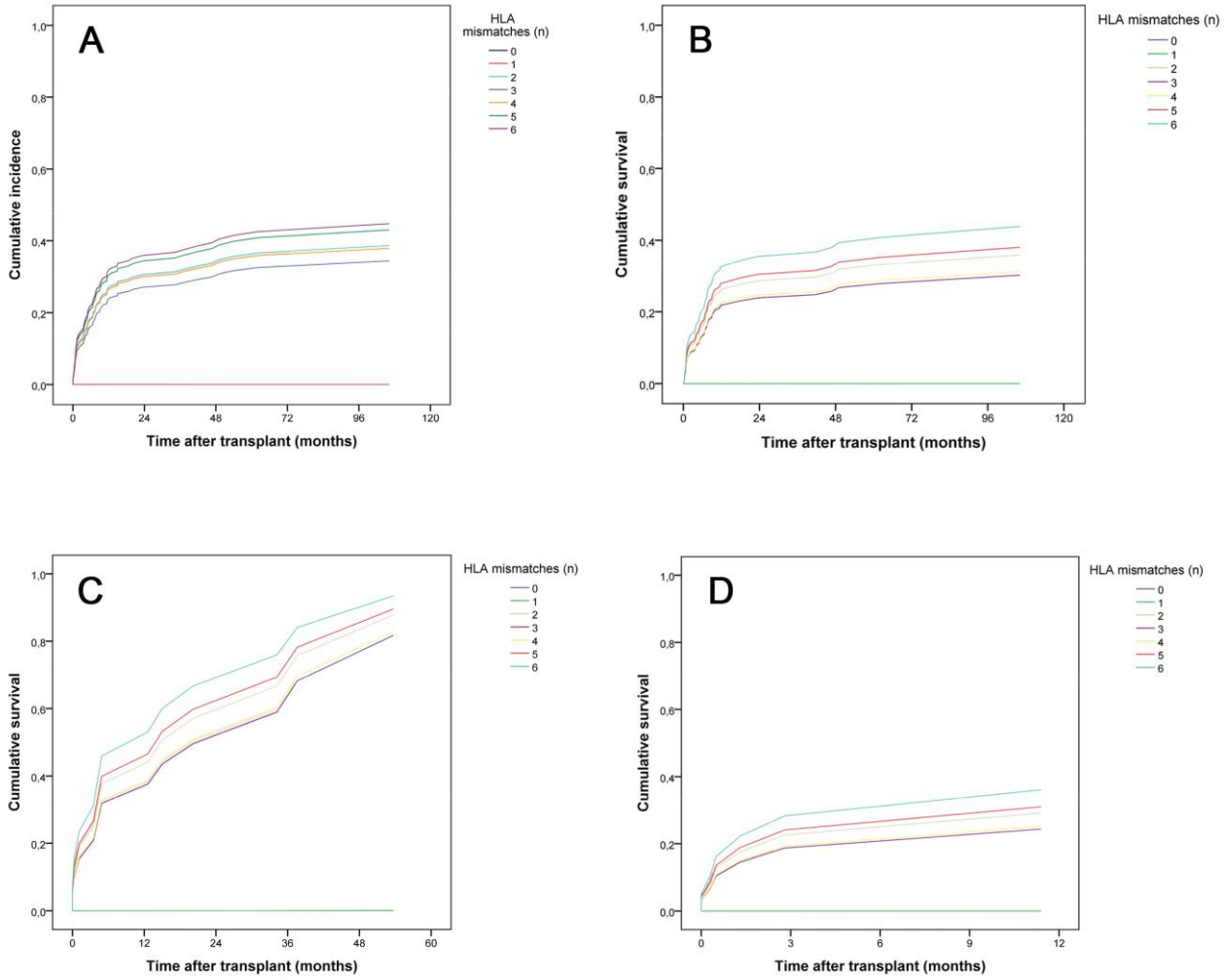
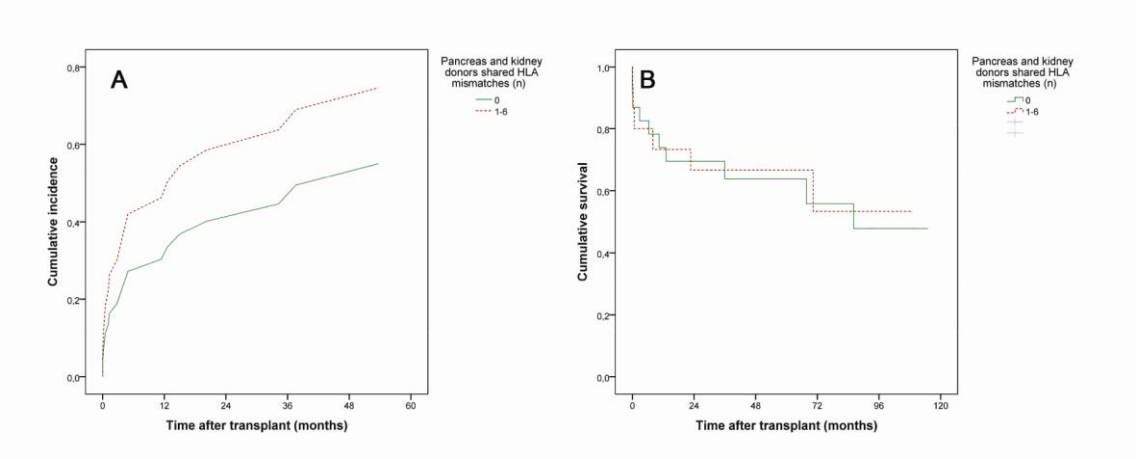

A
Cumulative incidence
Time after transplant (months)
HLA mismatches (n)
0
1
2
3
4
5
6
B
Cumulative survival
Time after transplant (months)
HLA mismatches (n)
C
Cumulative survival
Time after transplant (months)
HLA mismatches (n)
D
Cumulative survival
Time after transplant (months)
HLA mismatches (n)

FIGURE S3


A
Cumulative incidence
0,0
0,2
0,4
0,6
0,8
0
12
24
36
48
60
Time after transplant (months)
Pancreas and kidney donors shared HLA mismatches (n)
0
1-6
B
Cumulative survival
0,0
0,2
0,4
0,6
0,8
1,0
0
24
48
72
96
120
Time after transplant (months)
Pancreas and kidney donors shared HLA mismatches (n)
0
1-6