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ORIGINAL ARTICLE

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

Pedro Ventura-Aguiar[1,2], Joana Ferrer[3], Ignacio Revuelta[1,2,4], David Paredes[5], Erika de Sousa-Amorim[1], Jordi Rovira[2], Enric Esmatjes[6], Juan Carlos Garcia-Valdecasas[3], Josep M. Campistol[1,2,4], Federico Oppenheimer[1], Fritz Diekmann[1,2,4] and Maria José Ricart[1,4]

[1]Renal Transplant Unit, Nephrology and Kidney Transplantation Department, Hospital Clinic, Barcelona, Spain, [2]Laboratori Experimental de Nefrologia I Trasplantament (LENIT), CRB CELLEX, Fundació Clínic, IDIBAPS, Barcelona, Spain, [3]Hepatobiliopancreatic and Liver Transplant Department, Hospital Clinic, Barcelona, Spain, [4]REDinREN, Madrid, Spain, [5]Organ Transplantation Coordination Department, Hospital Clinic, Barcelona, Spain and [6]Diabetes Unit, Department of Endocrinology and Nutrition, Hospital Clinic, Barcelona, Spain

Correspondence and offprint requests to: Fritz Diekmann or Josep M. Campistol; E-mail: fdiekman@clinic.cat or jmcampis@clinic.ub.es; Twitter handle: @PVentura_Aguiar

ABSTRACT

Background. Pancreas outcomes in pancreas after kidney transplantation (PAK) patients have been reported as being inferior to those of patients who receive simultaneous pancreas and kidney transplantation (SPK). The influence of the kidney donor (i.e. living versus deceased) has never been previously addressed.

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

Results. Pancreas survival was similar between all groups, but inferior for PAldK when including only those with a functioning graft at day 90 post-transplantation ($P = 0.004$). Pancreas acute rejection was significantly increased in PAldK (67%; 1.8 ± 1.4 episodes/graft) when compared with PAddK (25%) and SPK (32%) ($P < 0.05$) patients. In a multivariate Cox regression model including known risk factors for pancreas rejection, PAldK was the only predictor of acute rejection (hazard ratio 6.82, 95% confidence interval 1.51–30.70, $P < 0.05$). No association was found between donor–recipient HLA mismatches and graft rejection. Repeated HLA mismatches between kidney and pancreas donors (0 versus 1–6) did not correlate with pancreas graft rejection or survival in either PAK transplantation group ($P > 0.05$).

Conclusion. Pancreas graft outcomes are worse for PAldK when compared with PAddK and SPK patients.

Keywords: acute rejection, graft survival, living donor kidney transplant, pancreas after kidney, pancreas transplantation

INTRODUCTION

Pancreas after kidney (PAK) transplantation is an alternative treatment to simultaneous pancreas and 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 an SPK compared with 81.7% for those who received PAK transplantation [1]. PAK transplantation reached a yearly peak of 412 procedures performed in the USA 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 living-donor kidney transplantation (LDKT) alone is similar to those receiving an SPK in the mid-term [5]. Nonetheless, several studies have demonstrated that patient survival is increased with a functioning pancreas graft [5–7]. The differentiating factor for these patients appears to be the time that they have to spend on a waiting list. In a UNOS/OPTN/IPTR registry analysis [1], survival curves on the waiting lists for SPK and PAK patients appeared to diverge further from the second year onwards. This has become more evident since many centres have implemented a policy of promoting LDKT prior to pancreas transplantation, particularly for those who have spent a long time on the waiting list.

LDKT followed by deceased-donor pancreas transplantation poses an appealing alternative to SPK. In the USA, the median waiting list time for an SPK is over 20 months [2]. When available, LDKT can be performed pre-emptively, avoiding dialysis or being performed with a short dialysis vintage, and thereafter patients can be maintained on the waiting list for a pancreas transplant. The advantages, in addition to reducing exposure to

uraemia, are a potential increase of standard-criteria donors in the deceased kidney donor pool and the optimization of the pancreas used for transplantation, avoiding conflicts with kidney allocation systems [8].

Results for PAK transplantation are most often analysed 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 the number LDKT procedures being performed followed by living-donor pancreas transplantation (PAldK) as an alternative to SPK, which might be explained by different experiences of the different centres somehow differing from those reflected by the registries. Herein, we report the outcomes of PAldK transplants from a large-volume centre in the current immunosuppression era.

MATERIALS AND METHODS

Patient population

Kidney and pancreas transplant was indicated to DM1 patients (C-peptide <1.0 ng/mL) with end-stage renal disease stages 4–5d (glomerular filtration rate <20 mL/min/1.73 m^2). Pre-transplant workup included biochemical and haematological parameters, cardiologic evaluation and a computed tomography scan of the splanchnic and iliac vessels. Immunological workup included complement-dependent cytotoxicity panel reactive antibodies (PRAs) for patients with low immunological risk (absence of previous blood transfusions or solid organ transplantation). Solid-phase Luminex® screening was performed for those with previous sensitization episodes, and solid-phase single-bead antigen analysis was performed in the presence of positive class I and/or II Luminex® screening.

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

Patients with a functioning kidney graft from a previous deceased-donor transplant (either kidney transplant alone or a previous SPK with pancreas graft failure), who received a pancreas transplant (pancreas transplantation after deceased-donor kidney transplantation, 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 performed at our centre from 1 January 2007 until 31 December 2015, including SPK, PAldK and PAddK recipients. Two patients received a pancreas transplant alone and were excluded from the analysis. Data were collected until 31 December 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 immunological information. Patient survival was defined as the 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 pancreas graft removal, C-peptide <1 ng/mL, total daily insulin need >0.5 U/kg or death, and for the kidney was defined as a return to dialysis, re-transplantation or death.

Immunosuppression

Induction therapy was used in all patients. In SPK patients, anti-interleukin-2 monoclonal antibody (basiliximab) 20 mg at Day 0 and Day 4 was used as standard therapy until July 2013, and thereafter replaced by rabbit anti-human lymphocyte polyclonal antibodies (either Thymoglobulin® 1.25 mg/kg/day or ATG® 2.5 mg/kg/day) for 4 consecutive days. In PAK patients, either PAldK or PAddK, these doses were extended to 7 consecutive days.

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

Acute rejection

Pancreas acute rejection was diagnosed based on clinical criteria: (i) acute elevation of pancreatic enzymes in the absence of other probable causes and (ii) 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 500 mg for 3 consecutive days, and grade II–III treated additionally with T-cell-depleting antibodies (either thymoglobulin® 1.25 mg/kg/day or ATG® 2.5 mg/kg/day) for 7 consecutive days. Antibody-mediated rejections (ABMRs) were treated with two doses of anti-CD20 monoclonal antibody (rituximab) 375 mg/m^2, plasma exchange (five sessions) and intravenous immunoglobulins 0.5 mg/kg.

Rejections diagnosed based on clinical criteria were treated with methylprednisolone 500 mg for 3 consecutive days. In the absence of improvement, corticoresistant rejection was presumed and patients were additionally treated 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 means $\pm$ standard deviations, and non-parametric as medians [interquartile ranges (IQRs)], and the corresponding tests used (t-test, ANOVA, Kruskal–Wallis). The Kaplan–Meier

test was used to estimate unadjusted patient and graft survival and compared using a log-rank test. A Cox proportional regression was performed to estimate graft hazards. A multivariate logistic regression model was designed to estimate the odds ratio (OR) for acute rejection. Statistical analysis was performed using SPSS (IBM, USA) software, with all tests two-tailed and significance considered if $P < 0.05$.

RESULTS

Demographics

A total of 185 pancreas transplantations were performed in 174 patients during the study period. Of these, 139 were SPKs, 18 PAldKs and 28 PAddKs. Both PAK transplantation groups had shorter waiting list times prior to pancreas transplantation, a shorter dialysis vintage and a lower prevalence of patients on peritoneal dialysis ($P < 0.05$) (Table 1). All other recipient- and donor-related demographic data, including sensitization prior to pancreas transplantation and the number of HLA mismatches (Table 1), were similar between the three groups.

Pancreas after LDKT

Eighteen pancreas transplants were performed to 15 recipients of LDKT [two ABO incompatible (ABOi), one paired kidney exchange programme]. Recipients were mostly from blood group O (61%) and often received a kidney transplant pre-emptively (33%), while the remainder had a median of only 11 months on haemodialysis (minimum 1; maximum 38). Donors were most frequently genetically related to recipients: either parents (39%) or siblings (28%). Patients were included on 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 LDKT. Three patients received a second pancreas transplant (two had lost the first graft due to thrombosis <48 h post-transplant, and a third due to chronic rejection 6.4 months post-transplant). Three patients died during follow-up (17%): one due to gastrointestinal bleeding, one due to infection and one with sudden death. All cases occurred at least 4 years after transplantation. Two of these patients had received pancreas re-transplantation.

Patient survival

Overall patient survival at 12, 36 and 60 months was 98, 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 $P > 0.05$) patients, even though there was a tendency toward inferior survival in PAldK [OR 3.75, 95% confidence interval (CI) 0.99–14.2, $P = 0.52$] patients when compared with the SPK group (Figure 1A).

Kidney graft survival

Overall kidney graft survival (death-censored) at 12, 36 and 60 months was 98, 97 and 96%, respectively, with similar results between all groups (Figure 1B). 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-censored) at 12, 36 and 60 months was 86, 79 and 75%, respectively. Surgical complications were the main causes of graft failure (42% of all failures). Excluding graft failure within the first 90 days, pancreas survival for the same period 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 patients when compared with SPK transplant (log-rank $P = 0.0001$ and $P = 0.031$, respectively; Figure 1C). When only those with a functioning graft on day 90 post-transplantation were included, survival for PAddK patients was similar to that of SPK patients (log-rank $P = 0.58$), but superior to PAldK patients (log-rank $P < 0.000$) (Figure 1D). Considering re-transplantations as a separate group, pancreas survival for PAldK and re-transplantation patients, but not those who underwent PAddK, were inferior to the SPK group (log-rank $P = 0.010$, 0.003 and 0.983, respectively; Supplementary data, Figure S1A). In a binary logistic regression for graft failure risk, and using SPK as a reference, PAldK patients presented an odds ratio (OR) of 3.58 (95% CI 1.59–8.08, $P = 0.002$) and PAddK patients a OR of 2.30 (95% CI 1.06–5.00, $P = 0.035$).

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 independently associated with graft failure. Pancreas transplant category did not reach statistical significance ($P = 0.15$).

We further investigated the association between PAldK and graft failure. First, we eliminated all variables deemed insignificant ($P > 0.20$) from the previous model. Recipient female gender (HR 2.45, 95% CI 1.28–4.71, $P = 0.007$) was the only risk factor associated with graft failure (data not shown). Pancreas transplant category was not significant ($P = 0.21$). Then, and since we had identified graft survival to be inferior in PAldK patients even when only those with a functioning graft at day 90 following transplantation were included, 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. Once again, pancreas transplant category did not reach statistical significance ($P = 0.70$).

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 ($P > 0.05$).

For the 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

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* (%)				0.04
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	0.00
Pancreas waiting list vintage (months)	19.3 ± 12.9	5.4 ± 2.7	3.9 ± 4.1	0.00
Re-transplantations, *n* (% of total)	1 (0.07)	3 (17)	21 (75)	0.00
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/m^2)	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	0.045
Cold ischaemia time, pancreas (h)	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				
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 (*n*)				
A+B		0.6 ± 0.7	0.6 ± 1.0	NS
DR		0.5 ± 0.6	0.6 ± 0.6	NS
Total		1.5 ± 1.5	1.8 ± 2.5	NS
Sensitization pre-pancreas transplant (%)[a]	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 (%)				0.00
Thymoglobulin	25.9	100	95.7	
Basiliximab	74.1	0	4.3	
Prednisone withdrawal (%)	30.2	0	3.6	0.00
Transplant vintage at withdrawal (months)	4.9 ± 0.8	0	5.0	

Data are presented as mean ± SD unless otherwise indicated.

[a]Sensitization pre-pancreas transplant, assumed as a PRA > 0% and/or a Luminex class I and/or class II positive.

CPR, cardiopulmonary arrest; CMV, cytomegalovirus; HD, hemodyalisis; PD, peritoneal dialysis; PDRI, pancreas donor risk index; NS, not significant ($P \geq 0.05$).

the first 12 months post-transplantation (78%; median 3.6 months). BPAR accounted for 75% of all acute rejection diagnoses in PAldK patients, while only up to 30 and 43% of diagnoses were made in the SPK and PAddK groups, respectively.

Pancreas graft rejection was significantly increased in PAldK (67%; 1.8 ± 1.4 episodes/graft) when compared with PAddK (25%) or SPK (32%) patients (Figure 2). These results were sustained even when pancreas re-transplantations were considered separately (Supplementary data, Figure S1B). The median times to first rejection episodes were 5.1 (2.3–17.6), 0.5 (0.3–2.8) and 6.2 (1.3–10.1) months for PAldK, PAddK and SPK patients, respectively ($P = 0.14$).

On a multivariate logistic regression model including known risk factors for pancreas rejection, such as pre-transplant

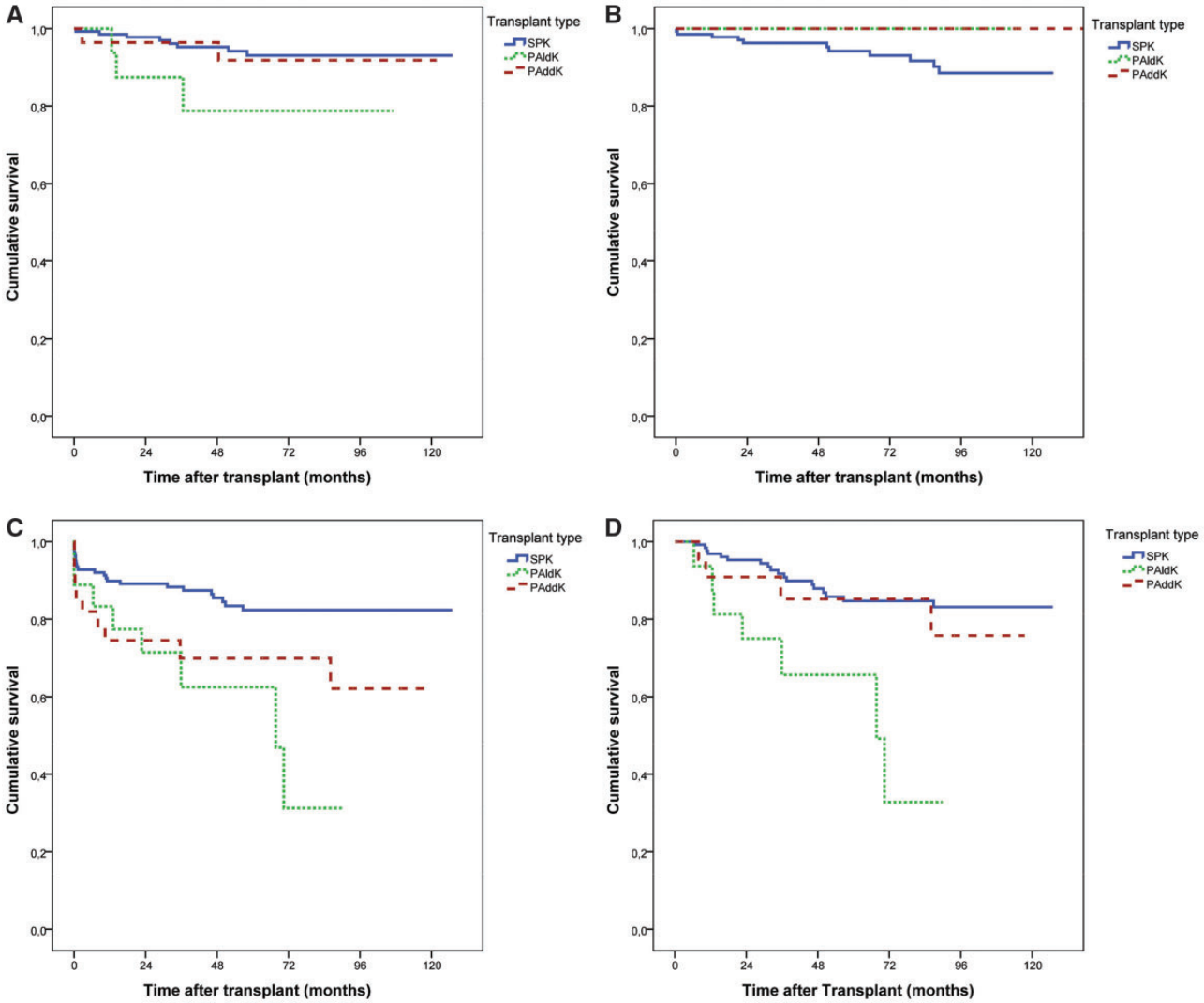

FIGURE 1: Kaplan–Meier estimate survivals by pancreas transplant modality for: (**A**) patients; (**B**) kidney grafts; (**C**) pancreas grafts; (**D**) pancreas grafts (if functioning at day 90 post-transplantation).

sensitization, donor age and body mass index (BMI), pancreas CIT, the induction of immunosuppression and mismatches between pancreas donors and recipients, PAldK (HR 6.82 95% CI 1.51–30.70, P = 0.012) was the only factor associated with graft rejection (Table 4). No association was found between donor–recipient HLA mismatches and graft rejection, either as a continuous variable or as a categorical one (P > 0.05) (Supplementary data, Figure S2A).

In an attempt to clarify this unexpected result, we analysed the effect of HLA mismatches on graft rejection per transplant category. No differences were found for any group (Supplementary data, Figure S2B–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 PAldK and PAddK patients were grouped into a single category (PAK) due to the small sample size. There was a tendency toward an increased incidence of rejection in those who had at least one HLA incompatibility between kidney and pancreas donors (0 versus 1–6; 58 versus 29%, P = 0.075) (Supplementary data, Figure S3A), though it was not associated with worse graft survival (Supplementary data, Figure S3B; P > 0.05). Finally, we evaluated whether repeated HLA compatibilities between kidney donors and recipients could influence pancreas graft rejection risk, based on the assumption that increased compatibilities would decrease the total alloantigen mass, possibly leading to an augmented immune response when the recipient was exposed to pancreas graft alloantigens. As expected, the number of HLA compatibilities between kidney donors and recipients was superior in PAldK recipients (3.4 ± 1.5 versus 5.0 ± 1.0 in PAddK; P = 0.001). Nonetheless, rejection risk was similar (P = 0.274) for those recipients sharing at least one haplotype, compared with those with two or fewer HLA compatibilities.

DISCUSSION

In this study, we evaluate the outcomes from three different pancreas transplant categories from a single centre. PAldK presented similar patient survival compared to SPK and PAlddK transplantation, but worse pancreas graft survival (compared to

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

	HR	95% CI		P
		Inferior	Superior	
Recipient age (years)	1.013	0.936	1.097	0.745
Recipient gender (female)	6.274	2.062	19.090	0.001
Recipient blood group				0.385
Group O	1.000	–	–	–
Group A	2.641	0.773	9.021	0.121
Group B	0.910	0.065	12.812	0.945
Group AB	0.000	0.000		0.981
Diabetes vintage (months)	1.045	0.981	1.113	0.174
Waiting list time (months)	0.983	0.924	1.046	0.598
Previous pancreas transplant (*n*)	4.997	0.676	36.950	0.115
Transplant category				0.149
SPK (reference)	1.000	–	–	–
PAldK	2.470	0.265	22.999	0.427
PAddK	0.264	0.017	3.994	0.337
Donor/recipient CMV status				0.128
−/− (reference)	1.000	–	–	–
−/+	0.186	0.037	0.931	0.041
+/−	0.675	0.126	3.608	0.646
+/+	0.374	0.066	2.104	0.264
Donor age (years)	1.009	0.953	1.068	0.755
Donor gender (female)	0.890	0.321	2.463	0.822
Donor BMI (kg/m^2)	1.070	0.906	1.263	0.428
Donor COD				0.081
Cerebrovascular disease (reference)	1.000			
Trauma	5.030	1.454	17.404	0.011
Cerebral anoxia	3.780	0.482	29.629	0.206
Other	0.717	0.056	9.106	0.797
Pancreas cold ischaemia time (h)	1.023	0.859	1.217	0.801
Sensitized pre-transplant (yes)	1.148	0.429	3.070	0.783
HLA mismatches (*n*)	1.084	0.705	1.667	0.713
Induction treatment (basiliximab)	0.577	0.124	2.675	0.482
Prednisone maintenance (yes)	1.298	0.402	4.192	0.663
Pancreas rejection (yes)	0.438	0.136	1.412	0.167
Kidney rejection (yes)	1.175	0.316	4.379	0.810
Year of transplantation				0.487
2007	1.000			
2008	0.385	0.065	2.283	0.29
2009	0.914	0.169	4.937	0.92
2010	0.550	0.079	3.817	0.55
2011	1.531	0.265	8.864	0.63
2012	2.036	0.260	15.952	0.50
2013	3.333	0.452	24.555	0.24
2014	0.660	0.062	6.989	0.73
2015	0.177	0.011	2.898	0.22

CMV, cytomegalovirus; COD, cause of death.

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	0.57
Recipient gender (female), *n* (%)	45 (63.4)	26 (36.6)	0.38
Diabetes vintage (years)	27.5 ± 8.6	28.5 ± 8.6	0.43
Dialysis pre-transplant, *n* (%)			0.16
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	0.006
Time on waiting list (months)	17.0 ± 13.9	13.0 ± 10.9	0.045
Donor age (years)	33.0 ± 10.7	32.0 ± 10.4	0.54
Donor gender (male), *n* (%)	68 (64.2)	38 (35.8)	0.72
Donor BMI (kg/m^2)	23.9 ± 3.0	23.7 ± 2.8	0.75
Donor COD, *n* (%)			0.4
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	0.70
Cold ischaemia time (h)	10.7 ± 2.8	11.5 ± 3.2	0.06
Sensitized pre-transplant, *n* (%)			0.3
No	91 (67.9)	43 (32.1)	
Yes	30 (58.8)	21 (41.2)	
HLA mismatches[a]	4.5 ± 1.3	4.1 ± 1.5	0.32
HLA mismatches[b], *n* (%)			0.78
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[c], *n* (%)			0.002
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			0.066
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, *n* (%)			0.43
Thymoglobulin	52 (68.4)	24 (31.6)	
Basiliximab	65 (62.5)	39 (37.5)	
Prednisone withdrawal, *n* (%)			0.004
No	85 (59.9)	57 (40.1)	
Yes	36 (83.7)	7 (16.3)	

Data are presented as mean ± SD unless otherwise indicated.
[a]HLA mismatches as a continuous variable.
[b]HLA mismatches as categorical variable.
[c]Rejection group data represented as rejection episodes during the first 12 months post-transplant/total number of rejection episodes during follow-up.
COD, cause of death; CVD, cardiovascular disease; PDRI, pancreas donor risk index.

SPK patients) and a significant increase in the incidence of acute rejection.

Pancreas graft survival has historically been inferior for PAK when compared with SPK transplantation [2, 11]. Significant improvements have been observed following the introduction of T-cell-depleting antibodies to immunosuppression induction protocols [12], and with reductions in surgical complications and early graft loss [7]. Despite this improvement, the most recent United Network for Organ Sharing (UNOS) and International Pancreas Transplant Registry (IPTR) registry data analysis still reports an inferior 1- and 3-years' of pancreas survival for PAK compared with SPK patients (84.4 versus 89.1% and 75.4 versus 82.2%, respectively). In this report, both PAK groups (PAldK and PAddK) are analysed together, and no reference is made to differences in the outcomes between the two groups. Of relevance, 80% of all of the PAK patients included

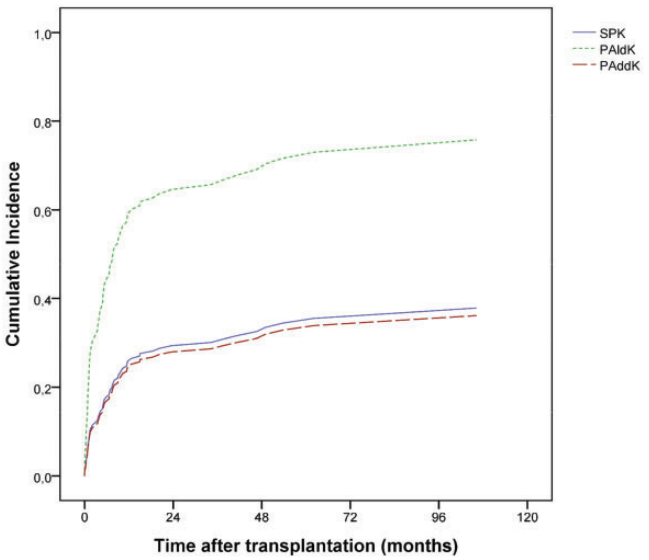

FIGURE 2: Pancreas graft rejection incidence according to pancreas transplant category.

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

	HR	95% CI		P
		Lower	Upper	
Sensitized pre-transplant (yes)	1.394	0.616	3.156	0.425
Donor age (years)	0.992	0.955	1.029	0.657
Donor BMI (kg/m^2)	0.945	0.823	1.084	0.418
Cold ischaemia time (h)	1.037	0.918	1.172	0.558
HLA mismatches (*n*)	1.206	0.874	1.665	0.255
Induction immunosuppression (basiliximab)	2.742	0.979	7.682	0.055
Transplant category				0.041
SPK (reference)	1.000			
PAldK	6.821	1.515	30.701	0.012
PAddK	1.461	0.345	6.181	0.606
HLA MM, A-B				0.61
0	1.000			
1	0.000	0.0000		0.999
2	0.316	0.033	3.004	0.316
3	0.506	0.057	4.468	0.540
4	0.710	0.093	5.429	0.741
HLA MM, DR				0.672
0	1.000			
1	1.370		6.236	0.684
2	0.729		3.132	0.671

MM, mismatches; SPK, simultaneous pancreas-kidney transplantation; PAldK, pancreas after living-donor kidney transplantation; PAddK, pancreas after deceased-donor kidney transplantation.

were PAldK recipients, and therefore the results most significantly represent those from this group. As for PAddK patients, the largest published series to date also comes from an analysis of the UNOS database, including only recipients of pancreas re-transplantations with a functioning kidney graft, and reports decreased graft survival compared with SPK patients [13]. Both these reports are in accordance with the results found from the analysis of our cohort. Nonetheless, we have found long-term PAddK graft survival to be similar to that of SPK patients, while those who underwent PAldK had 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 in the multivariate analysis.

The incidence of pancreas graft rejection was another outcome that was expected to be higher in PAK compared with SPK patients [2, 7, 14]. Uraemia-induced immunosuppression and the transplantation of a larger allogeneic mass in dual transplantation have both been proposed as factors that may be responsible for the better outcomes in SPK patients. Unexpected was the increased rejection incidence and decreased rejection-free graft survival in PAldK compared with PAddK patients. Baseline immunological factors were assumed to be 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 the 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 four to six 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 note, PAK transplantations were not included in any of these analyses. Also, in the UNOS/IPTR registry analysis, mismatches in DR were associated with a risk of immunological graft loss in SPK, but not in PAK patients. In our cohort, HLA mismatches could not explain the increased incidence of AR in the PAldK group. In this group, neither was the total number of HLA mismatches 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 the first donor's HLA incompatibilities confers a poorer graft prognosis [20]. In fact, some centres 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 relationship with 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, either as a continuous or as a categorical variable (data not shown). This remained true for repeated incompatibilities on the DR loci between pancreas donors and recipients, 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 small proportion 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, and therefore cannot explain the increased incidence of AR in the PAldK group. Moreover, prednisone withdrawal, controversially believed by some to be associated with acute rejection, was not performed in either of the PAK patient groups.

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

CONCLUSION

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

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

AUTHORS' CONTRIBUTIONS

P.V.-A. and J.F. were responsible for data collection and manuscript preparation. I.R. and D.P. were responsible for data collection and manuscript revision. E.d.S.-A. was responsible for data collection. J.R. was responsible for data collection and statistical analysis. E.E., J.C.G.-V., J.M.C., F.O. and F.D. were responsible for manuscript revision. M.J.R. was responsible for manuscript preparation and revision.

CONFLICT OF INTEREST STATEMENT

None declared.

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