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ORIGINAL ARTICLE

Association of human leukocyte antigen mismatches between donor-recipient and donor-donor in pancreas after kidney transplant recipients

Sandesh Parajuli[1], Dixon B. Kaufman[2], Arjang Djamali[1,2], Bridget M. Welch[2], Hans W. Sollinger[2], Didier A. Mandelbrot[1] & Jon S. Odorico[2]

1 Division of Nephrology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
2 Division of Transplantation, Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Correspondence
Sandesh Parajuli MBBS, 4175 MFCB, 1685 Highland Ave, Madison, WI 53705, USA.
Tel.: 608-265-0152;
fax: 6082626743;
e-mail: sparajuli@medicine.wisc.edu

SUMMARY

The effects of HLA mismatching on pancreas outcomes among pancreas after kidney (PAK) recipients are undefined. Outcomes might potentially differ depending on whether there is a mismatch between pancreas donor and recipient (PD-R) or pancreas donor and kidney donor(PD-KD). All primary PAK at our centre were included in this study. Patients were divided into two groups based on the degree of HLA mismatching: low (L-MM) as 0–4 and high (H-MM) as 5–6. We analysed all ($N = 73$) PAK for PD-R mismatch and the subset of PAK for PD-KD mismatch ($N = 71$). Comparing PD-R L-MM ($n = 39$) and H-MM ($n = 34$) PAKs, we observed no difference in the rate of pancreas graft failure. There was also no difference in the rate of rejection (L-MM 33% vs. H-MM 41%) or the severity of rejection. However, we observed a significantly ($P < 0.01$) shorter time to acute pancreas rejection in the H-MM group (6.8 ± 8.7 mo) versus the L-MM cohort (29.0 ± 36.2 mo) ($P < 0.001$). Similar to the PD-R mismatched cohort, we did not observe a detrimental effect of HLA mismatching on graft outcomes in the PD-KD cohort; time to rejection was again shorter in the H-MM subset. In this study, we found no impact of HLA mismatch on either pancreas graft survival or rejection rates, though rejection occurred earlier in high mismatched PAK transplants.

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Key words
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Background

Human leukocyte antigens (HLA) are encoded by the human major histocompatibility complex in a highly polymorphic region on the short arm of human chromosome 6 [1]. Anti-HLA antibodies pre or post-transplant in solid organ transplants are associated with inferior graft outcomes [2]. Similarly, a higher degree of HLA mismatch between organ donor and recipients is associated with inferior graft function, inferior graft and patient survival and increased risk of sensitization [3]. Long-term graft survival of deceased donor kidney-only transplant recipients with no HLA -A, -B and -DR mismatch was approximately 17–20% better than for fully

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mismatched grafts, with a stepwise reduction in survival with each additional mismatch [4,5].

However, the ongoing importance of HLA mismatches on transplant outcomes in the era of more potent immunosuppression, and improved perioperative care and surgical technique, remains debatable [3]. In one large registry study, utilizing Australia and New Zealand Dialysis and Transplant Registry data of kidney transplant recipients transplanted between 1998 and 2009, higher degrees of HLA mismatch were associated with inferior outcomes irrespective of immunosuppression or transplant era [6]. Even in more recent studies, a detrimental effect of a higher degree of HLA mismatch has been identified [7–9].

In the past, patient survival among pancreas after kidney transplant (PAK) recipients have been reported to be inferior to patient survival after simultaneous pancreas-kidney transplant (SPK) [10]. However, recently Fridell *et al*. [11] reported, compared with uremic diabetic waitlist patients, SPK and PAK recipients showed similar overall patient survival. Not only that, PAK recipients are in a unique situation, because of the immunological risk too. On one hand, these recipients have been immunosuppressed for months to years before their pancreas transplant. On the other hand, they will be exposed to new HLAs from the pancreas donor. Pancreas outcomes among PAK recipients based on the HLA mismatch between pancreas donor and the recipient (PD-R), or pancreas donor and kidney donor (PD-KD), also called shared mismatch [12] are unknown. In this study, we share our experience working with primary PAK recipients based on the HLA mismatch in two different contexts between PD-R and PD-KD.

Study population and methods

This was a single-centre study of all primary PAK recipients transplanted at the University of Wiscosin-Madison. All solitary pancreas were transplanted between 01/1997 and 06/2019 at the University of Wiscosin-Madison, while kidneys were transplanted any time before pancreas transplant at the same university or in a different transplant centre. All data were collected prospectively. To overcome the bias of multiple HLA exposures, only primary kidney followed by pancreas transplants were included. Recipients age less than 18 years at the time of kidney transplant were excluded. Patients were divided into two groups based on the degree of HLA mismatch: low mismatch (L-MM) as 0–4 and high mismatch (H-MM) as 5–6, for HLA -A, -B and –DR loci. We chose 0–4 as L-MM, as there were very few recipients with 0, 1 or 2 mismatches as most of them had 3 or more mismatches. We further looked at the outcomes stratifying HLA mismatch 0–3 versus 4–6. We looked at outcomes in two different HLA mismatch contexts based on the HLA mismatch of PD-R and PD-KD. We analysed all PAK for PD-R mismatch during the study period. However, for PD-KD mismatch, the subset of PAKs in whom both kidney and pancreas were transplanted at the University of Wiscosin-Madison were included, along with the another centre if HLA data were available. HLA data among recipients who had a kidney transplant at another centre or at the University of Wiscosin-Madison before 1994 were abstracted utilizing United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) file. At no time during this series or currently at our programme, was there a protocolized minimum overall or locus-specific HLA match required for PAK transplants.

At our centre, we continue to follow our PAK transplant recipients until patient death. Most of the recipients with kidney transplants performed at other centres, transfer their kidney transplant care to our centre after pancreas transplantation. Our centre has maintained a comprehensive database collecting prospective data on all intra-abdominal solid organ transplant recipients transplanted since 1994.

Pancreas graft outcomes including survival and rejection rates were of interest and determined over the entire period. Patients were followed until graft failure or death, or until the end of data analysis on 11/30/2020. Also, to overcome possible era effects, we looked at pancreas outcomes based on whether the kidney was transplanted before 1997 versus those transplanted in or after 1997. We chose 1997, as all pancreas grafts in this cohort were transplanted in or after 1997, and also exclusively all of them were maintained on the tacrolimus and mycophenolate-based maintenance immunosuppressive regimen. This study was approved by the University of Wiscosin-Madison Institutional Review Board.

Immunosuppression

Patients undergoing pancreas transplant received induction immunosuppression with a depleting agent (antithymocyte globulin or alemtuzumab) or nondepleting agent (basiliximab/daclizumab) based on immunological risk factors and practices have evolved with time. Recently, all patients with pre-transplant donor-specific antibody (DSA), recipients of PAK, secondary SPK or

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previous pancreas graft failure because of rejection or planned for early steroid withdrawal were more likely to receive depleting induction agent, previously described [13].

Patients were typically maintained on a triple immunosuppressive regimen, with a calcineurin inhibitor (tacrolimus), antiproliferative agent (mycophenolate mofetil or mycophenolic acid) and steroids. Doses and drug levels were individually adjusted based on the patient's clinical condition, including infection, malignancy and rejection. Recipients of PAK were maintained at a higher tacrolimus trough goal of 9 to 12 ng/ml for the entire post-transplant period unless there were infections or malignancy. The initial mycophenolate sodium dose was 720 mg 3 times daily for 1 month, then twice daily after that. Prednisone was tapered to 10 mg daily by 8 weeks post-transplant, with a further taper to 5 mg as determined by the managing provider [13].

Surgical technique

The technique was constant throughout the study period. All pancreas transplants were preserved with the University of Wisconsin solution. There was enteric drainage of exocrine secretions and systemic venous drainage of endocrine secretions. No roux-en-Y limb was performed. PAK was performed via a midline incision and in some cases was implanted ipsilaterally above the kidney on the right side and in some cases contralaterally on the left side [14,15]. The vast majority of pancreas transplants were performed by two surgeons Dr. Hans Sollinger and Jon Odorioc.

Anti-HLA antibody screening by solid-phase fluorescent beads

Donor-specific HLA Class I and II antibodies were detected pre and post-transplant using Luminex single antigen beads (One Lambda, Canoga Park, CA, USA) performed according to the manufacturer's instructions with the single modification in which a reduced volume of beads (3 vs. 5 μl) was used. Antibodies were identified using multiple criteria including patterns of epitope reactivity, mean fluorescent intensity (MFI) value, specific bead behaviours and assay background, as described previously [13,16]. The strength of DSA was represented as the sum of the mean fluorescence intensity value (MFIsum) of all DSA. Patients diagnosed with denovo DSA (dnDSA) had no detectable level of that DSA either pretransplant or post-transplant when tested before the diagnosis of dnDSA. dnDSA was monitored against all alleles including Cw, DQ and DP. Since 2014, routine post-transplant monitoring of DSA was performed on all transplant recipients at 6 and 12 months, and annually thereafter. The yearly DSA monitoring included patients transplanted before 2014 during their annual follow-up visit [13].

Pancreas allograft biopsy

The most common indication for pancreas graft biopsy was an unexplained rise in pancreatic enzymes. The practice patterns for the indication of pancreas biopsy have been consistent throughout the study period and were not guided by the degree of HLA mismatches. As previously described, our approach to the patient with elevated enzymes included history and physical examination (if possible), fasting C-peptide, HbA1C, DSA and an imaging study, preferably a CT scan of the abdomen and pelvis with IV and oral contrast. In our practice, if possible, we perform an ultrasound-guided biopsy with an 18-gauge automatic biopsy device [17,18]. Most of the biopsies were performed for cause, mainly for an unexplained rise in the pancreatic enzymes. However, recently we have implemented a practice to monitor DSA and perform protocol pancreas graft biopsy for dnDSA if no contraindication to the biopsy.

Pancreas rejection treatment

Treatment of pancreas rejection was based on the type and severity of rejection and was graded by the Banff criteria [19]. Briefly, acute cellular rejection (ACR) was treated with IV steroid pulse with or without antithymocyte globulin 6–12 mg/kg in 4–10 divided doses, while mixed rejection was treated with steroids, antithymocyte globulin, intravenous immunoglobulin (IVIG) and plasmapheresis. Antibody-mediated rejection (AMR) was treated with steroids, IVIG and plasmapheresis.

Statistical analysis

Continuous data were compared using Student's *t*-test or the Wilcoxon rank-sum test, when appropriate, while categorical data were analysed using Fisher's exact test or the chi-square test, when appropriate. Uncensored and death-censored graft failure was analysed using Kaplan–Meier analyses. Also, we analysed pancreas graft failure after excluding the pancreas grafts that failed

within 30 days of transplant. P values < 0.05 were considered statistically significant. Owing to the smaller number of events, risk factors associated with death-censored graft failure of pancreases were studied using multivariate Cox regression analyses in two different models. As total outcomes were also limited by the small size, only a few pertinent variables were looked into the multivariable analysis.

Results

Pancreas donor and recipient (PD-R) HLA mismatch cohort

A total of 73 PAK recipients fulfilled our selection criteria, 39 were in the L-MM group and 34 in the H-MM group (Table 1). Kidneys were transplanted between 1986 and 2018, and the pancreases were transplanted between 1997 and 2019. Among these pancreas donor and recipient (PD-R) mismatch cohort, no PAK recipients had 0 HLA mismatch, 2 had 1 HLA mismatch, 4 had 2 HLA mismatch, 12 had 3 HLA mismatch and 21 had 4 HLA mismatch in the L-MM group. In the H-MM group, 25 had 5 HLA mismatch and 9 had 6 HLA mismatch. There were no statistical differences in the baseline characteristics between the two groups. The mean HLA mismatch among the entire cohort was 4.23 ± 1.20 (Table 2). As expected, HLA mismatches against -A, -B or –DR were significantly higher in the H-MM group.

The mean post-pancreas transplant follow-up was similar between the groups, with 7.0 ± 6.1 years for the L-MM group and 6.8 ± 6.8 years for the H-MM group (P = 0.93) (Table 3). A total of 37 recipients underwent pancreas biopsy, 19 (49%) were in L-MM group and 18 (53%) (P = 0.72) in H-MM group. There were no major complications, graft losses or fistulas attributable to the biopsy. Outcomes including the number of recipients with dnDSA and strength of dnDSA were similar between the groups. There was also no difference in either the overall rate of rejection throughout the entire period [L-MM (13, 33.3%) vs. H-MM (14, 41.2%)] or the severity of rejection. We observed a statistically significantly earlier time to acute pancreas rejection in the H-MM group (6.8 ± 8.7 mo) versus the L-MM cohort (29.0 ± 36.2 mo) (P < 0.001). Also, one year rate of rejection, although not statistically significant, was higher in the H-MM group 32% versus L-MM group 15% (P = 0.08). When stratified according to the type of pancreas transplant induction agent, we observed the overall acute rejection rates to be similar: L-MM (depletional) 33.3% (6/18) versus L-MM (nondepletional agent) 33.3% (7/21) (P = 1.0); H-MM (depletional) 41.2% (7/17) versus H-MM (nondepletional agent) 41.2% (7/17) (P = 1.0). Also, we observed the uncensored graft failure rates to be similar: L-MM (depletional) 52% (13/25) versus L-MM (nondepletional agent) 48% (12/25) (P = 0.33); H-MM (depletional) 47.6% (10/21) versus H-MM (nondepletional agent) 52.3% (11/21) (P = 0.75).

Five (12.8%) in the L-MM group and 1 (2.9%) in the H-MM group had early pancreas graft failure within 30 days of transplant (P = 0.13). The total pancreas graft failure at last follow-up or death censored graft failure (DCGF) were also similar between the groups and was further confirmed by Kaplan–Meier analysis (Fig. 1), even after removing grafts that failed within 30 days of transplant (Fig. 2). When looking at the outcomes stratified based on the HLA mismatch of 0–3 versus 4–6 by Kaplan–Meier analysis, there was no difference in graft survival (Figure S1), even after removing grafts that failed within 30 days of transplant (Figure S2). Similarly, when

Table 1. Baseline demographics of pancreas donor-recipient HLA mismatch cohort.

Variables	All (n = 73)	Low Mismatch (n = 39)	High Mismatch (n = 34)	P
Age (years ± SD)	45.7 ± 8.3	46. 3 ± 6.9	45.0 ± 9.6	0.52
Male (%)	46 (63)	26 (67)	20 (59)	0.49
White (%)	71 (97)	38 (97)	33 (97)	0.92
Induction				
Basiliximab/daclizumab (%)	38 (52)	21 (54)	17 (50)	0.22
Antithymocyte globulin(%)	20 (27)	9 (23)	11 (32)	
Alemtuzumab (%)	15 (21)	9 (23)	6 (18)	
Types of donor: DBD (%)	73 (100)	39 (100)	34 (100)	1
Mean wait time (days)	179.3 ± 205.8	156.9 ± 174.9	205.0 ± 236.5	0.32
Interval between kidney and pancreas transplant (mo)	45.2 ± 42.2	43.2 ± 47.1	47.6 ± 36.3	0.66

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Table 2. Pancreas donor-recipient HLA mismatch.

Variables	All (n = 73)	Low mismatch (n = 39)	High mismatch (n = 34)	P
Mean HLA Mismatch (of 6)	4.23 ± 1.20	3.33 ± 0.87	5.26 ± 0.45	<0.001
A Mismatch				
0 (%)	10 (14)	10 (26)	0 (0)	<0.001
1 (%)	39 (53)	25 (64)	14 (41)	
2 (%)	24 (32)	4 (10)	20 (59)	
B Mismatch				
0 (%)	4 (5)	4 (10)	0 (0)	<0.001
1 (%)	24 (33)	19 (49)	5 (15)	
2 (%)	45 (62)	16 (41)	29 (85)	
DR Mismatch				
0 (%)	4 (5)	4 (10)	0 (0)	<0.001
1 (%)	30 (41)	24 (62)	6 (18)	
2 (%)	39 (53)	11 (28)	28 (82)	

Table 3. Pancreas outcomes based on pancreas donor-recipient HLA mismatch.

Variables	All (n = 73)	Low mismatch (39)	High mismatch (34)	P
Mean post- pancreas transplant follow up (years)	6.9 ± 6.4	7.0 ± 6.1	6.8 ± 6.8	0.93
Development of dnDSA (%)	7 (10)	4 (10)	3 (9)	0.97
Mean interval from transplant to dnDSA (yrs)	13.4 ± 3.3	13.3 ± 4.1	13.7 ± 2.7	0.63
Types of dnDSA	A23 n = 1 A2, B8, B38 n = 1 B81 n = 1 Cw7 n = 2 DR53 n = 1 DQ 7 n = 1	B81 n = 1 Cw7 n = 1 DR53 n = 1 DQ 7 n = 1	A23 n = 1 A2, B8, B38 n = 1 Cw7 n = 1	
Sum MFI of dnDSA	2105 ± 1369	2268 ± 1452	1888 ± 1529	0.87
Acute rejection(%)	27 (37)	13 (33)	14 (41)	0.43
Acute rejection within 1-year post transplant (%)	17 (23)	6 (15)	11 (32)	0.08
Interval from transplant to acute rejection (mo)	17.5 ± 27.7	29.0 ± 36.2	6.8 ± 8.7	<0.001
Types of acute rejection (%)				
Grade I	7 (10)	4 (10)	3 (9)	0.54
Grade II	11 (15)	4 (10)	7 (21)	
Grade III	7 (10)	3 (8)	4 (12)	
Grade IV	1 (1)	1 (3)	0 (0)	
Mixed	1 (1)	1 (3)	0 (0)	
Graft failure within 30 days of transplant	6 (8)	5 (13)	1 (3)	0.13
1 year pancreas graft survival (%)	59 (81)	31 (79)	28 (82)	0.76
Total number of pancreas graft failures at last follow up (%)	46 (63)	25 (64)	21 (62)	0.84
Death censored pancreas graft failures at last follow up (%)	27 (37)	18 (46)	9 (26)	0.08

looking at the outcomes stratified based on kidney transplant before or after 1997 by Kaplan–Meier analysis, there was also no difference in overall and death censored graft survival (Figure S3); after removing grafts that failed within 30 days of transplant graft survivals remained similar (Figure S4).

To address possible risk factors for pancreas DCGF, we performed a multivariable analysis using two different models (Table 4). None of the common risk factors evaluated in model 1, including HLA mismatch, rejection-free survival and nondepleting induction, were significantly associated with DCGF. Similarly, in model

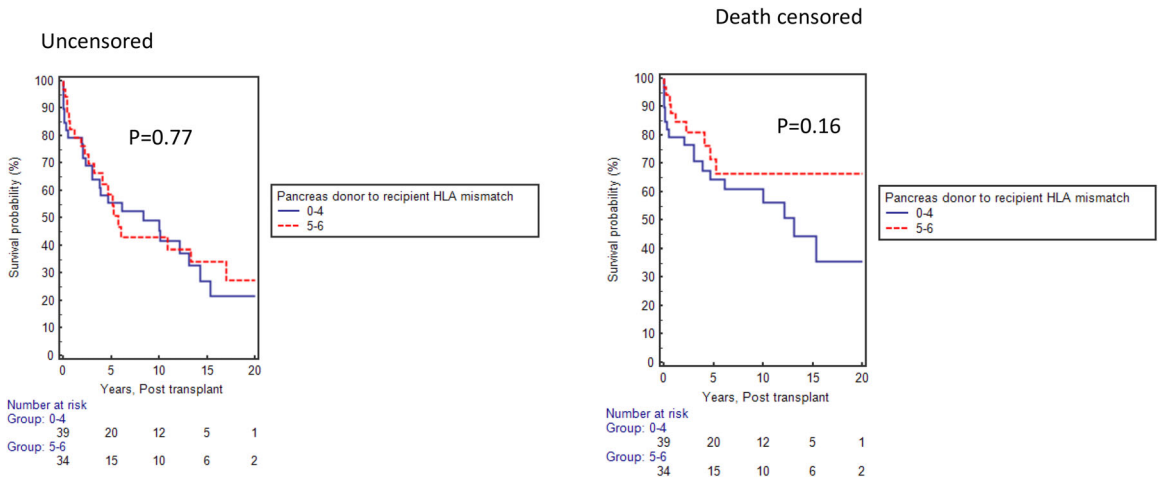

Figure 1 Uncensored and death censored pancreas graft survival among low-HLA mismatch and high-HLA mismatch PAK groups, based on pancreas donor and recipient HLA mismatch. (P = 0.77 and 0.16).

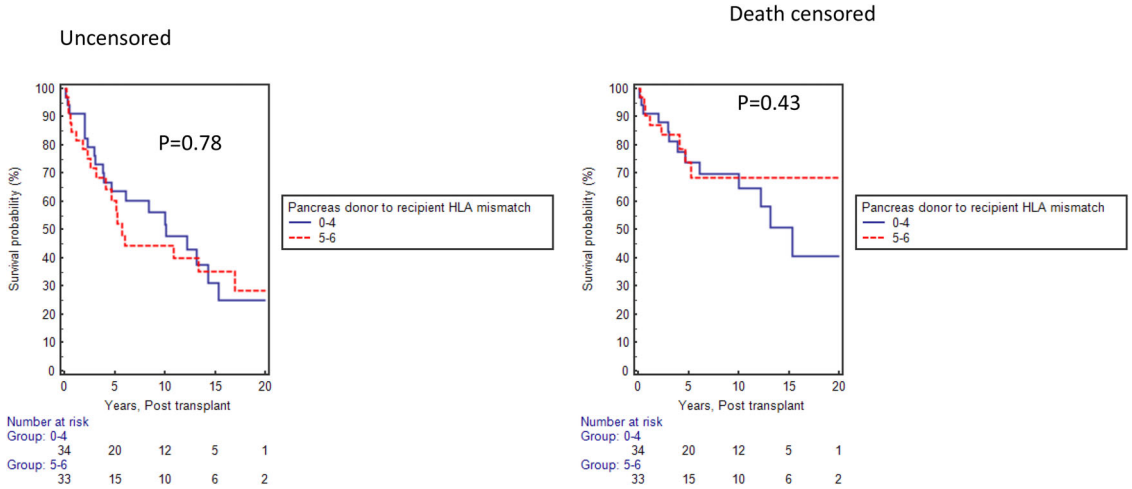

Figure 2 Uncensored and death censored pancreas graft survival, after removing grafts that failed within 30 days of transplant, among low-HLA mismatch and high-HLA mismatch PAK groups, based on pancreas donor and recipient HLA mismatch. (P = 0.78 and 0.43).

2, neither DR mismatch, interval from transplant to first rejection or interval between kidney and pancreas transplant were associated with DCGF.

Pancreas donor and kidney donor (PD-KD) HLA mismatch cohort

From the entire cohort of 73 PAK recipients, 71 were included for the PD-KD mismatch cohort. In 2 recipients, kidney HLA data were not available, as they had kidney transplants before the implementation of the STAR file. The baseline characteristics of these 71 patients at the time of their kidney and pancreas transplants are presented in Table 5. The mean interval between the two transplants was 41.7 ± 36.7 months. All kidneys were transplanted between 1986 and 2018, and pancreases were transplanted between 1997 and 2019. Forty-eight received a kidney from a living donor and the remaining 23 from the deceased donor. Among 48 living donor kidney recipients, 17 were from the HLA-matched siblings. The details of HLA mismatch are presented in Table 6, there was a significantly fewer degree of HLA mismatch between a kidney donor and recipient in the low mismatch group. The HLA mismatches between pancreas donors and recipients, and kidney donors and recipients are presented in Table 7.

The mean HLA mismatch among the entire cohort of pancreas donors and kidney donors (PD-KD) was 5.0 ± 1.1 (Table 7). As expected, overall mean or HLA PD-KD mismatches against -A, -B or –DR were

Table 4. Factors associated with pancreas death censored graft failure based on pancreas donor-recipient HLA mismatch.

	Risk factors for pancreas DCGF (multivariable analyses)			
	Variables	HR	95% CI	*P*
Model 1	HLA mismatch (per 1)	1.01	0.73–1.37	0.98
	Rejection free survival	0.67	0.26–1.55	0.32
	Non-depleting induction	1.51	0.68–3.37	0.31
Model 2	DR mismatch (per 1)	2.05	0.39–10.87	0.40
	B mismatch (per 1)	0.18	0.02–1.51	0.11
	Interval from pancreas transplant to first rejection	1.01	0.98–1.03	0.75
	Interval between kidney and pancreas transplant	1.01	0.99–1.03	0.35

Table 5. Baseline demographics of pancreas donor and kidney donor HLA mismatch cohort.

	Variables	All (*n* = 71)	Low mismatch (*n* = 24)	High mismatch (*n* = 47)	*P*
Pancreas data (*n* = 71)	Mean age (years)	45.7 ± 8.4	46.6 ± 7.6	45.2 ± 8.8	0.52
	Male (%)	46 (65)	14 (58)	32 (68)	0.42
	White (%)	69 (97)	24 (100)	45 (98)	0.31
	Induction				
	Basiliximab/daclizumab (%)	36 (51)	12 (50)	24 (51)	0.87
	Antithymocyte globulin(%)	20 (28)	6 (25)	14 (30)	
	Alemtuzumab (%)	15 (21)	6 (25)	9 (19)	
	Types of donor: DBD (%)	70 (99)	24 (100)	46 (98)	0.09
	Interval between kidney and pancreas transplant (mo)	41.7 ± 36.7	43.4 ± 43.6	40.8 ± 33.0	0.78
Kidney data (*n* = 71)	Mean age (years)	42.3 ± 9.1	43.0 ± 8.5	41.9 ± 9.5	0.65
	Types of donor (%)				
	Living	48 (68)	16 (67)	32 (68)	0.90
	Deceased	23 (32)	8 (33)	15 (32)	
	Induction (%)				
	Basiliximab	12 (17)	5 (21)	7 (15)	0.45
	Anti-thymocyte globulin	10 (14)	4 (17)	6 (13)	
	Alemtuzumab	5 (7)	1 (4)	4 (9)	
	OKT3	8 (11)	6 (25)	2 (4)	
	Other /unknown	36 (51)	8 (33)	28 (59)	

significantly higher in the H-MM group. There was 1 recipient with 0 HLA PD-KD mismatch, 0 PAK recipients had 1 or 2 PD-KD HLA mismatch, 6 had 3 HLA PD-KD mismatch and, 17 had 4 HLA PD-KD mismatch in the L-MM group. In the H-MM group, 25 had 5 HLA PD-KD mismatch and 22 had 6 HLA PD-KD mismatch. None of the baseline characteristics at the time of kidney or pancreas transplants were significantly different between the groups.

The mean post-pancreas transplant follow-up was similar between the groups, with 8.7 ± 6.3 years for the L-MM group and 6.0 ± 6.4 years for the H-MM group ($P = 0.10$) (Table 8). Outcomes, including the number of recipients with dnDSA and the MFI sum of dnDSA, were similar between the groups. There was also no difference in the overall rate of rejection throughout the entire period [L-MM (8, 33%) vs. H-MM (19, 41%)] or the severity of rejection. In contrast, we observed a statistically longer time to acute pancreas rejection in the L-MM group (33.9 ± 44.2 mo) than in the H-MM group (10.5 ± 13.4 mo) ($P < 0.001$). Also, one year rate of rejection, although not statistically significant was higher in the H-MM group 30% versus L-MM group 13% ($P = 0.11$). When stratified according to the type of pancreas transplant induction agent, we observed the overall acute rejection rates to be similar: L-MM (depletional) 50%(4/8) versus L-MM (nondepletional agent) 50% (4/8) ($P = 1.0$); H-MM (depletional) 47.4% (9/19) versus H-MM (nondepletional agent) 52.6% (10/19) ($P = 0.96$). Also, we observed the

Table 6. Kidney donor-recipient HLA mismatch.

	HLA Mismtach	All (n = 71)	Low mismatch (n = 24)	High mismatch (n = 47)	P
Kidney donor- kidney recipient	0	17 (24)	5 (21)	12 (26)	0.005
	1	5 (7)	1 (4)	4 (9)	
	2	11 (15)	5 (21)	6 (13)	
	3	15 (21)	11 (46)	4 (9)	
	4	8 (11)	1 (4)	7 (15)	
	5	7 (10)	0 (0)	7 (15)	
	6	8 (11)	1 (4)	7 (15)	

Table 7. HLA mismatch between pancreas donor-kidney donor and kidney donor-kidney recipient.

	Variables		All (n = 71)	Low mismatch (n = 24)	High mismatch (n = 47)	P
Pancreas donor- Kidney donor	Mean HLA Mismatch (of 6)		5 ± 1.1	3.6 ± 0.9	5.5 ± 0.5	<0.001
	A Mismatch (%)	0	1 (1)	1 (4)	0 (0)	<0.001
		1	32 (45)	19 (79)	13 (28)	
		2	38 (54)	4 (18)	34 (72)	
	B Mismatch (%)	0	1 (1)	1 (4)	0 (0)	<0.001
		1	18 (25)	13 (54)	4 (11)	
		2	52 (73)	10 (42)	42 (89)	
	DR Mismatch (%)	0	3 (4)	3 (13)	0 (0)	<0.001
		1	23 (32)	16 (67)	7 (15)	
		2	45 (63)	5 (21)	40 (85)	
Kidney donor- Kidney recipient	Mean HLA Mismatch (of 6)		2.6 ± 2.0	2.3 ± 1.5	2.8 ± 2.2	0.25
	A Mismatch (%)	0	28 (39)	10 (42)	18 (38)	0.14
		1	28 (39)	12 (50)	16 (34)	
		2	15 (21)	2 (8)	13 (28)	
	B Mismatch (%)	0	27 (38)	8 (33)	19 (40)	0.01
		1	23 (32)	13 (54)	10 (21)	
		2	21 (30)	3 (13)	18 (38)	
	DR Mismatch (%)	0	26 (37)	9 (37)	17 (36)	0.43
		1	27 (38)	11 (46)	16 (34)	
		2	18 (25)	4 (17)	14 (30)	

uncensored graft failure rates to be similar: L-MM (depletional) 61.5% (8/13) versus L-MM (nondepletional agent) 38.4% (5/13) (P = 0.23); H-MM (depletional) 48.3% (15/31) versus H-MM (nondepletional agent) 51.6% (16/31) (P = 0.92).

Three patients (12.5%) in the L-MM group and 2 (6.4%) in the H-MM group experienced early pancreas graft failure within 30 days of transplant (P = 0.38). The total pancreas graft failure at last follow-up or DCGF were also similar between the groups and was further confirmed by the Kaplan–Meier analysis (Fig. 3), even after removing grafts that failed within 30 days of transplant (Fig. 4). When looking at the outcomes stratified based on the HLA mismatch of 0–3 versus 4–6 alleles by the Kaplan–Meier analysis, we observed no difference in the overall and death censored graft survival (Figure S5). Furthermore, if grafts that failed within 30 days of transplant were removed from the analysis, the graft survivals were similar (Figure S6).

Looking at the risk of pancreas DCGF by multivariable analysis using two different models (Table 9), none of the common risk factors evaluated in model 1, including HLA mismatch, rejection-free survival and nondepleting induction, were significantly associated with DCGF. In model 2, DR mismatch, interval from transplant to rejection and interval between kidney and pancreas transplant were also not significantly associated with DCGF.

Similarly, looking at the kidney outcomes (Table 10), the post-kidney transplant follow-up interval was

Table 8. Pancreas outcomes based on pancreas-donor and kidney-donor HLA mismatch.

Variables	All (n = 71)	Low mismatch (n = 24)	High mismatch (n = 47)	P
Mean post- pancreas transplant follow up (years)	6.9 ± 6.5	8.7 ± 6.3	6.0 ± 6.4	0.10
Development of dnDSA (%)	6 (8)	3 (13)	3 (7)	0.50
Mean interval from transplant to dnDSA (mo)	12.9 ± 3.2	12.2 ± 4.2	13.7 ± 2.7	0.63
Types of dnDSA		DR53 DQ7 CW7	Cw7 A2,B8,B38 A23	
Sum MFI of dnDSA	1834 ± 1277	1780 ± 1316	1887 ± 1529	0.85
Acute rejection (%)	27 (38)	8 (33)	19 (41)	0.52
Acute rejection within 1-year post-transplant (%)	17 (24)	3 (13)	14 (30)	0.11
Interval from transplant to acute rejection (mo)	17.4 ± 27.7	33.9 ± 44.2	10.5 ± 13.4	<0.001
Types of Acute rejection				
Grade I	7 (10)	2 (25)	5 (25)	0.90
Grade II	11 (15)	4 (50)	7 (35)	
Grade III	7 (10)	2 (25)	5 (25)	
Grade IV	1 (1)	0	1 (5)	
Other	1 (1)	0	1 (5)	
Pancreas grafts failed within 30 days of transplant	6 (8)	3 (13)	3 (6)	0.38
1 year pancreas graft survival (%)	57 (80)	21 (88)	36 (77)	0.28
Total number of pancreas graft failures at last follow up (%)	44 (62)	13 (54)	31 (66)	0.34
Death censored pancreas graft failures at last follow up (%)	26 (37)	8 (33)	18 (38)	0.69

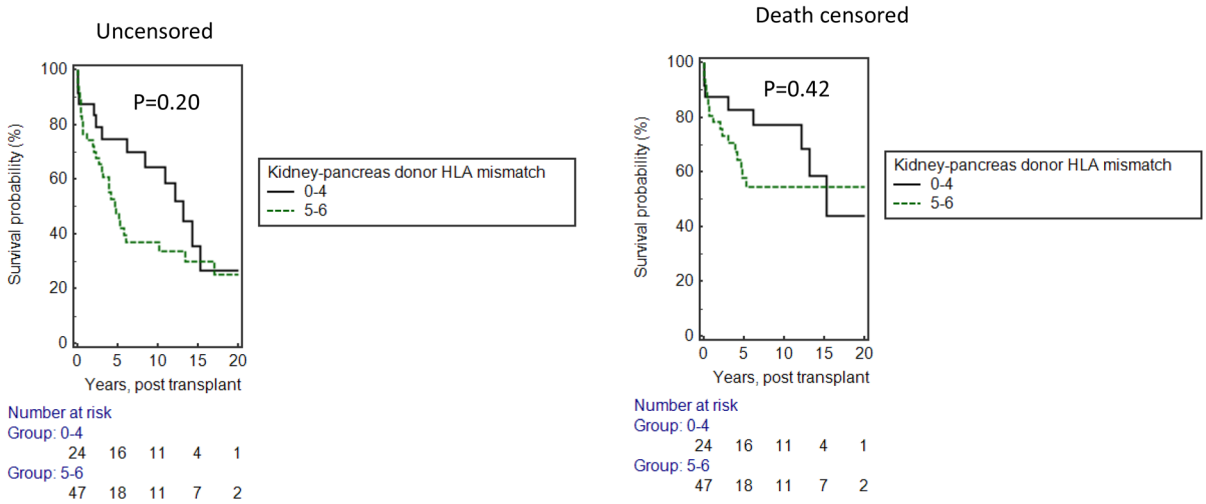

Figure 3 Uncensored and death censored pancreas graft survival among low-HLA mismatch and high-HLA mismatch PAK groups, based on pancreas donor and kidney donor HLA mismatch. (P = 0.20 and 0.42).

similar between the groups. Six recipients in the H-MM group and one in the L-MM group developed kidney dnDSA. dnDSA was persistent for more than one time or till last follow-up. Also, 5 of 7 recipients with dnDSA had kidney graft failure at last follow-up. The interval from kidney transplant to first rejection was significantly shorter in the low mismatch group, however, the rate and types of rejections or total kidney graft failure were similar between the two groups.

Discussion

In this series of 73 PAK recipients, a higher degree of HLA mismatch was associated with significantly early pancreas rejection. However, HLA mismatch was not associated with inferior pancreas graft outcomes. Even among 71 PAK recipients for whom we had data about kidney and pancreas HLA, a higher degree of pancreas donor versus kidney donor mismatch was not associated

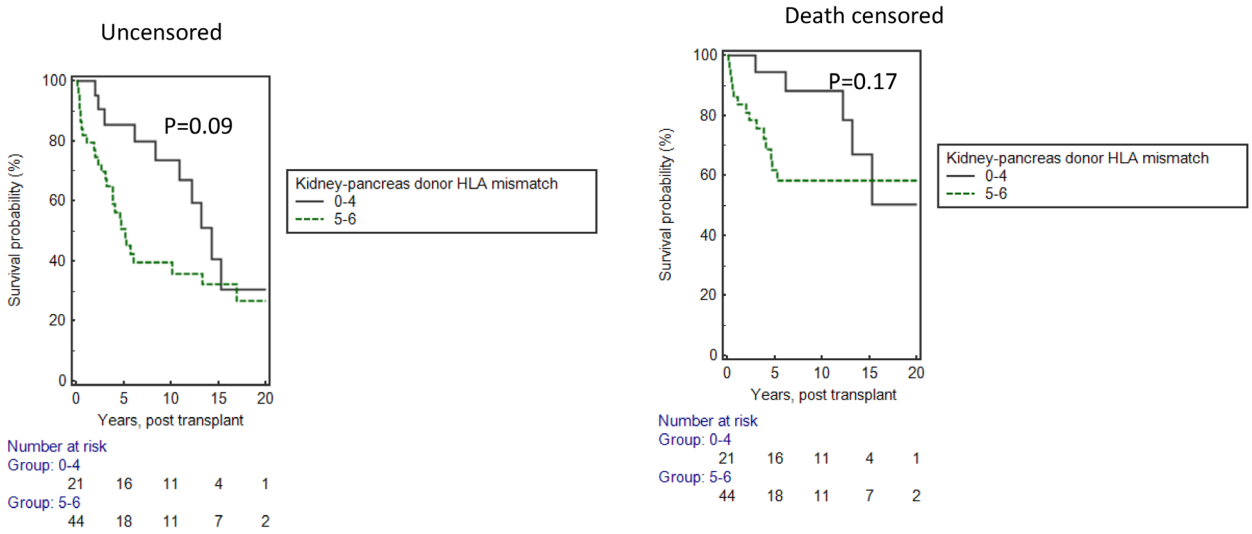

Figure 4 Uncensored and death censored pancreas graft survival, after removing grafts that failed within 30 days of transplant, among low-HLA mismatch and high-HLA mismatch PAK groups, based on pancreas donor and kidney donor HLA mismatch. (P = 0.09 and 0.17).

Table 9. Factors associated with pancreas death censored graft failure based on pancreas-donor and kidney-donor HLA mismatch.

	Risk factors for pancreas DCGF (multivariable analyses)			
	Variables	HR	95% CI	*P*
Model 1	HLA mismatch (per 1)	1.15	0.81–1.64	0.44
	Pancreas rejection free survival	0.54	0.22–1.32	0.18
	Non-depleting induction	1.75	0.78–3.92	0.18
Model 2	DR mismatch (per 1)	1.52	0.40–5.79	0.53
	B mismatch (per 1)	6.89	0.22–21.54	0.27
	Interval from pancreas transplant to pancreas rejection	1.02	0.98–1.05	0.24
	Interval between kidney and pancreas transplant	1.01	0.99-1.02	0.52

with inferior pancreas or kidney outcomes. Similar to the higher degree of HLA mismatch between pancreas donors and recipients, a higher degree of HLA mismatches between pancreas donors and kidney donors was associated with early rejection.

In a large meta-analysis with 486 608 kidney-only transplant recipients, each incremental increase of HLA mismatch was significantly associated with a higher risk of uncensored graft failure, DCGF and all-cause mortality [20]. In the same study, HLA-DR mismatches were significantly associated with a 12% higher risk of uncensored graft failure. HLA -A mismatches and HLA-B mismatches were not associated uncensored graft failure [20]. However, another study by Massie *et al.* with 106 019 kidney transplant recipients, utilizing data from the Scientific Registry for Transplant Recipients, revealed that HLA -B mismatch was also significantly associated with worse graft survival outcomes [21]. However, in our this study, we did not find any significant association of HLA-DR or HLA-B mismatches in both cohorts in term of pancreas DCGF.

The negative impact of a higher degree of HLA mismatch on graft or patient survival has been observed in various other solid organ transplants including heart, [22] lung [23] and even among liver [24] transplant recipients. Likewise, in one previous study with different immunosuppressive regimens which included various types of pancreas transplants including living donor pancreas grafts, repeat pancreas transplants, solitary pancreas transplants and SPK recipients, Squifflet *et al.*, [25] noticed the importance of minimizing HLA mismatch among pancreas recipients.

However, in another small study among six PAK recipients, Basadonna *et al.* [26] concluded that in the context of new immunosuppressive agents and clinical care, PAK transplantation can achieve good results even

Table 10. Kidney outcomes based on pancreas-donor and kidney-donor HLA mismatch.

Variables	All (n = 71)	Low mismatch (n = 24)	High mismatch (n = 47)	P
Mean post- kidney transplant follow up (yrs)	11.6 ± 6.2	14.5 ± 7.0	10.2 ± 5.3	0.09
Development of kidney dnDSA (%)	7 (10)	1 (4)	6 (13)	0.19
Mean interval from kidney transplant to dnDSA (years)	10.4 ± 4.5	18.6	9.1 ± 3.0	-
Types of dnDSA		DQ	DR and DQ DQ A1,B27 and DQ A24 A1 DR3	
Sum MFI of dnDSA	9800 ± 10725	3857	10791 ± 11392	-
Acute rejection (%)	8 (11)	2 (9)	6 (13)	0.58
Interval from kidney transplant to acute rejection (mo)	33.5 ± 50.1	2.31 ± 1.6	43.8 ± 54.7	0.04
Types of Acute rejection				0.38
TCMR	4 (6)	2 (100)	2 (33)	
AMR	4 (6)	0	4 (67)	
1 year kidney graft survival after pancreas transplant (%)	71 (100)	24 (100%)	47 (100%)	1
Total number of kidney graft failures at last follow up (%)	40 (56)	12 (50)	28 (60)	0.44
Death censored kidney graft failures at last follow up (%)	16 (23)	7 (29)	9 (19)	0.34

in the presence of poor HLA matching. Similarly, among SPK transplant recipients, a higher rate of acute rejection was observed in cases with poor HLA matches; however, short-term patient and graft survival at 3 years post-transplant were similar between 0 to 3 vs. 4 to 6 donor-recipient HLA mismatches [27,28]. In a recent study, Rudolph *et al.* noted a linear correlation between rejection among pancreas recipients and several mismatches, mainly –B and –DR mismatches [29]. In the same study, HLA mismatch did not affect graft or patient survival rates but was associated with an increased risk of opportunistic infections [29]. Similar to our study, in their analysis of PAK recipients, HLA -A, - B and –DR mismatches had no impact on pancreas DCGF in multivariable analysis [29]. However, surprisingly in a bivariate analysis, PAK recipients with zero mismatch had worse graft survival than 1 to 3 ($P = 0.066$) or 4 to 6 mismatches ($P = 0.02$). In another study, Ventura-Aguiar *et al*, [30] did not find any correlation with pancreas graft rejection or survival in PAK recipients based on the repeated HLA mismatch of 0 vs. 1 to 6.

This study has the expected limitations of a single-centre observational study, reflecting our specific population and clinical approach. Also, our study was limited by a relatively small sample size. Similar to most previous studies, mismatches against all the alleles including Cw, DQ and DP were not available. Also, not all HLA antigens share the same antigenicity, as there is no linear relationship between HLA mismatches and the immune response, as Cw and DP are less immunogenic. Our findings are reflective of our practices and this should be factored into the interpretation. However, we were able to provide more granular data than what is available in registries. Another potential advantage of our single-centre data is that it reflects a more homogeneous clinical approach to patient selection, surgical technique and medical management, in contrast to registry data involving multiple centres. Also, to the best of our knowledge, this is the largest series from a single centre looking at HLA mismatch among PAK recipients, not only based on the recipient and donor mismatch but also shared mismatches between pancreas donor and kidney donor.

In summary, in this study, except for the earlier acute pancreas rejection among PAK recipients with a higher degree of HLA mismatch, we did not find any other detrimental effects of HLA mismatch, including rates or severity of rejection or graft failure. Even among shared HLA mismatch between pancreas and kidney donor, a higher degree of HLA mismatch was not associated with detrimental effects on immunological and pancreas graft survival outcomes; however, more studies are needed to confirm these findings.

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AUTHOR CONTRIBUTION

Parajuli: concept, design, data collection, analysis, manuscript preparation; Kaufman: manuscript

preparation, editing; Djamali: manuscript preparation, editing; Welch: data collection, editing; Sollinger: manuscript preparation, editing; Mandelbrot: manuscript preparation, editing; Odorico: concept, design, editing.

Conflict of interest

Dr. Odorico is co-founder of Regenerative Medical Solutions, Inc., has stock equity, and is chair of the Scientific Advisory Board. He receives clinical trial funding from Veloxis, CareDx, Vertex and Natera.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Uncensored and death censored pancreas graft survival among HLA mismatch 0–3 and HLA mismatch 4–6, PAK groups, based on pancreas donor and recipient HLA mismatch. (P = 0.09 and 0.16).

Figure S2 Uncensored and death censored pancreas graft survival among HLA mismatch 0–3 and HLA mismatch 4-6, PAK groups, based on pancreas donor and recipient HLA mismatch, after excluding early pancreas graft failure. (P = 0.07 and 0.23).

Figure S3 Uncensored and death censored pancreas graft survival based on the year of a kidney transplant. (P = 0.52 and 0.18).

Figure S4 Uncensored and death censored pancreas graft survival based on the year of a kidney transplant, after excluding early pancreas graft failure. (P = 0.95 and 0.63).

Figure S5 Uncensored and death censored pancreas graft survival among HLA mismatch 0–3 and HLA mismatch 4–6, PAK groups, based on pancreas donor and kidney donor HLA mismatch. (P = 0.06 and 0.20).

Figure S6 Uncensored and death censored pancreas graft survival among HLA mismatch 0–3 and HLA mismatch 4–6, PAK groups, based on pancreas donor and kidney donor HLA mismatch, after excluding early pancreas graft failure. (P = 0.19 and 0.20).

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