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Pancreas transplants from small donors: are the outcomes acceptable? A retrospective study

Talal M. Al-Qaoud[1], Jon S. Odorico[1], David P. Al-Adra[1], Dixon B. Kaufman[1], Hans W. Sollinger[1], Glen Leverson[2], Bridget Welch[2] & Robert R. Redfield III[1]

1 Division of Transplantation, Department of Surgery, University of Wisconsin, Madison, WI, USA
2 Division of Research, Department of Surgery, University of Wisconsin, Madison, WI, USA

Correspondence
Talal M. Al-Qaoud MD, Division of Transplantation, Department of Surgery, H4/752 Clinical Science Center, University of Wisconsin, 600 Highland Avenue, Madison, WI 53792-7375, USA.
Tel.: +1-608-265-3664;
fax: +1 608 262 6280;
e-mail: al-qaoud@surgery.wisc.edu

ABSTRACT

Despite good organ quality, pancreata from extremely small pediatric donors (<30 kg) are generally avoided by many centers because of concerns of reduced islet cell mass and early technical failure. Therefore, we sought to compare the outcomes of small pancreas grafts (<30 kg) to those from higher weight donors from transplants performed between 1994 and 2015 (n = 1183). A total of 33 pancreata were from donors' ≤30 kg (3%), with a mean weight of 23.8 kg and mean age of 7.8 years. Patient survival was similar at 1, 5, and 10 years between recipients of ≤30 and >30 kg donors (≤30 kg: 96.8%, 86.8%, and 78.1% vs. >30 kg: 96.8%, 89.5%, and 79.1%, P = 0.5). Pancreas graft survival at 1, 5, and 10 years was also similar, ≤30 kg: 93.9%, 73.2%, and 61.0% vs. >30 kg: 87%, 73.3%, and 58.3% (P = 0.7). This graft survival pattern was also seen when comparing pancreata from ≤20 kg donors to those from >20 to 30 kg. Cause of graft loss, and metabolic and physiologic outcomes did not differ between the groups. After assessing the impact of donor weight as a continuous variable and calculating recipient-to-donor weight ratio (RDWR), we observed no effect of donor weight on patient and graft outcomes.

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Introduction

Strategies at optimizing organ recovery and preservation have blossomed over the years; however, there remains a discrepancy with pancreas transplantation lagging behind. Pancreas grafts remain underutilized, with a decline in the number of pancreas transplants being performed over the last decade, reasons for which are not fully understood, especially in the context of steadily improving patient and graft survival [1,2]. Reasons for the disparities in organ utilization include nonuniform criteria on direct examination of the pancreas to determine organ suitability during recovery, the level of technical comfort in splitting the liver and pancreas vasculature in instances where a replaced right hepatic artery off the superior mesenteric artery is encountered, and trauma to the pancreas occurring at the time of organ procurement [2,3]; more than 50% of recovered pancreata had at least one injury, most commonly a short portal vein (21.5%) and capsular damage (13.6%). Hence, there is a need for maximizing the organ pool and emphasizing on recovery expertise.

Pancreata from pediatric donors are significantly underutilized and remained steady at 3–5% of the total pancreas donors recovered over the last two decades [1,2]. National and single-center reports demonstrate

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equivalent patient and graft outcomes in recipients of younger pancreas grafts to those from older donors [4–9]. However, owing to the assumption that young donors have reduced islet cell mass and that the surgical procedure demands greater technical skill and possible higher risks of vascular thrombosis, many centers are reluctant to utilize these grafts. We have previously demonstrated in SPK recipients the metabolic outcomes of pediatric organs are equivalent to grafts from older donors, and in fact, kidney and pancreas graft survivals were superior [10]. In congruence with our previous findings, and those of another center demonstrating excellent short-term outcomes among a small cohort of patients receiving pancreata from donors ≤28 kg [11], we sought to analyze and present short- and long-term outcomes of pancreas transplantation from a larger cohort of recipients from donors ≤30 kg.

Patients and Methods

The University of Wisconsin maintains a database of all transplant recipients. Data were retrospectively obtained from June 1994 to June 2015. We included all pancreas transplant recipients: simultaneous kidney and pancreas (SPK), pancreas after kidney (PAK), and pancreas transplant alone (PTA). Objectives of the analysis were as follows: (i) to compare recipient pancreas graft survival, patient survival, and rejection-free survival among donors ≤30 kg vs. >30 kg. (ii) to compare recipient pancreas graft survival, patient survival, and rejection-free survival among donors ≤20 kg vs. >20–30 kg, (iii) to compare outcome measures including HbA1c, C-peptide, rejection, and graft failure/resumption of insulin in the ≤30 kg vs. >30 kg group and the ≤20 kg vs. >20–30 kg group, and (iv) to determine whether a weight discrepancy between recipient and the <30 kg donor was associated with worse outcomes and to see whether a threshold for good versus poor outcomes can be identified. Toward this later goal, we performed further analysis using donor weight as a continuous variable and different recipient-to-donor weight ratio (RDWR) cutoffs: ≤2 vs. >2, ≤2.25 vs. >2.25, ≤2.5 vs. >2.5, ≤2.75 vs. >2.75, ≤3 vs. >3, ≤3.25 vs. >3.25, and ≤3.5 vs. >3.5. After adjusting for recipient and donor BMI, donor and recipient age, and pancreas transplant type, noncensored and death-censored pancreas graft survival and patient survival analysis were performed for donor weight as a continuous variable and for each RDWR category.

Our techniques for both organ procurement and pancreas transplantation have been previously published [12,13]. The pancreatic allograft was prepared on the back table as described previously. Bladder drainage was accomplished with a side-to-side anastomosis between the antimesenteric border of the duodenal segment and the bladder up to 1996. In enteric-drained grafts used thereafter, an opening was made in the antimesenteric border of the duodenal segment measuring 2–3 cm in length. The site of anastomosis was either the ileum or the jejunum and performed as a two-layer hand-sewn anastomosis. Drain placement was surgeon- and case-dependent. With respect to our immunosuppression regimens, initial protocols consisted of quadruple sequential treatment with azathioprine (AZA), prednisone, cyclosporine A, and antibody induction (1994–1996: murine antihuman CD3 monoclonal antibody (OKT3, Muromonab; Ortho Pharmaceuticals, Raritan, NJ, USA); 1996–1997: horse antithymocyte globulin (ATGAM; Upjohn, Kalamazoo, MI, USA); 1997-current: basiliximab (SDZ CHI 621, Simulect; Novartis Pharmaceuticals, Basel, Switzerland), daclizumab (Zenapax; Roche Laboratories, Nutley, NJ, USA), and rabbit antithymocyte globulin (Thymoglobulin; SangStat Medical Corp., Fremont, CA, USA). In 1995, tacrolimus (FK506, Prograf; Fujisawa USA, Deerfield, IL, USA) replaced CSA, and mycophenolate mofetil (MMF, CellCept, Roche Laboratories) replaced AZA. Maintenance immunosuppression consists of tacrolimus, mycophenolic acid, and prednisone (dose/continuation dependent on induction agent used); antibiotic, antifungal, and antiviral prophylaxis is protocolized in all patients.

We evaluated the following donor and recipient demographics. Donor demographics included age, gender, race, weight, and cause of death. Recipient demographics for analysis included age, gender, race, body mass index (BMI), cold ischemia time, human leukocyte antigen (HLA) mismatch, panel-reactive antibody (PRA), transplant type (SPK, PTA, and PAK), transplant number, maintenance antimetabolite [mycophenolate mofetil, mycophenolic acid (myfortic), and azathioprine (AZA)], maintenance calcineurin inhibitor (tacrolimus and cyclosporine), and induction agent (thymoglobulin, alemtuzumab, basiliximab, muromonab, daclizumab, and rituximab). Outcome data on hemoglobin A1C (HbA1c) in those with a functioning graft, fasting C-peptide, rejection episodes, and causes of graft loss were analyzed. Graft loss was defined as graft removal, resumption of insulin, relisting, or death with a functioning graft. Pancreas allograft biopsies were performed for increased enzymes in the majority of cases, or hyperglycemia in a minority, to confirm pancreas graft rejection [14–17].

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Our objective in this study was to compare outcomes between donor weight groups. Continuous variables were described by reporting means and standard deviations and compared between groups with *t*-tests. Categorical variables were summarized by reporting the number and percentage of subjects falling into a category. These percentages were compared between groups using a Fisher's exact test, when possible, and otherwise using a chi-squared test. Survival outcomes, including graft survival, death-censored graft survival, patient survival, and rejection-free survival, were estimated utilizing the methods of Kaplan and Meier and compared between groups with a log-rank test. Additionally, multivariable Cox proportional hazards models were used to estimate the impact of donor weight group, as well as other factors thought to be influential on outcomes. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). *P*-values less than 0.05 were considered to be significant.

Results

Demographics

A total of 1183 transplants had been performed with data available for analysis from our database. 33 (3%) transplants were from donors' ≤30 kg, with a mean weight of 23.8 kg and mean age of 7.8 years (Table 1). There was a significant difference in the mean recipient weight, 65.8 kg in the ≤30 kg group vs. 73.5 kg in the >30 kg group ($P = <0.01$), with a higher proportion of female recipients in the smaller donor group (67% vs. 40%). The majority of the donors were donors after brain death (DBD). Proportions of SPK and solitary pancreas transplants were similar in both the ≤30 and >30 kg cohorts; in the ≤30 kg cohort, 22 (67%) cases were SPK, 5 (15%) were PTA, and 6 (18%) were PAK. Owing to different eras of transplantation, there were inherent differences in the induction agents utilized, with basiliximab being the most common agent used during the overall study period (Table 1). Looking at the subset data of donors ≤20 kg vs. >20–30 kg, there were differences in donor weight and age, but otherwise no significant differences in other demographics (Table 2).

Patient and graft survival

Patient survival was similar at 1, 5, and 10 years between the ≤30 kg and the >30 kg group (≤30 kg: 96.8%, 86.8%, and 78.1% vs. >30 kg group: 96.8%, 89.5%, and 79.1%, $P = 0.5$, Fig. 1a). Pancreas graft survival at 1, 5, and 10 years was also similar (Fig. 2a, ≤30 kg: 93.9%, 73.2%, and 61.0% vs. >30 kg: 87%, 73.3%, and 58.3%, $P = 0.7$). Similarly, death-censored pancreas graft survival at 1, 5, and 10 years was not significantly different (≤30 kg: 96.9%, 88.8%, and 79.9% vs. >30 kg: 90.0%, 79.0%, and 70.0%, $P = 0.40$). Rejection-free survival was similarly equivalent between the groups (≤30 kg: 78.0%, 74.7%, and 71.1% vs. >30 kg: 77.5%, 72.9%, and 70.0%, $P = 0.42$).

The 1-, 5-, and 10-year patient (Fig. 1b, ≤20 kg: 87.5%, 72.9%, and 58.3% vs. >20–30 kg: 95.4%, 86.3%, and 80.1%, $P = 0.7$) and pancreas graft (Fig. 2b, ≤20 kg: 88.5%, 73.7%, and 58.5% vs. >20–30 kg: 96.1%, 67.4%, and 56.1%, $P = 0.3$) survival were noninferior in the ≤20 kg group compared to the >20–30 kg group. There was a trend toward a significant difference in death-censored pancreas graft survival favoring the ≤20 kg donor group (≤20 kg: 100%, 100%, and 87.8% vs. >20–30 kg: 96.1%, 78.6%, and 65.6%, $P = 0.05$). Interestingly, rejection-free pancreas graft survival was 100% at 10 years in the ≤20 kg group vs. 61.9% in the >20–30 kg group ($P = 0.03$).

Metabolic and physiologic parameters

Metabolic and physiologic outcomes did not differ between the groups (Table 3). In the ≤30 kg vs. the >30 kg group, the mean HbA1c at 10 years was 5.7% vs. 5.6% ($P = 0.6$). Although the mean C-peptide was lower at 10 years in the ≤30 kg group, it was not significantly different compared to the >30 kg group (1.7 ng/ml vs. 3 ng/ml, $P = 0.3$). Similarly, the percentage of patients in whom resumption of insulin was the identified reason for graft failure was not statistically significantly higher in the >30 kg compared to the ≤30 kg group, although the percentage was numerically higher (Table 3).

Causes of graft loss and mortality

When tabulating the underlying causes of pancreas graft losses, we were unable to detect a significant difference between the donor weight cohorts (Table 4). There were 18 (54%) graft losses in the ≤30 kg group vs. 534 (46%) in the >30 kg group ($P = 0.71$). The majority of graft losses in the ≤30 kg group were secondary to death with a functioning graft (56%), and those in the >30 kg group were secondary to resumption of insulin (45%). Interestingly, rates of resumption of insulin were

Table 1. Donor and recipient demographics comparing the ≤30 kg donor group to the >30 kg donor group (SD = standard deviation).

	≤30 kg D (*N* = 33)	>30 kg (*N* = 1150)	*P* value
Donor weight, mean kg (SD), range	23.8 (4.1), 15–29.9	73.3 (16.5), 31.8–160	<0.01
Donor age, mean years (SD), range	7.8 (4.8), 3–32	30.8 (12.8), 6–59	<0.01
CIT, mean hours (SD), range	15.9 (5.3), 5.25–29	15.1 (4.4), 3–31	0.3
Recipient age at transplant, mean years (SD), range	41.7 (9.1), 26.09–67.35	40.7 (7.9), 18.05–66.42	0.5
Recipient weight at transplant, mean kg (SD), range	65.8 (16.7), 43–116	73.5 (14.3), 34–144	<0.01
Donor gender			
Female (%)	14 (42)	455 (40)	0.7
Male (%)	19 (58)	695 (60)	
Recipient gender			
Female (%)	22 (67)	453 (40)	<0.01
Male (%)	11 (33)	697 (60)	
Donor type			
DBD	31 (94)	1041 (91)	0.8
DCD	2 (6)	109 (9)	
Transplant type			
SPK	22 (67)	907 (79)	0.2
PTA	5 (15)	113 (10)	
PAK	6 (18)	130 (11)	
Antimetabolite			
Azathioprine	1 (3)	74 (6)	0.7
Mycophenolate	30 (97)	1054 (93)	
Myfortic	0 (0)	4 (1)	
Calcineurin inhibitor			
Cyclosporin	6 (18)	232 (21)	0.7
Tacrolimus	27 (82)	896 (79)	
Induction agent			
Thymoglobulin	10 (30)	249 (22)	0.01
Alemtuzumab	1 (3)	238 (21)	
Basiliximab	14 (43)	482 (42)	
Muromonab	2 (6)	102 (8)	
Daclizumab	6 (18)	77 (7)	
Rituximab	0 (0)	1 (0)	
Recipient transplant number			
1st transplant	25 (76)	952 (83)	0.1
2nd transplant	5 (15)	168 (15)	
>2 transplants	3 (9)	30 (2)	

higher in the >30 kg group, and thrombosis occurred in only 1 out of two grafts (11%) that required transplant pancreatectomy in the <30 kg group (in a 29 kg donor) vs. a higher rate of explanting the pancreas in the >30 kg group (21%). There were no graft losses secondary to thrombosis or resumption of insulin in the ≤20 kg group; the majority were secondary to death with a functioning graft.

Predictors of pancreas graft and patient survival

On multivariate analysis, when comparing the >30 kg to the ≤30 kg group, donor weight did not exert a statistically significant effect on either death-censored or noncensored multivariate models of pancreas graft survival, and patient survival (Table 5). Significant predictors of pancreas graft survival were as follows: recipient age at transplant (protective, HR: 0.95, $P = 0.03$), donor age (negative, HR: 1.02, $P = <0.01$), and nonprimary transplant (negative, HR: 1.61, $P = <0.01$). In addition, death-censored multivariate analysis revealed pancreas transplant type was a negative predictor when PAK and PTA were compared to SPK transplants (PTA HR: 1.68; PAK HR: 1.32, $P = <0.01$), and increasing recipient BMI was also a negative predictor, of less magnitude (HR: 1.03, $P = 0.04$). Increasing recipient age at transplant, increasing donor age, pancreas transplant type, and nonprimary transplant were all significant predictors of patient survival.

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Table 2. Donor and recipient demographics comparing the ≤20 kg donor group to the >20–30 kg donor group (SD = standard deviation).

	≤20 kg (*N* = 8)	>20–30 kg (*N* = 25)	*P* value
Donor weight, mean kg (SD), range	18.3 (2.2), 15–20	25.6 (2.8), 20.4–29.9	<0.01
Donor age, mean years (SD), range	4.5 (1.2), 3–6	8.8 (5.1), 4–32	0.02
CIT, mean hours (SD), range	18.8 (2.6), 14–23.32	15.1 (5.8), 5.25–29	0.08
Recipient age at transplant, mean years (SD), range	39.0 (6.6), 28.82–45.84	42.5 (9.7), 26.09–67.35	0.3
Recipient weight at transplant, mean kg (SD), range	59 (9.3), 43–71	68 (18.1), 43–116	0.07
Donor gender			
Female (%)	4 (50)	10 (40)	0.6
Male (%)	4 (50)	15 (60)	
Recipient gender			
Female (%)	7 (88)	15 (60)	0.2
Male (%)	1 (12)	10 (40)	
Donor type			
DBD	8 (100)	23 (92)	0.4
DCD	0 (0)	2 (8)	
Transplant type			
SPK	7 (88)	15 (60)	0.3
PTA	0 (0)	5 (20)	
PAK	1 (12)	5 (20)	
Antimetabolite			
Azathioprine	1 (14)	0 (0)	0.06
Mycophenolate	6 (86)	24 (100)	
Calcineurin inhibitor			
Cyclosporin	2 (25)	4 (16)	0.6
Tacrolimus	6 (75)	21 (84)	
Induction agent			
Thymoglobulin	1 (13)	9 (36)	0.4
Alemtuzumab	1 (13)	0 (0)	
Basiliximab	4 (50)	10 (40)	
Muromonab	1 (12)	1 (4)	
Daclizumab	1 (12)	5 (20)	
Recipient transplant number			
1st transplant	5 (63)	20 (80)	0.2
2nd transplant	1 (12)	4 (16)	
>2 transplants	2 (25)	1 (4)	

Impact of donor weight and recipient-to-donor weight ratio

Using donor weight as a continuous variable, adjusted Cox proportional hazards model demonstrated no effect on pancreas graft survival or patient survival (pancreas graft survival HR of 0.99, 95% CI: 0.99–1.01, $P = 0.78$; death-censored pancreas graft survival HR of 0.99, 95% CI: 0.98–1.01, $P = 0.48$; patient survival HR of 1.01, 95% CI: 0.99–1.02, $P = 0.21$). We further investigated the relationship between donor weight and pancreas graft survival by fitting a cubic spline with three knots equally spaced between the extreme weights and still found no significant association ($P = 0.25$). When solely focusing on recipients from donors ≤30 kg, none of the different cutoffs of RDWR had an effect on pancreas graft survival or patient survival (Table 6). Broadening the RDWR analysis to include the whole cohort of recipients also demonstrated no observed effect of RDWR using cutoffs (Table 7) on pancreas graft survival and patient survival. Similarly, using RDWR as a continuous variable, there was no significant effect on pancreas graft or patient survival (HR: 1.05, $P = 0.59$ and HR: 1.04, $P = 0.74$, respectively); hence, recipient–donor weight matching does not appear to be an important determinant of outcomes.

Discussion

In an era where new-onset diabetes affects approximately 10% of the US population every year [18], and despite advances in insulin delivery and continuous

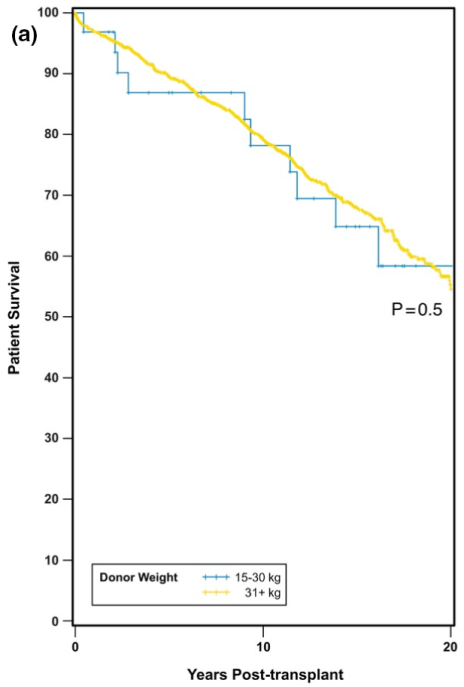

Figure 1 Kaplan–Meier survival graphs demonstrating patient survival in the ≤30 kg vs. >30 kg group (a), and the ≤20 kg vs. >20–30 kg group (b).

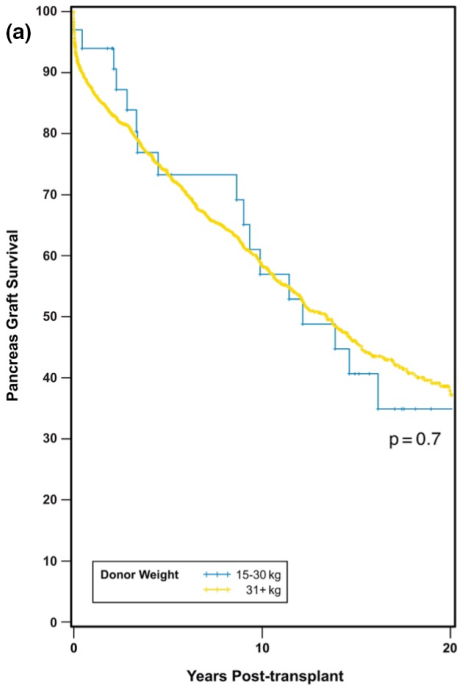

Figure 2 Kaplan–Meier survival graphs demonstrating pancreas graft survival in the ≤30 kg vs. >30 kg group (a), and the ≤20 kg vs. >20–30 kg group (b).

glucose monitoring, many patients are still unable to achieve consistent normoglycemia and are plagued by many end-organ complications. The ultimate solution is pancreas transplantation; however, the gap between demand and organ availability [1,2] persists. While the expectation of a "perfect" pancreas donor is a 20–30-year-old person, with weight of 60–90 kg with a BMI of 23–25, with excellent kidney function, the number of these "ideal" donors is not sufficient to close the gap in demand. Consequently, we and others have considered pancreata from small donors as a potential solution to the shortage. Here, we have corroborated our previous

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Table 3. Pancreas transplant outcomes comparing the ≤30 kg donor group to the >30 kg donor group, and the subgroup of ≤20 kg donors to the >20–30 kg donor group (SD = standard deviation).

	≤30 kg	>30 kg	*P*	≤20 kg	>20–30 kg	*P*
HbA1c, mean (SD), range						
At 1 year	5.3 (0.4), 4.3–6.5	5.5 (0.7), 4–10.9	0.2	5.1 (0.4), 4.4–5.6	5.4 (0.5), 4.3–6.5	0.3
At 5 years	5.3 (0.5), 4.8–6.6	5.6 (0.6), 4–8.2	0.2	5.5 (0.7), 4.9–6.6	5.2 (0.3), 4.8–5.8	0.4
At 10 years	5.7 (1.3), 4.7–9.0	5.6 (0.6), 3.6–8	0.6	5.4 (0.5), 5–5.9	5.9 (1.6), 4.7–9	0.6
Fasting C-peptide, mean (SD), range						
At 1 year	3.4 (4.1), 0–15.9	2.6 (2.3), 0–17.3	0.3	1.5 (1.1), 0–2.5	4.1 (4.7)	0.3
At 5 years	1.7 (1.4), 0–3.6	2.2 (1.9), 0–11.1	0.5	2.7 (0.8), 2.2–3.6	0.6 (1.0)	0.05
At 10 years	1.7 (0.6), 0.9–2.4	3 (2.8), 0.2–20.6	0.3	1.3 (NA)	1.7 (0.7)	0.6
History of rejection (%)	11 (33)	309 (27)	0.5	0 (0)	11 (44)	0.03
Resumption of insulin (%)	6 (33)	45 (46)	0.7	1 (13)	6 (24)	0.06

HbA1c and C-peptide values represent patients with a functioning graft who have not returned to exogenous insulin.

Table 4. Different etiologies for graft loss in the recipients of ≤30 kg vs. >30 kg donors.

Graft losses and their etiology		
	≤30 kg *N* = 33	>30 kg *N* = 1150
Death with failed graft (%)	0 (0)	1 (0.2)
Death with functioning graft (%)	10 (56)	172 (32)
Death with unknown graft function (%)	0 (0)	6 (1.2)
Pancreatectomy for graft thrombosis and enteric leak (%)	2 (11)	107 (21)
Initiated oral hypoglycemic agent (%)	0 (0)	1 (0.2)
Resumption of insulin (%)	6 (33)	245 (45)
Total graft losses (%)	18 (54)	534 (46)
P value	0.71	

findings [10] demonstrating that in an even smaller weight group of donors, the outcomes are noninferior to the "normal" weight donors.

The pancreas graft survival at 10 years in this cohort was 61% for the ≤30 kg group (death-censored graft survival was 79.9%) and 58.3% for the ≤20 kg group (death-censored graft survival was 87.8%). Although statistical significance was not achieved, there was a trend toward better pancreas graft survival in the smallest donor groups, while patient survival was similar between the groups. We acknowledge the important caveat in interpreting the findings as the number of recipients of ≤30 kg donors is small; however, this cohort of small donor pancreata is the largest single-center series in the literature, of longer follow-up than previous studies, and represents the majority of the cases in the UNOS registry. Our outcomes may also reflect our center expertise with high-volume pancreas transplantation based on the literature on pancreas transplant outcomes correlating with center volume [19,20]. A recent analysis of UNOS registry data demonstrated superior outcomes in recipients of pediatric donors (larger than 30 kg) compared to recipients of adult donors further supporting the use of these pediatric donor organs [8]. Their analysis illustrates the relevance of considering careful selection and weight matching of donor and recipient.

Of pertinence to considering the use of small pediatric donors is the potential for technical complications, mainly graft thrombosis, a notion that has long inhibited the acceptance of these organs. None of the graft thromboses that occurred in our cohort were in the ≤20 kg donor group, and only 1 occurred in the ≤30 kg donor group. In the UNOS analysis, only two grafts (6.5%) were lost within 2 weeks of transplant for reasons presumably associated with vascular complications [8]. The smallest organ recovered and used for transplantation in our cohort was of a 15 kg donor, and the graft was lost secondary to death with a functioning graft 9 years following transplantation. This low

Table 5. Multivariate Cox regression analysis of pancreas graft survival and patient survival in the ≤30 vs. >30 kg donor groups.

Variable	Hazard ratio (HR)	95% CI	*P*-value
Pancreas graft survival			
Donor weight group			
≤30 kg	0.60	0.16–1.14	0.07
Recipient age at transplant	0.98	0.92–0.99	0.02
Donor age at time of transplant	1.01	1.00–1.04	<0.01
Recipient BMI	1.01	0.98–1.14	0.17
Donor BMI	0.99	0.99–1.18	0.84
Transplant type (vs. SPK)			0.06
PAK	1.14	0.93–1.54	0.51
PTA	1.43	0.98–1.88	0.02
Nonprimary transplant	1.68	1.34–2.02	<0.01
Gender			
Female	0.93	0.75–1.10	0.51
Induction group			0.63
Alemtuzumab	0.89	0.63–1.15	
Muromonab	0.99	0.67–1.31	
Basiliximab	0.88	0.66–1.10	
Patient survival			
Donor weight group			
≤30 kg	0.67	0.11–1.35	0.25
Recipient age at transplant	1.02	1.01–1.04	<0.01
Donor age at time of transplant	1.01	1.01–1.03	<0.01
Recipient BMI	0.99	0.95–1.02	0.53
Donor BMI	0.98	0.95–1.02	0.42
Transplant type (vs. SPK)			0.05
PAK	0.84	0.48–1.2	0.56
PTA	0.42	0.04–0.84	0.01
Nonprimary transplant	1.97	1.73–2.21	<0.01
Gender			
Female	1.07	0.95–1.19	0.54
Induction group			
Alemtuzumab	1.01	0.81–1.20	0.94
Muromonab	1.33	1.13–1.53	0.15
Basiliximab	1.10	0.85–1.15	0.57

pancreas graft thrombosis rate is in congruence with our previous findings on outcomes of simultaneous kidney and pancreas transplants from pediatric donors (6.8% pancreas thrombosis rate) [10]. In the series by Illanes *et al.* [11], no thromboses occurred in 8 pediatric donors <28 kg, and in the series by Socci *et al.* [4], the thrombosis rate was lower in the pediatric group compared to the adult group donors. In one series of patients demonstrating negative outcomes of pediatric donors in the literature, there was heterogeneity in use of preservation solution, exocrine drainage, and venous drainage [7]; furthermore, there were no comparison group data presented. Plausible explanations for lower graft thromboses rates include meticulous effort to avoid capsular injury and a short portal vein during the recovery, selection bias toward organs with good-sized splenic artery/superior mesenteric artery stumps for reconstruction, minimizing cold and warm time, and attempting to mitigate risk of ischemia–reperfusion injury (which may be the major cause of thrombosis rather than technical causes). Additionally, younger beta cells may be more resilient and therefore, at the time of transplantation and engraftment, able to withstand the hypoxic and inflammatory stressors [21,22]. Also, higher volume centers performing more transplants from pediatric donors will inherently have better outcomes and hence lower graft thromboses rates.

With respect to metabolic outcomes, our results challenge existing theories that claim pediatric donor organs having insufficient beta-cell mass to meet the requirements of older and higher weight/BMI recipients. In support of the hypothesis that pediatric donor pancreata have sufficient beta-cell mass to be able to achieve normoglycemia, we found no significant differences in the 1-, 5-, and 10-year HbA1c and fasting C-peptide values in recipients of ≤30 kg donors compared to recipients of >30 kg donors. Furthermore, whereas the

Table 6. The effect of recipient-to-donor weight ratio cutoffs on pancreas graft and patient survival in recipients from donors ≤30 kg (*N* = 33).

RDWR	Pancreas graft survival Hazard ratio (confidence interval)	*P* value	Patient survival Hazard ratio (confidence interval)	*P* value
2.00	1.29 (0.17–9.81)	0.89	0.86 (0.11–6.85)	0.88
2.01–2.25	1.16 (0.43–3.17)	0.75	0.94 (0.26–3.33)	0.92
2.26–2.50	1.01 (0.38–2.62)	0.98	1.20 (0.34–4.17)	0.77
2.51–2.75	1.23 (0.46–3.26)	0.67	1.18 (0.33–4.25)	0.79
2.76–3.00	2.19 (0.81–5.92)	0.11	1.91 (0.52–6.95)	0.32
3.01–3.25	2.37 (0.81–6.91)	0.11	1.93 (0.49–7.58)	0.34
3.26–3.50	0.98 (0.22–4.32)	0.97	0.93 (0.11–7.43)	0.94

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Table 7. The effect of recipient-to-donor weight ratio cutoffs on pancreas graft and patient survival in all recipients (N = 1183).

RDWR	Pancreas graft Survival Hazard ratio (confidence interval)	*P* value	Patient survival Hazard ratio (confidence Interval)	*P* value
0.50	1.05 (0.87–1.26)	0.59	1.04 (0.80–1.34)	0.74
0.51–0.75	1.06 (0.79–1.27)	0.96	0.93 (0.69–1.27)	0.67
0.76–1.00	0.99 (0.83–1.17)	0.92	0.98 (0.79–1.23)	0.91
1.01–1.25	0.95 (0.77–1.15)	0.61	0.98 (0.75–1.28)	0.90
1.26–1.50	1.01 (0.83–1.39)	0.56	1.09 (0.77–1.55)	0.61
1.51–1.75	1.08 (0.76–1.55)	0.63	1.08 (0.66–1.77)	0.73
1.76–2.00	0.99 (0.62–1.53)	0.97	1.09 (0.61–1.93)	0.77
2.01–2.25	0.87 (0.49–1.55)	0.65	0.97 (0.46–2.07)	0.95
2.26–2.50	1.08 (0.83–1.39)	0.56	1.28 (0.57–2.87)	0.55
2.51–2.75	1.25 (0.62–2.51)	0.53	1.46 (0.60–3.53)	0.40
2.76–3.00	1.76 (0.87–3.54)	0.11	1.92 (0.81–4.77)	0.13

most common cause of graft loss in the ≤30 kg donor cohort was death with a functioning graft, resumption of insulin was the commonest cause of graft loss in the >30 kg group. These findings collectively do not support the proposed aforementioned claims. Instead, they indicate that sufficient functional beta-cell mass from pancreata from <30 kg donors exists to meet the physiologic demands of the average adult recipient.

The multivariate model analysis findings were consistent with findings of prior literature, where risk factors were analyzed in cohorts receiving pancreata from primarily adult donors [23]. The current study demonstrated younger recipient age at transplant was protective, while increasing donor age and nonprimary transplants impacted outcomes negatively. The death-censored pancreas graft survival analysis revealed pancreas transplant type was a negative predictor when PAK and PTA were compared to SPK transplants. This should be interpreted with caution as the number of cases is small, the majority of cases were SPKs, and we have previously shown that solitary pancreas transplants are an independent risk factor for pancreas rejection [24].

We acknowledge the patient selection bias that resulted in more pediatric organs transplanted into female, younger, and smaller/lower BMI recipients. This inherently could have biased the outcomes and magnified favorable graft and patient survival. However, although it would make sense to try and pair donors and recipients by body mass or, at least, reduce recipient–donor weight discrepancies, it does not appear to be critical to a successful outcome. We performed recipient-to-donor weight ratio (RDWR) survival analysis on the cohort of recipients of the ≤30 kg donors and on the whole group of transplants from 1994 to 2015. At multiple RDWR cutoffs, and when using RDWR as a continuous variable, we found no impact on pancreas graft survival and patient survival.

There are some weaknesses to our study. Inherent to any retrospective nonrandomized comparison are possible unintentional selection, management, and treatment biases. We narrowed the analysis down to include only pancreas graft outcomes as we previously published the kidney graft outcomes in SPK patients [10]. We also limited our discussion of immunologic aspects as we had little analysis on immunologic outcomes owing to the small cohort size and the fact that only after 1997 were pancreas allograft biopsies routinely performed at our center. Despite our firm opinions, we acknowledge the small number of patients especially in the 15–20 kg group. Although these data are from a single-center retrospective review with inherent biases, to our knowledge, this is the largest single-center series with the longest follow-up, suggesting that the use of ≤30 kg pediatric donors is associated with excellent functional long-term outcomes. Moreover, use of very small pediatric donors did not negatively impact patient survival, rejection rates, and surgical complications, including graft thrombosis.

Reflecting on the national data, the alarming number of pediatric pancreata not being recovered (>50% of all pediatric donors) from donors with a median weight higher than this presented cohort [8] is discouraging. In light of this underutilization statistic and the excellent outcomes reported here, we strongly advocate for the use of this precious pediatric organ pool. The use of these pediatric donor pancreata resulted in excellent short- and long-term outcomes, with few surgical complications and excellent patient and graft survival mirroring those of normal weight donors. The stereotyped notion that these grafts have higher technical

complications and lower beta-cell mass should be abandoned, and the "ideal" donor should include these underutilized organs.

Authorship

TMA-Q: formulated the study concept, wrote the manuscript, and analyzed part of the data. JSO, DPA-A, DBK, and HWS: wrote part of/edited the manuscript. GL: analyzed most of the data. BW: compiled the data. RRR III: formulated the study concept, wrote part of/edited the manuscript, and analyzed part of the data.

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