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Donor age is the most important predictor of long term graft function in donation after cardiac death simultaneous pancreas-kidney transplantation: A retrospective study

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ABSTRACT

Background: Allografts donated after cardiac death (DCD) are the fastest growing organ source worldwide. Unfortunately, information is lacking on how to judge these organs' viability. Here, we analyzed the effects of donor characteristics, including age and BMI, on outcomes of DCD simultaneous-pancreas-kidney transplantation (SPK).

Methods: We evaluated UNOS DCD-SPK transplants from 1988 to 2012. Effects of donor characteristics on graft and recipient survival were evaluated using Cox Regression and the Kaplan-Meier method, and compared to predictions from the pancreas and kidney donor risk indices (PDRI, KDRI).

Results: Compared to grafts≤40(n = 38), grafts>40(n = 189) had lower 1-year (73.4% ± 7.2% vs 88.2% ± 2.4%) and 10-year (50.3% ± 10% vs 66.3% ± 6.9%) pancreas survival, and twice the rate of kidney failure (HR2.1, 95%CI 1.15–3.83, $p < 0.05$) and pancreas failure (HR2.07, 95%CI 1.16–3.70, $p < 0.05$). BMI correlated with pancreas failure and recipient mortality.

Conclusions: Donor age and BMI are significant predictors of DCD-SPK outcomes. Graft age appears to be as good a predictor of outcome as PDRI and KDRI.

Introduction

The average American patient waits approximately 3 years for a simultaneous pancreas-kidney (SPK) transplant.[1] Although traditionally neurologically deceased donors (DBD) have been the mainstay for many programs performing multi-organ transplants, primarily due to improved graft outcomes, in more recent decades, organs procured from donors after cardiac death (DCD) have been used to help bridge the gap between the number of patients on the waiting list for an organ, and the number of organs that are available.[2,3] DCD donors are now commonly accepted as an additional source of allografts and represent the fastest growing population of deceased donor organs globally.[4–6]

Unfortunately, studies show that DCD SPK grafts have inferior outcomes compared to grafts taken from DBD donors, including longer hospital stays and higher risk of delayed graft function.[7,8] There is a growing need for predictive tools to judge the 'quality' of a DCD-SPK graft by using known donor information to predict graft outcome.

In 2007, Salvalaggio et al. looked at 8850 SPK transplants and concluded that grafts recovered from donors>45 had inferior outcomes, including higher rates of kidney and pancreas failure at 5-years, when compared to grafts from younger donors.[9] However, this study pooled DCD and DBD transplants together, and since DBD organs made up the majority of allografts, this data cannot be accurately used to apply directly to DCD-SPK grafts. Another study in the UK looked at 1009 pancreas transplants, with

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and without simultaneous kidney transplantation, and found that pancreas grafts from DCD donors<60 had similar outcomes to DBD pancreas grafts.[10] This study, however, focused mainly on pancreas only grafts and had a relatively small number of DCD-SPK transplants (n = 79). Furthermore, the DCD pancreas donors had a much lower median age than DBD donors (28 vs. 37), and the authors did not specifically examine the effects of DCD donor age as a confounder.

Although there is a current tool available for predicting the outcomes of SPK transplants (PDRI: Pancreas Donor Risk Index calculator), the impact of the DCD nature of the donor, the donor age, and the kidney cold ischemic time (CIT) were not heavily weighted at its time of creation based on the available data in 2009.[11,12] As an example, although the study had a large total sample size, the subgroup of DCD-SPK transplants only numbered 87. Furthermore, the tool is mainly for short term predictions and does not provide transplant outcomes beyond the 1 year mark.

Despite the significant gains in our understanding of the impact of donor traits on SPK grafts in general, there still exists a void regarding the effect of donor age on DCD-SPK grafts specifically. Since DCD organs are already believed to have worse outcomes, this lack of knowledge leaves surgeons unsure of whether to accept a potential pancreas-kidney graft from an older DCD donor. To address this problem, we used data from UNOS[13] to perform the largest study to date looking at SPK transplants from DCD donors alone. Our main goal was to determine a donor age at which we would be concerned about a significant decrease in DCD-SPK outcomes. In the Salvalaggio et al. paper on SPK transplants (mostly DBD but some DCD), the age of 45 appeared to be an arbitrarily chosen cut-off for donor age.[9] Since we are examining DCD organs alone, and DCD organs are generally thought to have inferior outcomes compared to DBD grafts, we lowered the donor age threshold by 5-years to 40 years of age to be more in keeping with the current trends in utilization of DCD SPK grafts. However, to ensure that we would not be overemphasizing the age cut-off, we also evaluated older donors sequentially with subgroup analyses. Although the emphasis was on donor age, we evaluated other donor traits including CIT, kidney warm ischemic time (WIT), donor BMI, and pancreas preservation time (PPT). Using graft survival, recipient survival, and kidney delayed graft function (DGF) as our endpoints, we analyzed both short-term and long-term graft outcomes predicted by these donor traits.

Methods

We performed a retrospective cohort study of all 264 DCD-SPK transplants recorded in the UNOS database from October 1987 to December 2012. The transplants' Pancreas Donor Risk Indices (PDRI) and their donor-specific Kidney Donor Profile Indices (KDPI) were calculated using formulae described by their respective authors.[11,14] KDPI was calculated using the scaling factor from 2014.[15] Thirty seven transplants with incomplete values required for PDRI and KDPI were excluded. This brought the study sample size to 227 DCD-SPK transplants. Since age >45 was an important predictor for SPK graft outcomes overall, and DCD grafts are felt to fare slightly worse than grafts overall, we chose to stratify our data by age >40. This gave us 189 transplants with grafts from donors ≤40 years old, and 38 with grafts from donors >40.

We examined the effects of deceased donor age, donor BMI, CIT, WIT, and PPT as predictors of SPK transplant outcome. PPT was defined as the sum of the pancreas graft's cold ischemic time and warm ischemic time.

Our primary endpoints for this study were kidney graft survival time and pancreas graft survival time. Our secondary endpoints were recipient survival time, and DGF. Recipient and graft survivals were death censored. For the purpose of this study, DGF was defined as the need for dialysis during the first week post-transplant. There were 4 transplants where the listed pancreas graft survival time did not equal the recipient survival time, even though the pancreas graft was still functioning. In these cases, we assumed the recipient survival time was correct for graft survival.

Statistical analysis was conducted using SAS software (Version 9.4, SAS Institute Inc., Cary, NC). Univariate analysis was performed using Cox Regression and the Kaplan Meier method for graft and recipient survival analysis. Logistic regression was used for DGF analysis. Multiple regression using backward elimination was performed to identify all variables significant for graft outcome. Specifically, proportional hazard regression was used to find factors significant for recipient and graft survival, and logistic regression was used for DGF analysis. A p-value of 0.05 was considered significant.

Results

This study looked at 227 DCD-SPK transplants in total, with 189 from DCD donors≤40 years old, and 38 from donors>40 (Fig. 1). The oldest graft used was 56 years. The study's baseline characteristics are summarized in Table 1.

Our DCD donor population was 71.4% male, with a mean age of 26.14 ± 0.73 years. 11.9% of the total population died from cerebrovascular causes (CVA). Understandably, the older group of donors >40 had a higher percentage of deaths by CVA causes compared to donors≤40 (31.6% vs. 7.9%). The older group also had a greater percent of donors with hypertension (7.9% vs. 2.6%), and donors with a terminal lab creatinine greater than 1.5 mg/dL (8% of donors>40 vs. 5% of donors≤40). There was no significant difference in the BMI of the two donor groups. The mean follow-up duration for transplants from donors≤40 was 4 years and 101 days (±83.6 days), while the mean follow-up for transplants from donors>40 was 5 years and 80 days (±210 days).

The mean recipient age in our study was 41.67 years, and there was no appreciable difference between the ages of patients receiving grafts>40 years old vs. ≤40 years old. 62.6% of recipients were male.

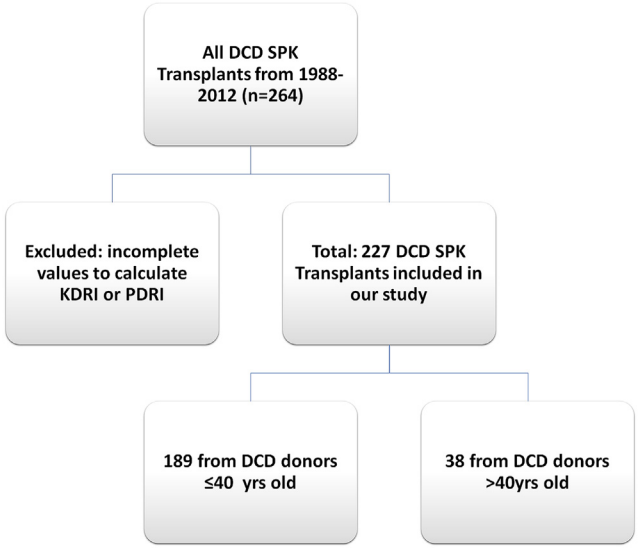

Fig. 1. Inclusion and Exclusion Criteria. DCD, Donation after Cardiac Death; SPK, simultaneous pancreas-kidney transplant; KDPI, kidney donor profile index; PDRI, pancreas donor risk index.

Table 1a
Baseline characteristics of DCD donors.

	Total (n = 227)	Donor age≤40 (n = 189)	Donor age >40 (n = 38)	p-value
Male Donor	71.4%	75.7%	50.0%	
Hx HTN	3.5%	2.6%	7.9%	
Death from CVA	11.9%	7.9%	31.6%	
Terminal Cr > 1.5 mg/dL	5%	5%	8%	
Mean BMI	24.16 ± 0.5268; 95%CI 23.13–25.19	24.21 ± 0.6208; 25%CI 23.00–25.42	23.89 ± 0.6185; 95%CI 22.69–25.08	*0.82*
Mean Donor Age (years)	26.14 ± 0.7299; 95%CI 24.71–27.56	22.22 ± 0.5175; 95%CI 21.21–23.23	45.63 ± 0.5775; 95%CI 44.51–46.75	<0.0001
Mean Follow-up Duration (days)	1618 ± 78.3; 95%CI 1465-1772	1561 ± 83.62; 95%CI 1397-1724	1905 ± 210.3; 95%CI 1498-2311	*0.10*

DCD, Donation after Cardiac Death; Hx HTN, history of hypertension; CVA, cerebrovascular accident; Cr, creatinine.

Table 1b
Baseline characteristics of DCD SPK recipients.

	Total (n = 227)	Donor age ≤ 40 (n = 189)	Donor age >40 (n = 38)	p-value
Mean Recipient Age (years)	41.67 ± 0.54; 95%CI 40.62–42.73	41.70 ± 0.58; 95%CI 40.56–42.84	41.55 ± 1.44; 95%CI 38.77–44.33	*0.92*
Male Recipient	62.6%	64.0%	55.3%	

DCD, Donation after Cardiac Death; Hx HTN, history of hypertension; CVA, cerebrovascular accident; Cr, creatinine.

Table 2
Graft Outcomes for Transplants from Donors ≥40 vs. Donors <40.

	Hazard Ratio	95% CI	P-value
Kidney Failure	2.10	1.15–3.83	<0.05
Pancreas Failure	2.07	1.16–3.70	<0.05
Recipient Mortality	1.91	0.81–4.46	*0.14*

Table 3
Donor age and graft/recipient survival.

		Donor Age ≤40	Donor Age >40
		n = 189	n = 38
Kidney Survival	1 yr	93.5% ± 1.8%	94.7% ± 3.7%
	10 yrs	66.0% ± 7.8%	46.4% ± 11.8%
Pancreas Survival	1 yr	88.2% ± 2.4%	73.4% ± 7.2%
	10 yrs	66.3% ± 6.9%s	50.3% ± 10.0%
Recipient Survival	1 yr	95.7% ± 1.5%	94.7% ± 3.7%
	10 yrs	85.7% ± 4.1%	81.7% ± 6.8%

Univariate analysis by donor age

Univariate analysis showed that SPK grafts from DCD donors>40 had double the rates of both kidney failure (HR 2.1, 95%CI 1.15–3.83, p < 0.05) and pancreas failure (HR 2.07, 95%CI 1.16–3.70, p < 0.05) compared to grafts from donors≤40. Pancreas graft survival rates at 1-year (88.2% ± 2.4% vs 73.4% ± 7.2%) and 10-years (66.3% ± 6.9% vs 50.3% ± 10.0%) were also less for donors>40. The two groups had comparable kidney graft survivals at 1-year (93.5% ± 1.81% vs 94.7% ± 3.67%), but by 10-years the >40 group again had lower survival rates (66% ± 7.8% vs. 46.4% ± 11.84%). Surprisingly, patients with grafts from donors≤40 vs. >40 had comparable 1-year (95.7% ± 4.34% vs. 94.7% ± 3.67%) and 10-year (85.7% ± 4.10% vs. 81.7% ± 6.84%) survival rates. The overall recipient mortalities were not significantly different (HR 1.9, 95%CI 0.81–4.46, p = 0.14).

Lastly, donor age was associated with a small but significant increase in DGF, with a 3% increase in the odds ratio per 1-year increase in age (OR 1.030, 95%CI 1.003–1.057, p < 0.05) (Tables 2 and 3; Figs. 2–4).

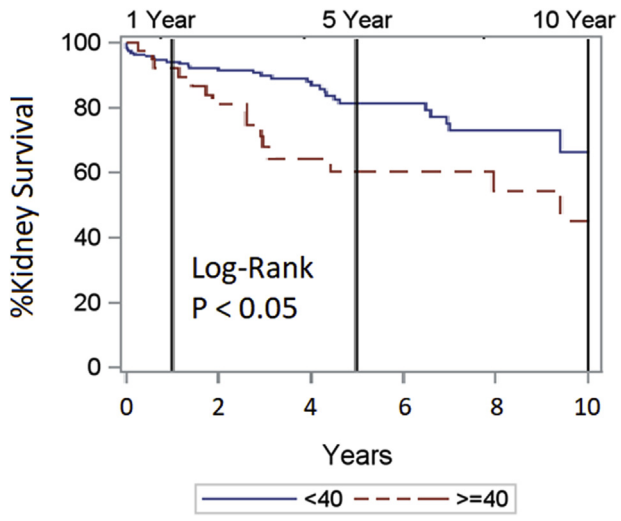

Fig. 2. Comparing death censored kidney graft survival of DCD-SPK transplants by donor age.

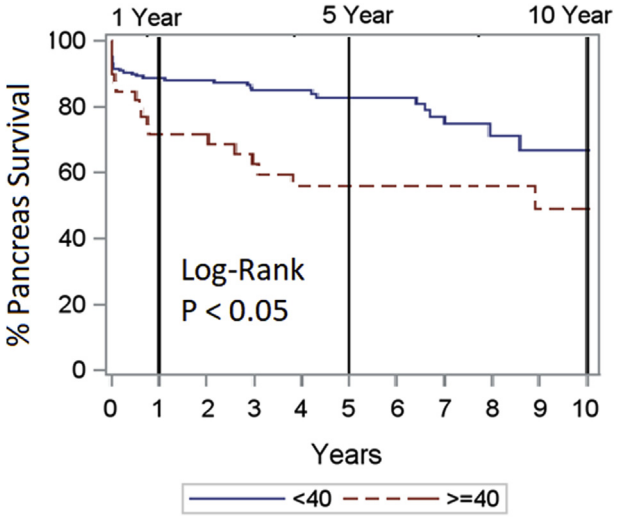

Fig. 3. Comparing death censored pancreas graft survival of DCD-SPK transplants by donor age.

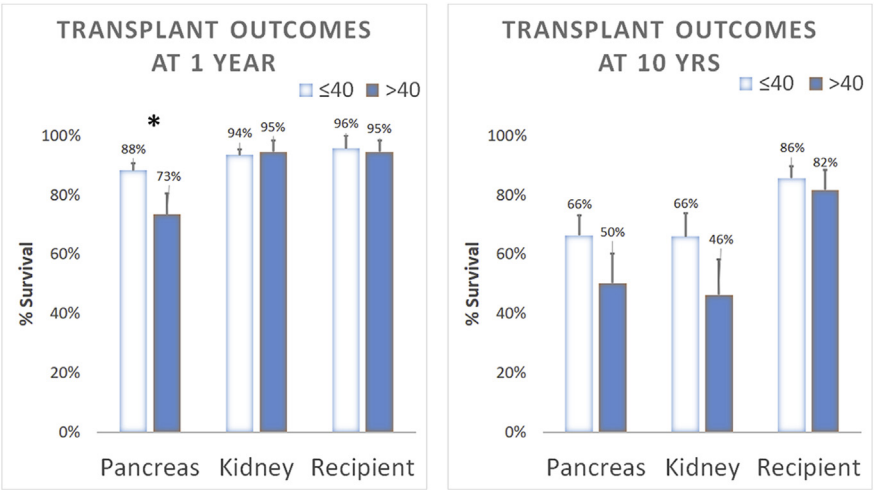

Fig. 4. 1-Year and 10-Year Outcomes of DCD-SPK Transplants by Donor Age ≤40 vs. >40.

Subgroup analysis of donor age>40

We further divided the donor age > 40 group into age 40.1–45 versus age > 45 to see if transplants from DCD donors slightly older than 40 might still be acceptable. There were 19 transplants from donors 40.1–45, and 19 from donors >45.

Results showed that risk of kidney failure was significantly higher for grafts from donors >45 in comparison to those from donor age 40.1–45 (HR 4.1, $p < 0.05$). At five years post-transplant, kidney failure rates were 50% for SPK donors>45 years and 26.5% for SPK donors 40–45 years. No significant difference was found between the two groups for pancreas failure, recipient mortality, or delayed graft function (Figs. 5–7).

Analysis of donor age ≤35 vs. >35

Having found that donor age >40 is significant for kidney and pancreas survival, we wanted to investigate younger donors to further delineate the donor age at which DCD-SPK graft quality decreases. To do this, we repeated our analysis but with donor age divided into age ≤35 versus age >35, to see if using graft age 35 as a cut-off would offer any additional benefit compared to graft age 40. There were 178 DCD-SPK grafts from donors ≤35, and 49 from donors >35. Univariate analysis (Table 4a) showed that SPK grafts from DCD-donors >35 were twice as likely to experience kidney failure (HR2.29, 95%CI1.29–4.07, $p < 0.005$), 2.5 times more likely to experience pancreas failure (HR2.59, 95%CI1.50–4.46, $p < 0.001$) and recipient failure (HR2.48, 95%CI1.11–5.53, $p < 0.05$), and twice as likely to have DGF (OR2.10, 95%CI1.07–4.12, $p < 0.05$). These values are similar to the increased risk experienced by DCD-donors >40. Furthermore, 1-year and 10-year kidney-, pancreas-, and recipient-survivals for grafts ≤35 also showed no significant improvement compared to grafts ≤40 (Table 4b). To further confirm these findings, we did multivariate analysis to rule out possible confounding effects from the following donor variables:

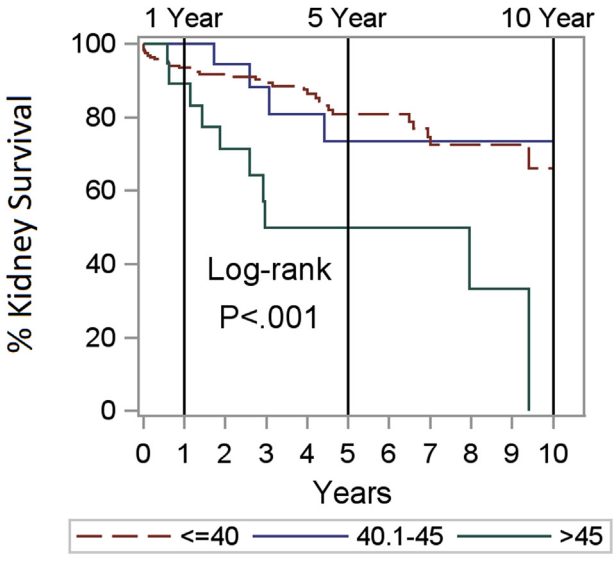

Fig. 5. Death censored kidney graft survival of DCD-SPK transplants from older donors.

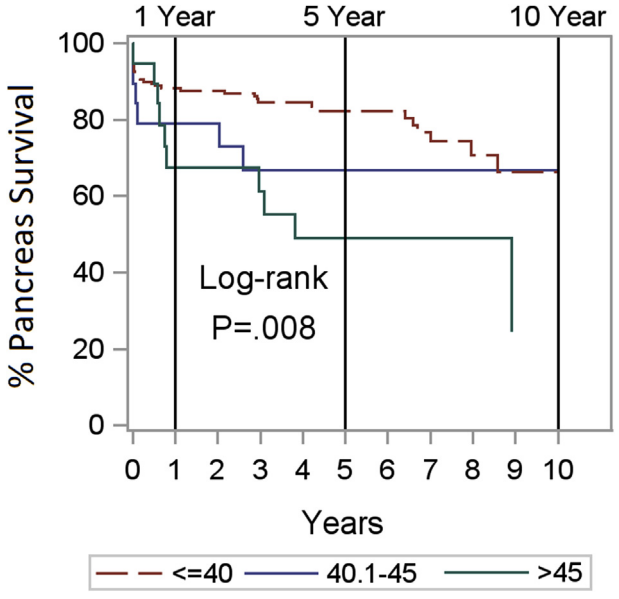

Fig. 6. Death censored pancreas graft survival of DCD-SPK transplants from older donors.

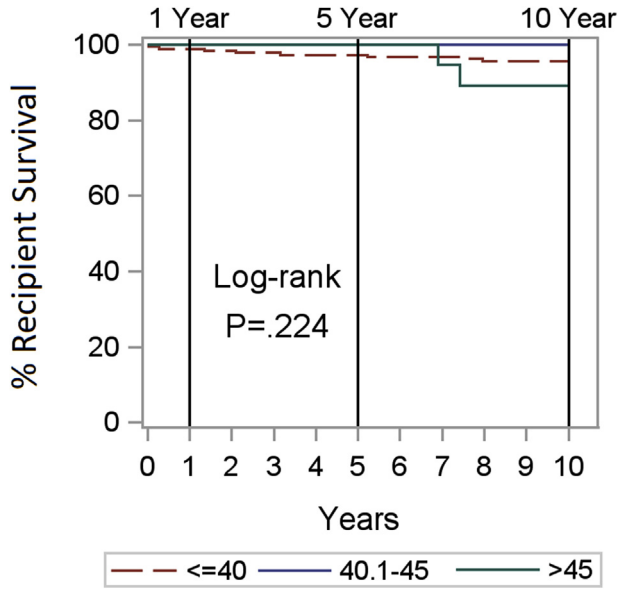

Fig. 7. Death censored recipient survival of DCD-SPK transplants from older donors.

Table 4a
Graft Outcomes for Transplants from Donors >35 vs. ≤35.

	Hazard Ratio	95%CI	P-value
Kidney Failure	2.29	1.29–4.07	<0.005
Pancreas Failure	2.59	1.50–4.46	<0.001
Recipient Failure	2.48	1.11–5.53	<0.05
	Odds Ratio	**95%CI**	**P-value**
DGF	2.10	1.07–4.12	<0.05

Table 4b
Graft/Recipient Survival for Donor Age ≤35 vs. ≤40.

		Donor Age ≤35	Donor Age ≤40
		n = 178	n = 189
Kidney Survival	1 yr	93.7% ± 1.8%	93.5% ± 1.8%
	10 yrs	66.2% ± 8.4%	66.0% ± 7.8%
Pancreas Survival	1 yr	89.2% ± 2.3%	88.2% ± 2.4%
	10 yrs	67.8% ± 7.3%	66.3% ± 6.9%
Recipient Survival	1 yr	96.0% ± 1.5%	95.7% ± 1.5%
	10 yrs	86.4% ± 4.2%	85.7% ± 4.1%

donor bmi, donor history of hypertension, and pancreas preservation time. Multivariate analysis did not show donor age >35 to be a significant predictor of recipient mortality (p = 0.07), but otherwise results were fairly consistent showing donor age >35 to correlate with a doubled risk of kidney failure, pancreas failure, and DGF (Table 5; Figs. 8–10).

Univariate analysis by donor BMI

Allografts with donor BMI <20, 20–29.9, and ≥30 did not have significantly different transplant outcomes (p > 0.5 for all endpoints, data not shown). We then looked at the general effect of increasing BMI by 1-unit. In general, higher donor BMI was predictive of pancreas failure (HR1.024 per 1-unit increase of BMI, 95% CI 1.007–1.042, p < 0.01). A 1-unit BMI increase was also associated with recipient mortality (HR1.022, 95% CI 1.003–1.041, p < 0.05)

Table 5
Independent predictors of graft outcomes based on multivariate analysis, with donor age stratified by age 35.

Kidney Graft Failure		Hazard Ratio	95% CI	P-value
	Donor Age >35	2.65	(1.24, 5.68)	<0.05
Pancreas Graft Failure	**Donor Age > 35**	2.65	(1.53, 4.59)	<0.001
	Donor BMI[A]	1.03	(1.01, 1.04)	<0.005
Recipient Mortality	**Donor Hx of HTN**	5.47	(1.60, 18.74)	<0.01
	Donor BMI[A]	1.02	(1.00, 1.04)	<0.05
DGF		**Odds Ratio**	**95% CI**	**P-value**
	Donor Age > 35	2.00	(1.01, 3.97)	<0.05
	Donor BMI[A]	1.12	(1.04, 1.21)	<0.005

Hx HTN, history of hypertension; DGF, delayed graft function.
[A] Average effect per 1-unit increase in donor BMI.

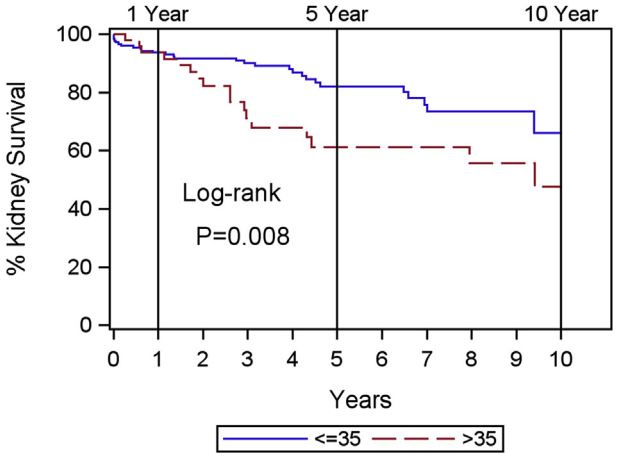

Fig. 8. Comparing Death Censored Kidney Graft Survival of DCD-SPK Transplants by Donor Age ≤35 vs. >35.

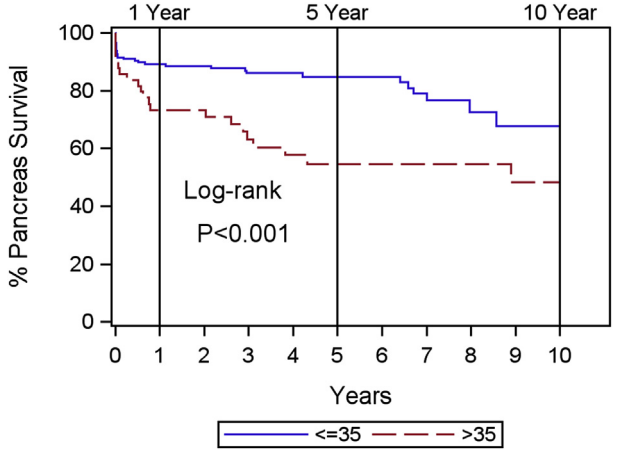

Fig. 9. Comparing Death Censored Pancreas Graft Survival of DCD-SPK Transplants by Donor Age ≤35 vs. >35.

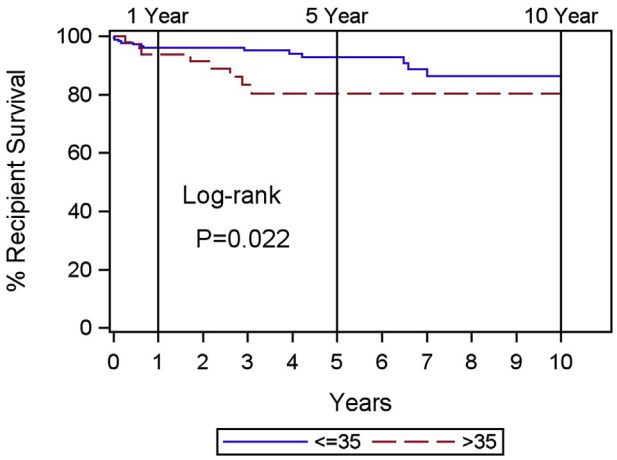

Fig. 10. Comparing Death Censored recipient Survival of DCD-SPK Transplants by Donor Age ≤35 vs. >35.

Table 6
Graft outcomes with a BMI increase of 1-unit.

	HR or OR	95% CI	P-value
Kidney Graft Failure	HR 1.01	1.00–1.03	*0.12*
Pancreas Failure	HR 1.02	1.01–1.04	<0.01
Recipient Mortality	HR 1.02	1.00–1.04	<0.05
DGF	OR 1.12	1.04–1.21	<0.005

DGF, delayed graft function.

and DGF (OR1.119, 95%CI, 1.035–1.208, $p < 0.005$), but did not affect kidney graft failure (HR 1.014, 95%CI 0.996–1.032, $p = 0.119$) (Table 6).

Univariate analysis by CIT, WIT, and PPT

We performed univariate analysis by CIT, WIT, and PPT. CIT was a significant predictor of pancreas failure (Table 7a). Transplants with CIT 10–12.49 h were 3.95 fold more likely to experience pancreas failure (HR 3.95, 95%CI 1.43–10.89, $p < 0.05$) and those with CIT 17.5–19.99 h were 3.83 times more likely to experience failure (HR 3.83, 95%CI 1.29–11.34, $p < 0.05$) when compared to transplants with CIT<10 h s. Surprisingly, the other CIT categories, including CIT≥20 h s, were not significant for pancreas failure. On closer inspection of the raw data, these groups had much smaller sample sizes after censoring for transplants that did not reach the endpoint of pancreas failure, compared to groups that did achieve significance (Table 7b). CIT did not affect kidney graft function, recipient survival, or DGF (Table 7c–e).

WIT was not found to have a significant effect on graft or recipient survival (Table 8a–c). There was insufficient data on DGF

Table 7a
Pancreas failure as a function of kidney cold ischemic time.

Cold Ischemic Time	Hazard Ratio[A]	95% CI
Per average 1-hr increase	1.01	0.96–1.06
10–12.49 h	3.95	1.43–1 0.89
12.5–14.99 h	1.54	0.44–5.37
15–17.49 h	1.08	0.34–3.48
17.5–19.99 h	3.83	1.29–11.34
≥20 h	1.90	0.59–6.08

P-value = 0.01.
[A] Hazard ratios are expressed in comparison to cold ischemic time <10 h.

Table 7b
Number of transplants that met the endpoint of pancreas failure.

Cold Ischemic Time	Sample Size	Number of Pancreas Failures	% Censored
<10 h	52	5	90.38
10–12.49 h	46	15	67.39
12.5–14.99 h	27	5	81.48
15–17.49 h	40	7	82.5
17.5–19.99 h	23	10	56.52
>=20 h	27	8	70.37
Total	**215**	**50**	**76.74**

Table 7c
Recipient mortality as a function of kidney cold ischemic time.

Cold Ischemic Time	Hazard Ratio[A]	95% CI
Per average 1-hr increase	1.03	0.96–1.11
10–12.49 h	7.64	0.92–63.58
12.5–14.99 h	2.84	0.25–31.67
15–17.49 h	2.92	0.82–26.81
17.5–19.99 h	8.10	0.93–70.13
≥20 h	4.05	0.43–37.84

P-value = 0.22.
[A] Hazard ratios are expressed in comparison to cold ischemic <10 h.

Table 7d
Kidney failure as a function of kidney cold ischemic time.

Cold Ischemic Time	Hazard Ratio[A]	95% CI
Per average 1-hr increase	1.01	0.96–1.07
10–12.49 h	2.83	0.98–8.16
12.5–14.99 h	1.51	0.43–5.25
15–17.49 h	1.15	0.37–3.62
17.5–19.99 h	2.70	0.89–8.22
≥20 h	1.78	0.56–5.61

P-value = 0.20.
[A] Hazard ratios are expressed in comparison to cold ischemic time <10 h.

Table 7e
DGF per 1-hour increase in kidney cold ischemic time.

	Hazard Ratio	95% CI	p-value
Per average 1-hr increase	1.03	0.98–1.08	*0.30*

DGF, delayed graft function.

Table 8a
Recipient Mortality as a Function of Kidney Warm ischemic Time.

Warm ischemic Time	Hazard Ratio relative to WIT≤20 min	95% CI
20.1–40 min	0.72	*0.25–2.12*
≥40 min	*No Available Data*	

P-value = 0.84.
WIT, warm ischemic time.

Table 8b
Pancreas Failure as a Function of Kidney Warm ischemic Time.

Warm ischemic Time	Hazard Ratio relative to WIT≤20 min	95% CI
20.1–40 min	0.95	*0.49–1.85*
≥40 min	0.47	*0.06–3.42*

P-value = 0.75.
WIT, warm ischemic time.

Table 8c
Kidney Failure as a Function of Kidney Warm ischemic Time.

Warm ischemic Time	Hazard Ratio relative to WIT≤20 min	95% CI
20.1–40 min	0.84	*0.40–1.74*
≥40 min	0.46	*0.06–3.39*

P-value = 0.68.
WIT, warm ischemic time.

Table 8d
Delayed Graft Function by Kidney Warm ischemic Time[A].

Raw Data				
	WIT≤20 min	**WIT 20.1–39.9 min**	**WIT≥40 min**	**Total**
No DGF	117	36	7	160
	54.42	16.74	3.26	74.42
	73.13	22.50	4.38	
	74.52	70.59	100.00	
Yes DGF	40	15	0	55
	18.60	6.98	0.00	25.58
	72.73	27.27	0.00	
	25.48	29.41	0.00	
Total	157	51	7	215
	73.02	23.72	3.26	100.00

Statistical Test	**P-Value**
Chi-Square	P = 0.247
Cochrane – Armitage Test	P = 0.661

WIT, kidney warm ischemic time; DGF, delayed graft function.
[A] 12 data points were null for DGF (not shown here).

to perform logistic regression analysis by WIT, however a chi-square test of what data was available showed a lack of significance for DGF as well (Table 8d).

As shown in Table 9a–b, PPT also had no effect on kidney graft function, pancreas graft function, or recipient survival. PPT and DGF were shown to be dependent variables ($Chi^2 < 0.05$); accordingly, upon investigating the effect of increasing PPT by 1-unit, no significant difference was found in DGF odds (OR1.04, 95% CI 1.00–1.09, $p > 0.05$).

Table 9a
Graft outcomes as a function of pancreas preservation time.

Outcome	Pancreas Preservation Time	Hazard Ratio[A]	95% CI	p-value
Recipient Mortality	**10–14.9 h**	0.51	0.14 –1.81	*0.42*
	≥ 15 h	1.07	0.39 –2.90	
Pancreas Graft Failure	**10–14.9 h**	0.59	0.26 –1.33	*0.18*
	≥ 15 h	1.16	0.61 –2.23	
Kidney Graft Failure	**10–14.9 h**	0.94	0.39 –2.29	*0.29*
	≥ 15 h	1.55	0.72 –3.34	

[A] Hazard ratios are expressed in comparison to graft outcomes for pancreas preservation time <10 h.

Table 9b
Delayed graft function per 1-hour increase in pancreas preservation time.

	Hazard Ratio	95% CI	p-value
Per average 1-hr increase	1.04	1.00–1.09	*0.068*

Table 10
Independent predictors of graft outcomes based on multivariate analysis.

Kidney Graft Failure		**Hazard Ratio**	**95% CI**	**P-value**
	Donor Age > 40	3.13	(1.37, 7.13)	<0.01
	Donor BMI[A]	1.1	(1.00, 1.20)	<0.05
Pancreas Graft Failure	**Donor Age > 40**	2.35	(1.32, 4.19)	<0.005
	Donor BMI[A]	1.03	(1.01, 1.04)	<0.005
Recipient Mortality	**Donor Hx of HTN**	5.47	(1.60, 18.74)	<0.01
	Donor BMI[A]	1.02	(1.00, 1.04)	<0.05
DGF		**Odds Ratio**	**95% CI**	**P-value**
	Donor BMI[A]	1.12	(1.04, 1.21)	<0.005

Hx HTN, history of hypertension; DGF, delayed graft function.
[A] Average effect per 1-unit increase in donor BMI.

Multivariate analysis

We performed multivariate analysis to confirm if our findings were dependent upon one another. The same donor variables were preserved, and analyzed with the same endpoints in order to find variables which are independent predictors of graft outcomes (Table 10). A few additional factors were also included in our multivariate analysis, including: donor gender, donor history of hypertension (dHTN), HLA match level, peri-operative use of vasopressin (ddAVP), recipient age, and recipient gender.

Multivariate analysis determined that donor age and donor BMI are both independent predictors of kidney graft failure and pancreas graft failure. SPK grafts from donors>40 were three times more likely to result in kidney failure, and two times more likely to result in pancreas failure. Donor BMI was also found to have a mild effect on increasing both DGF (OR 1.12, 95%CI 1.04–1.21, $p < 0.005$), and recipient mortality (HR1.02, 95%CI 1.00–1.04, $p < 0.05$). The only variable to profoundly affect recipient mortality was dHTN, which increased recipient mortality 5-fold.

Subgroup analysis of transplants performed after 2000

Our study cohort spans transplants performed over a relatively long period of time (October 1987 to December 2012). Given that no significant changes in transplant eligibility criteria or transplantation protocols were made during this time, we feel that this data is representative of the current population. However, in order to clarify this concern, we confirmed our findings by performing a subgroup analysis of transplants performed after January 2000 as this marks a change in the era of immunosuppression modification (Table 11; Figs. 11–13).

Table 11
Subgroup analyses of transplants performed Post-2000.

Kidney Graft Failure		**Hazard Ratio**	**95% CI**	**P-value**
	Donor Age > 40	2.34	(1.23, 4.44)	<0.01
	Donor Hx of HTN	5.76	(2.23, 14.87)	<0.0005
Pancreas Graft Failure	**Donor Age > 40**	2.45	(1.33, 4.52)	<0.005
	Donor Hx of HTN	2.95	(1.16, 7.48)	<0.05
Recipient Mortality	**Donor Age > 40**	2.74	(1.08, 6.95)	<0.05
	Donor Hx of HTN	5.29	(1.54, 18.16)	<0.01
DGF		**Odds Ratio**	**95% CI**	**P-value**
	Donor BMI[A]	1.13	(1.04, 1.23)	<0.005

Hx HTN, history of hypertension; DGF, delayed graft function.
[A] Average effect per 1-unit increase in donor BMI.

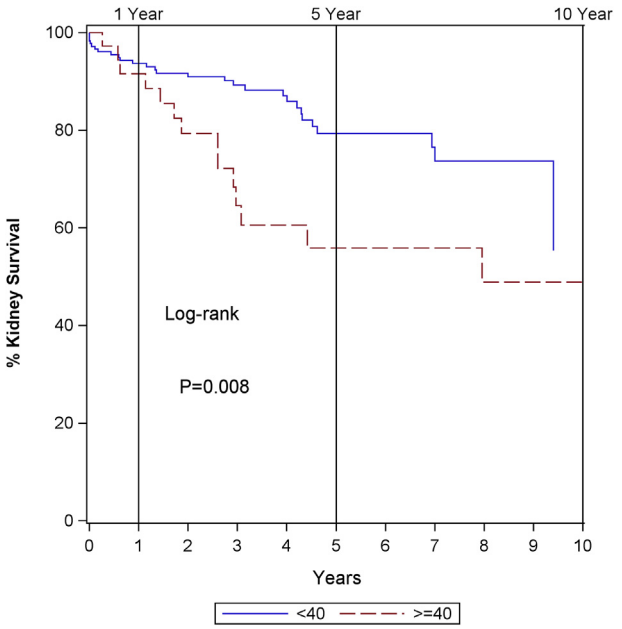

Fig. 11. Death censored kidney graft survival of DCD-SPK transplants after 2000.

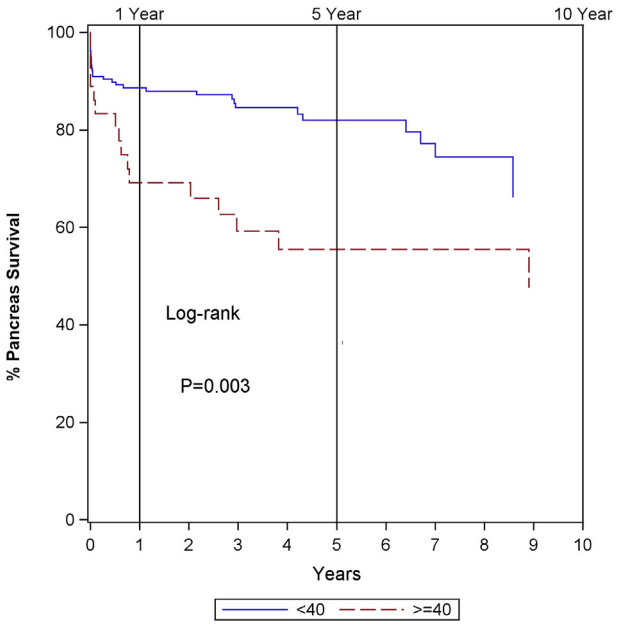

Fig. 12. Death censored pancreas graft survival of DCD-SPK transplants after 2000.

After removing all transplants performed before the year 2000, 179 transplants remained in the donor≤40 group, and 35 remained in the donor>40 group. Results from univariate analyses of the more recent transplants confirmed that donor age>40 doubled the rates of both kidney failure (HR 2.34, 95%CI 1.23–4.44, P < 0.01) and pancreas failure (HR 2.45, 95% CI 1.33–4.52, p < 0.005). Furthermore, donor age>40 correlated with higher recipient mortality (HR 2.74, 95%CI 1.08–6.95, p < 0.05), even though this had not reached significance in the overall 25-year data.

Donor history of hypertension was confirmed to predict higher recipient mortality (HR 5.29, 95%CI 1.54–18.16, p < 0.01), although surprisingly it was also predictive of pancreas failure (HR 2.95, 95% CI 1.16–7.48, p < 0.05) and kidney failure (HR 5.76, 95% CI 2.23–14.87, p < 0.0005), neither of which had reached significance in the 25-year data.

Lastly, donor BMI was predictive of higher rates of DGF, with a 5% increase in the odds of DGF per 1-unit increase in BMI (OR1.133, 95%CI 1.04–1.23, p < 0.005). Donor BMI was not predictive of pancreas failure, kidney failure, or recipient survival in post-2000 transplants. WIT, PPT, and CIT did not reach significance for any endpoint.

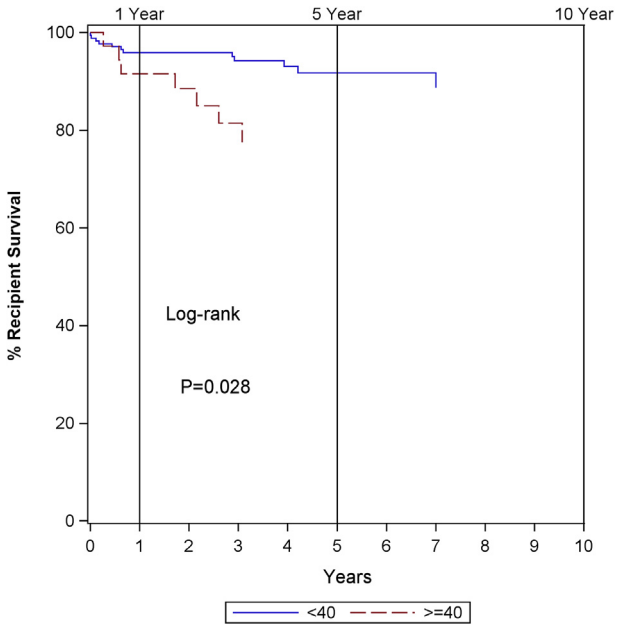

Fig. 13. Death censored recipient survival of DCD-SPK transplants after 2000.

Comparison of donor age>40 versus PDRI and KDPI

Based on our findings that donor age is an independent predictor of SPK graft function, we wanted to take a closer look at the predictive value of DCD donor age>40, and how it compares to the predictive value of the PDRI.

We calculated the predicted 1-year pancreas and kidney graft survivals for each individual SPK transplant, using the KDPI and PDRI formulas. These survivals were then averaged for donors>40 and donors≤40, and compared to the survival predicted by donor age alone. The average 1-year pancreas graft survival for donors>40 as calculated from the PDRI was 77.3% ± 0.1%. This is within range of the 73.4% ± 7.2% 1-year pancreas survival that we found for donors>40. Donors≤40 had a PDRI predicted 1-year pancreas survival of 82.4% ± 0.4%, which is considerably less than the survival of 88.2% ± 2.4% we found in our donor age≤40 population.

The 1-year kidney graft survivals predicted by KDPI were statistically different for grafts>40 vs. ≤40, with 90.4% ± 0.7% of the older grafts predicted to survive at 1-year, compared to 93.0% ± 0.2% of grafts ≤40. In comparison univariate analysis with age>40 alone gave graft survivals which were in range of the KDPI predictions (94.7% ± 3.67% for grafts>40, and 93.5% ± 1.81% for grafts≤40), but were not statistically different between the two groups.

Discussion

Over recent decades, DCD organs have become increasingly accepted as alternative sources of organ allografts.[4,5] Although DCD-SPK organs generally fare worse than DBD-SPK organs in

terms of DGF and recipient length of stay in hospital,[7,16] studies have also shown that accepting an available DCD graft is often preferable to remaining on the waiting list.[8,9] That being said, the decision on whether or not to take a potential DCD-SPK organ is still a challenging one. This is in part due to the impossibility of predicting future graft availability if the patient decides to wait, and in part due to our lack of knowledge on how to predict a DCD-SPK graft's outcomes based on donor and organ information available prior to organ retrieval. To help bridge this knowledge gap, our group performed a retrospective chart review of UNOS data looking at the effect of donor and organ factors on DCD-SPK transplant outcomes. Results from this project, which is the largest study to date focusing specifically on DCD-SPK transplants, along with our focus on both short and long-term outcomes, will add to the current knowledge base on predictors of DCD-SPK graft function.

Our findings showed that SPK grafts from DCD donors>40 have a 2-fold risk of pancreas graft failure and of kidney graft failure. This confirms findings from previous studies looking at donor age and graft loss in SPK transplants.[9,17] In particular, Salvalaggio et al.'s study using pooled DCD- and DBD-SPK data showed that donor age>45 was associated with a 1.28-fold increase in kidney failure and 1.32-fold increase in pancreas failure.[9] This suggests that the effect of older donor age on DCD-SPK transplants is more extreme than it is for SPK transplants in general, with a lower age cut-off and a higher risk of graft failure once that age is exceeded.

It should be noted that transplants with grafts from donors>40 vs. $\leq$40 had similar recipient ages and donor BMI, therefore eliminating these as possible confounders. We found that a greater percentage of the older donors had a history of hypertension, death due to cerebrovascular causes, or died with a terminal creatinine over 1.5 mg/dl. All of these worsen prognosis and could help explain the higher rates of graft loss from older donors. Subgroup analysis of the older donor group showed that as donor age increases to >45, risk of kidney graft failure becomes 4.1 times that of donors 40.1–45 years old. There was, however, no difference in pancreas graft survival or recipient survival for donors>45 when compared to donors 40.1–45. Lastly, we repeated our analysis with a donor age cut-off of $\leq$35 vs. >35, to assess if age 40 is the true threshold at which DCD-SPK outcomes significantly worsen, or if the increased risk starts at a donor age even younger than donor age 40. Findings showed no significant improvement in graft and recipient survival with grafts $\leq$35 compared to $\leq$40, confirming that there is limited benefit to using a stricter cut-off than donor age 40.

Our study uses data from transplantations performed over 25 years, a relatively broad time range. To substantiate the validity of our findings to present day populations, we repeated key univariate analyses using only recent data from 2000 to 2012. This subgroup analysis of more recent data confirmed our key findings, with donors>40 having a doubled risk of both kidney and pancreas failure.

Although transplants from DCD donors>40 experienced significantly more graft failure, this did not translate to a statistically significant difference in recipient mortality. Possible explanations include lack of power in terms of sample size and follow-up time, successful retransplantations for these patients, or perhaps simply because kidney recipients often have multiple co-morbidities and may die of other causes, thus diminishing the correlation between graft survival and recipient mortality. Importantly, analysis of donor age in general did show a small, but statistically significant increase of 3.6% in recipient mortality per 1-year increase in age. Furthermore, there was a trend towards lower 10-year survival for recipients of grafts from donors>40 (81.7% ± 6.8% vs. 85.7% ± 4.1%). It may therefore be beneficial to perform another study in the future when more data is available and with longer follow-up times, to more accurately examine the relation between donor age>40 on recipient mortality. However, when considering the alternative of staying on the transplant waitlist and experiencing the gradually worsening end organ effects of diabetes, it is likely a discussion which should be conducted with the potential recipients. Importantly, our analysis suggests that predictions for kidney and pancreas graft survival using KDPI and PDRI were comparable to survival predictions obtained using donor age alone. Moreover, unlike the PDRI, our study provides predictions of outcomes up to ten years post-transplant. This suggests that in circumstances where not all data for PDRI are available, donor age may be used as an acceptable approximator of DCD-SPK graft quality and transplant outcomes.

Although donor BMI was found to increase pancreas graft failure, recipient mortality, and DGF, these associations disappeared when we stratified BMI into the commonly accepted categories (BMI <20, 20–29, $\geq$30). Therefore, while we know that it is an important factor, it is hard to define a donor BMI cut-off that can be used as a marker for inferior outcomes. Further experimentation with more data, or with different stratifications, may yield clearer results.

WIT and PPT were not found to impact graft or patient survival of DCD-SPK organs. CIT did impact pancreas survival ($p = 0.01$), with CIT 10–12.49 h s and CIT 17.5–19.99 h s conferring higher risk of pancreas failure in comparison to CIT<10 h s. The absence of significance for CIT intervals in between these times (i.e. CIT 12.5–14.99 h s and 15–17.49 h) can be explained by their smaller sample size, suggesting that greater power is needed to fully delineate the predictive effect of CIT. This is in line with our initial hypothesis, based on previous research, that CIT would negatively impact long-term DCD-SPK outcomes. A previous study of 170 SPK transplants (both DCD and DBD) showed that cold ischemic time was an independent predictor of early pancreatic graft loss occurring within 3 months of SPK transplantation.[17] Another research group also found a significant association between CIT>20 h and decreased pancreas graft survival amongst 376 SPK transplants.[18] Interestingly, this same study went further and separated transplants from younger vs. older donors and found that while older donors (>25 years old) were much more susceptible to inferior outcomes from prolonged CIT, younger donors (<25 years old) experienced minimal impact from CIT. As a comparison, the average donor age in our study was 26 years and the average CIT was 14 h s. Therefore we had expected to see inferior outcomes with prolonged CIT. Other possible explanations for the lack of effect for CIT 12.5–17.49 h s and CIT$\geq$20 h s include the DCD nature of transplants in our study, since previous studies did not have enough DCD-SPK transplants to achieve significance. Furthermore, our study only had 27 DCD-SPK transplants with CIT>20 h, which may be insufficient to demonstrate the effect seen with previous research.

Surprisingly, donor history of hypertension was found to be the strongest predictor of recipient mortality, increasing it by 5-fold. This is perplexing because donor hypertension was not found to have a significant effect on kidney or pancreas graft failure, making the mechanism of increased mortality unclear. A recent UK study on DCD kidney transplantation also identified donor hypertension as a predictor for recipient mortality.[19] Although the study only found a hazard ratio of 1.27, it helps to confirm our finding that donor hypertension in an important variable, and therefore worthy of future study in the DCD-SPK population. This finding is likely attributable to microvascular disease and atherosclerosis which are commonly found in patients with hypertension.[20,21] It is plausible that grafts coming from hypertensive individuals require a greater mean arterial pressure to maintain adequate microperfusion of the graft, and hence have poorer outcomes in non-hypertensive recipients. Unfortunately we were unable to further pursue this

theory due to lack of data on recipient blood pressures after receiving grafts from hypertensive vs. non-hypertensive donors, so this hypothesis would need to be further evaluated in future studies.

There are some limitations to our study design which are important to note. Firstly, this was a retrospective review of a large database with inherent errors, so there may be confounders or inaccurate entries which we could not account for. There was a limited amount of data available on transplants from older donors>40, and this may impact the power of our study. The inherently complex nature of transplantation also means that multiple factors contribute to the success of transplantation, not all of which can be accounted for in a single study that is limited by what is available in the UNOS databank. Lastly, biases may have been made in the process of allocating grafts to different recipients by the various programs, all of which have inherent protocols they abide by. A future prospective study would help to validate our findings.

In conclusion, donor age appears to be the most important predictor of long-term graft function in a DCD-SPK transplant. Donor age>40 results in transplants with double the risk of kidney graft failure and pancreas graft failure, compared to donor age$\leq$40. Increasing donor age is also associated with increased recipient mortality and DGF. Donor BMI was also a predictor of pancreas failure, recipient mortality, and DGF. This study contributes to our ability to predict long term graft outcomes following DCD-SPK transplantation and suggests that donor age may be as important a predictor as the KDPI or PDRI indices.

Conflicts of interest

The authors declare no conflicts of interest.

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