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Original Article

The impact of time to death in donors after circulatory death on recipient outcome in simultaneous pancreas-kidney transplantation

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ABSTRACT

The time to arrest donors after circulatory death is unpredictable and can vary. This leads to variable periods of warm ischemic damage prior to pancreas transplantation. There is little evidence supporting procurement team stand-down times based on donor time to death (TTD). We examined what impact TTD had on pancreas graft outcomes following donors after circulatory death (DCD) simultaneous pancreas-kidney transplantation. Data were extracted from the UK transplant registry from 2014 to 2022. Predictors of graft loss were evaluated using a Cox proportional hazards model. Adjusted restricted cubic spline models

Abbreviations: DCD, donation after circulatory death; FWIT, functional warm ischemia time; IQR, interquartile range; NHSBT, NHS Blood and Transplant; NRP, Normothermic regional perfusion; SPK, simultaneous pancreas-kidney transplantation; TTD, time to death.

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were generated to further delineate the relationship between TTD and outcome. Three-hundred-and-seventy-five DCD simultaneous kidney-pancreas transplant recipients were included. Increasing TTD was not associated with graft survival (adjusted hazard ratio HR 0.98, 95% confidence interval 0.68-1.41, $P = .901$). Increasing asystolic time worsened graft survival (adjusted hazard ratio 2.51, 95% confidence interval 1.16-5.43, $P = .020$). Restricted cubic spline modeling revealed a nonlinear relationship between asystolic time and graft survival and no relationship between TTD and graft survival. We found no evidence that TTD impacts pancreas graft survival after DCD simultaneous pancreas-kidney transplantation; however, increasing asystolic time was a significant predictor of graft loss. Procurement teams should attempt to minimize asystolic time to optimize pancreas graft survival rather than focus on the duration of TTD.

1. Introduction

Simultaneous pancreas-kidney (SPK) transplantation is the optimum therapy for selected patients with end-stage renal disease and insulin-dependent diabetes mellitus.[1-5] Despite this, a mismatch between the number of organs available and the number of patients on the waiting list limits access to SPK transplantation. So far, in 2023, the NHS Blood and Transplant (NHSBT) pancreas transplant waiting list is the highest it has been during the last 10 years, highlighting the shortage of organs and the need to optimize utilization. In the UK, pancreas grafts from donors after circulatory death (DCD)[6] have been used to good effect in order to improve access to beta cell replacement therapy.[6,7]

Some centers, however, remain reluctant to use pancreas grafts from DCD[6] because of historical reports suggesting that these grafts have higher failure rates than pancreas grafts from donors after brainstem death.[8-10] Nevertheless, improving the utilization of the DCD pancreas donor pool is likely to significantly shorten waiting times and reduce the SPK waiting list, especially when used in conjunction with other advances in organ preservation, such as normothermic regional perfusion (NRP).[11-13] Previous retrospective studies have demonstrated equivalent short- and long-term outcomes after DCD SPK transplantation when comparing DCD grafts with donors after brainstem death grafts.[4,7,14-16] Indeed, some studies even suggest the outcomes are even better for DCD SPK.[14]

Following the withdrawal of life-sustaining treatment, time to death (TTD) can vary with fluctuations in hemodynamic parameters leading to variable periods of warm ischemia to the abdominal viscera. Donors may decline rapidly, gradually, or demonstrate a period of relative stability followed by a rapid decline after treatment withdrawal.[17] Time pressures may constrain organ procurement teams from waiting indefinitely for donor asystole, leading to the team standing down unnecessarily. Hypotension, hypoxia, and vascular shunting toward the brain and heart may also lead to organ injury that is not fully reflected in the donor's systolic blood pressure or oxygen saturation.[18] It is accepted that reducing stand-down times for procurement teams leads to less ischemic injury in grafts; however, this will have significant implications for the number of grafts available, waiting list management, and a poorer utilization rate. With this in mind, there is no national or international consensus on what is accepted practice at stand-down times for SPK DCD transplants.

We aimed to assess what impact donor TTD had on pancreas graft outcome in DCD SPK transplantation. We hypothesize that a prolonged TTD is associated with an increased risk of pancreas graft loss.

2. Materials and methods

2.1. Setting

We performed a retrospective review of adult ($\geq$ 18 years) DCD SPK graft recipients in the UK from January 1, 2014 to December 31, 2022. Data were extracted from the UK Transplant Registry maintained by NHSBT following approval from the UK Pancreas Advisory Group. The common closure date of the study was April 1, 2023. Patients are placed on a combined waiting list for SPK, solitary pancreas transplantation (pancreas after kidney transplantation and pancreas transplantation alone), and islet-cell transplantation (islet-cell transplantation alone, simultaneous islet cell and kidney transplantation, or islet cell after kidney transplantation), with offers made on a named-patient basis determined by the National Pancreas Offering Scheme.[19] All donors were within Maastricht criteria III (controlled DCD).[20] Contraindications to pancreas donation in the UK have been previously described in the most current British Transplantation Society guidelines.[21] Potential recipients for SPK transplantation are listed based on nationally agreed criteria as previously described[22] but must have an estimated glomerular filtration rate $\leq$20 mL/min and insulin-treated diabetes mellitus. SPK transplantation is performed by 8 transplant units in the UK; all data was anonymized, including the transplant center.

2.2. Organ procurement and transplantation

In the UK a 5-minute "no-touch" time is observed for confirmation of donor death as previously described.[23] Medical interventions to facilitate organ donation (eg, systemic heparinization

and vascular cannulation) cannot be performed prior to confirmation of death. Organ procurement is commenced once death is confirmed, and the no-touch period has been observed. In the UK, procurement teams will wait up to 3 hours for circulatory arrest following treatment withdrawal for donor asystole to occur,[24] however, implanting centers generally decline pancreas grafts after 1 hour. Pancreas and kidney grafts are placed into static cold storage boxes for transportation to implanting centers. NRP was used variably by the organ procurement teams. Transplantation and post-operative immunosuppression protocols were determined by the implanting center.

2.3. Definitions and outcomes

TTD was defined as the time from withdrawal of life-sustaining treatment to donor asystole (absence of a palpable arterial pulse and/or cessation of cardiac electrical activity) (Fig. 1). Asystolic time was from asystole until cold aortic perfusion. Functional warm ischemia time (FWIT) was the time from donor systolic blood pressure <50 mmHg and/or arterial oxygen saturation (SaO_2) <70% to cold aortic perfusion. Pancreatectomy time was from cold aortic perfusion to placement of the pancreas graft in ice on the back table. Our primary outcome was time to pancreas graft failure, which was defined as a return to sustained exogenous insulin treatment or graft pancreatectomy, whichever occurred first. This was censored for deaths with a functioning graft or those with a functioning graft at the common closure data of the study. The Igls criteria[25] was not used, as NHSBT only routinely began collecting this data from 2019 onward. Death-censored kidney graft failure was defined as a return to dialysis or retransplantation, whichever occurred first. Patient survival was calculated from the time of transplantation to death.

2.4. Statistical analyses

Continuous variables are presented as means/medians with standard deviations/interquartile ranges (IQR). Missing explanatory data were imputed with multiple imputations using the fully conditional specification technique, applied to generate 5 imputed datasets. Supplementary Table 1 summarizes missing data; those variables with missing data were imputed. All variables listed in Supplementary Table 1, plus graft loss at 1 year, were used as predictors in the imputation model.

Continuous variables were compared using the t-test. Categorical variables were compared using the Chi-squared test or Fisher exact test, where appropriate. Cox regression was used to build multivariable graft survival models. Donor, graft, recipient, and operative factors were initially screened and included in multivariable models if they had previously been described as predictors of graft outcome or if they were retained as significant predictors in our cohort (using backward likelihood ratio stepwise selection). For Cox regression models, results from the 5 imputed datasets were pooled according to Rubin's rules. To assess the assumption of proportional hazards for Cox regression models scaled Schoenfeld residual versus time plots were assessed visually. In addition, Schoenfeld tests were performed, assessing whether scaled Schoenfeld residuals changed over time. There was no evidence of violation of the proportional hazards assumption in any of our Cox regression models, either on visual assessment or Schoenfeld tests (at the $P < .05$ level). The results of these models are presented as adjusted hazard ratios with 95% confidence intervals. As there were only 9 TTD >60 minutes, a sensitivity analysis was performed with these "extreme" values removed.

Ischemic times were kept as continuous variables, and those that were right-skewed (all except cold ischemic time) were log-

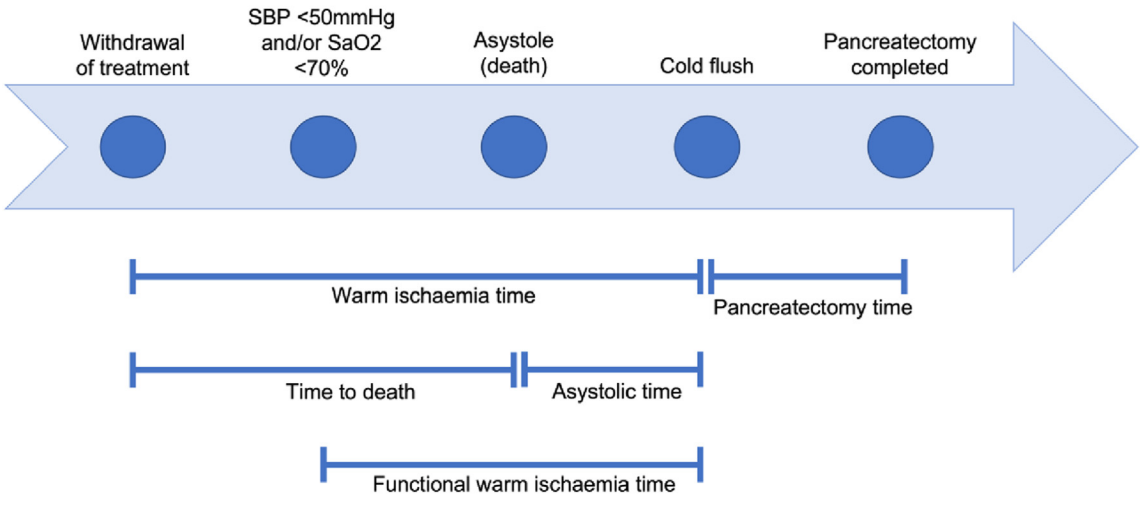

Figure 1. Timeline of events following withdrawal of life-sustaining treatment from a donor after circulatory death. SBP, systolic blood pressure.

transformed (base 2) prior to fitting into our main Cox regression models. TTD, time to FWIT, and FWIT all overlap (Fig. 1); these factors were fitted into separate regression models to avoid multicollinearity. Models were also fitted for recipient survival. As an additional analysis, we repeated our main Cox regression models for graft survival using the restricted cubic spline approach (3 knots located at the 10th, 50th, and 90th percentiles) to assess the impact of TTD and asystolic time on outcome without assuming a linear relationship. The Kaplan-Meier method was used to estimate graft and patient survival, with the log-rank test used for comparisons between groups. Nonimputed data was used for this exploratory analysis. For all statistical tests, significance was set at $P < .05$. All analyses were performed using SPSSversion 26 (IBM Corp), and figures were generated using R (R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Demographic variables in the donors and recipients. Continuous variables are presented as means ± standard deviation and categorical variables are presented as frequencies and percentages.

Variable	Value	Percentage (%)
Donor		
Age (y)	30.7 ± 12.8	-
Sex		
Male	231	61.6%
Female	144	38.4%
Cause of death	176	46.9%
Hypoxic brain injury	100	26.7%
Intracranial hemorrhage	46	12.3%
Trauma	14	3.7%
Cerebral vascular accident Other cause	39	10.4%
Normothermic regional perfusion	43	11.5%
Recipient		
Age (y)	41.5 ± 8.7	
Sex		
Male	223	59.5%
Female	152	60.5%
BMI (kg/m^2)	25.2 ± 3.6	
Diabetes		
Type 1	274	73.1%
Type 2	14	3.7%
Missing	87	23.2%
Waiting time (d)	371.8 ± 289	
Dialysis	213	56.8%
Pretransplant hemoglobin A1c (%)	35.6 ± 11.9	
First pancreas transplant	371	98.9%
Duct management		
Enteric side-to-side	247	65.9%
Enteric Roux en Y	78	20.8%
Missing	50	13.3%

BMI = body mass index.

3. Results

3.1. Donor, recipient, and organ procurement characteristics

From January 1, 2014, to December 31, 2022, 375 adult patients underwent DCD SPK transplantation (the first pancreas graft in 371 [98.9%] patients); 189 patients were transplanted from 2014 to 2017, and 186 from 2018 to 2022. TTD was not available for 20.5% of patients. A summary of missing data is given in Supplementary Table 1, and the patterns of missing data are shown in Supplementary Figure 1. The donor and recipient characteristics are described in Table 1. Hypoxic brain injury was the most common cause of death (46.9%). Forty-three SPK transplants were from grafts procured from donors who underwent NRP. The mean waiting time for transplantation was 371.8 days ± 289 days, with 213 patients on dialysis immediately prior to SPK transplantation (56.8%). Donor procurement times are presented in Table 2. The median TTD was 13 minutes (IQR 10-16 minutes), the median FWIT was 27 minutes (IQR 23-31 minutes), and the median asystolic time was 13 minutes (IQR 11-15 minutes). TTD was >30 minutes in 20 (5.3%) donors and >60 minutes in 9 (2.4%) donors, with a maximum value of 407 minutes in 1 donor. Overall cold ischemic time was >12 hours in 75 (20%) grafts. Demographic variables comparing TTD ≤60 minutes with TTD >60 minutes are presented in Supplementary Table 2.

3.2. Recipient outcomes

Patient survival at 1-, 3-, and 5-years in the entire cohort was 98.0%, 94.0%, and 90.6%, respectively. Pancreas graft survival at 1-, 3-, and 5-years in the entire cohort was 90.6%, 86.7%, and

Table 2
Donor procurement times.

Variable	Median	Interquartile range	Range
Cold ischemic time (h)	10	9-12	6-18
Warm ischemic time (min)	27	23-31	12-66
Functional warm ischemia time (min)	21	17-25	9-58
Asystolic time (min)	13	11-14	3-33
Time to death (min)	13	10-16	0-407
Donor pancreatectomy time (min)	48.0	39-64	15-188

Table 3
Causes of pancreas graft failure in recipients.

Cause of graft failure	Frequency	Percentage
Pancreatitis	7	16.7%
Graft thrombosis	7	16.7%
Anastomotic leak	5	11.9%
Chronic rejection	3	7.1%
Infection	2	4.8%
Acute rejection	1	2.4%
Primary nonfunction	1	2.4%
Unknown/other	16	38.1%

80.7%, respectively. Pancreas graft failure occurred in 42 (11.2%) patients, with the cause of graft failure described in Table 3. Kidney graft failure occurred in 23 recipients, with graft survival at 1-, 3-, and 5-years were 96.3%, 93.3%, and 93.3%, respectively.

Table 4
Multivariable Cox regression analysis of potential predictors of pancreas graft loss, modeling time to death. Pooled data from 5 imputed datasets.

Variable	Adjusted HR	95% CI	*P*-value
Time to death*	0.98	0.68-1.41	.901
Asystolic time*	2.51	1.16-5.43	.020
Pancreatectomy time*	0.98	0.49-1.97	.947
Cold ischemic time (h)	0.93	0.80-1.08	.354
Donor age (y)	0.99	0.96-1.02	.315
Donor BMI (kg/m^2)	1.17	1.07-1.27	$<$ .001
Cause of death			
Hypoxic brain injury	Reference	-	-
Cerebral vascular accident	1.07	0.47-2.41	.880
Trauma	0.90	0.35-2.30	.825
Other	0.90	0.30-2.72	.847
Year of transplant	0.79	0.65-0.95	.012
Normothermic regional perfusion	0.27	0.04-1.82	.181
Recipient age (y)	0.91	0.87-0.95	$<$ .001
Diabetes			
Type 1	Reference	-	-
Type 2	5.62	1.47-23.50	.013

BMI = body mass index; CI, confidence interval; HR, hazard ratio.

* Time to death, asystolic time, and pancreatectomy time were log-transformed prior to inclusion in this model, due to right-skew. Their effect estimates relate to a unit increase in $\log_2$(time period); ie, the adjusted hazard ratio associated with a doubling of the respective time.

3.3. Impact of donor time to death on recipient outcome

A multivariable analysis of potential predictors of graft failure (including TTD) is presented in Table 4. Donor body mass index (BMI), recipient age, year of transplant, diabetes cause, and asystolic time were retained as significant predictors, with NRP, donor age, and donor cause of death added to the model based on previous research and clinical expertise. Donor TTD was not significantly associated with pancreas graft loss (adjusted hazard ratio [aHR] 0.98, 95% confidence interval [CI] 0.68-1.41, P = .901); however, asystolic time was significantly associated with pancreas graft loss (aHR 2.51, 95% CI 1.16-5.43, P = .020). These aHR relate to changes on the Log2 scale, so this represents a 2.51-fold increase in hazard each time asystolic time doubles. A Kaplan-Meier plot comparing pancreas graft survival and patient survival across TTD categories is presented in Supplementary Figure 2. Of note, the recipient of the pancreas graft with a donor TTD of 407 minutes was alive with a functioning graft at 4 years posttransplant.

Other significant predictors were donor BMI, recipient age, year of transplant, and type 2 diabetes in the recipient. Pancreatectomy time was not a significant predictor in this model. Sensitivity analysis excluding recipients of grafts from donors with TTD >60 minutes was performed, with no difference in the results noted.

The impact of TTD and asystolic time may be different in donors undergoing NRP. This hypothesis was tested by adding interaction terms to the model shown in Table 4. There was no evidence that the impact of TTD or asystolic time on pancreas graft survival was different in donors receiving NRP (interaction P = .167 and P = .553, respectively). In addition, sensitivity analysis was performed by removing recipients of SPK grafts from donors who had undergone NRP, with no difference in significant predictors of outcome in non-NRP donors.

TTD was not a significant predictor of recipient mortality (analysis not shown). TTD and asystolic time were not identified as predictors of kidney graft survival in separate modeling (analysis not shown). The majority of DCD SPK transplants from grafts with a donor TTD exceeding 60 minutes were performed, by a single center (Supplementary Fig. S3). A sensitivity analysis was performed, including this implanting center as a confounder in the model with no impact on the results (analysis not shown).

3.4. Impact of functional warm ischemia time on recipient outcome

Multivariable analyses of potential predictors of pancreas graft failure (including FWIT but not TTD) are presented in Table 5. Donor FWIT was identified as a significant predictor of pancreas graft loss (aHR 2.21, 95% CI 1.06-4.61, P = .035). Donor BMI, year of transplant, recipient age, and type 2 diabetes in the recipient were also found to be significant predictors in this model. Pancreatectomy time was not a significant predictor in this model.

Table 5
Multivariable Cox regression analysis of potential predictors of pancreas graft loss, modeling functional warm ischemia time. Pooled data from 5 imputed datasets.

Variable	Adjusted HR	95% CI	*P*-value
Functional warm ischemia time*	2.21	1.06-4.61	.035
Pancreatectomy time*	0.97	0.46-2.04	.930
Cold ischemia time (h)	0.96	0.82-1.13	.594
Donor age (y)	0.98	0.95-1.01	.236
Donor BMI (kg/m^2)	1.17	1.07-1.27	< .001
Cause of death			
Hypoxic brain injury	Ref	-	-
Cerebral vascular accident	1.10	0.49-2.46	.826
Trauma	0.87	0.35-2.18	.770
Other	0.81	0.26-2.51	.717
Year of transplant	0.77	0.64-0.93	.006
Normothermic regional perfusion	0.30	0.04-2.34	.249
Recipient age (y)	0.91	0.87-0.94	< .001
Diabetes			
Type 1	Ref	-	-
Type 2	3.54	1.07-11.74	

BMI = body mass index; CI, confidence interval; HR, hazard ratio.

* Functional warm ischemia time and pancreatectomy time were log-transformed prior to inclusion in this model, due to right-skew. Their effect estimates relate to a unit increase in log2(time period); i.e. the adjusted hazard ratio associated with a doubling of the respective time.

Adding an interaction term to the model in Table 5 found no evidence that the impact of FWIT on pancreas graft survival was modified by NRP (interaction $P = .607$). Sensitivity analysis excluding NRP grafts demonstrated no change to the identified predictors of pancreas graft loss in non-NRP donors (analysis not shown). In separate modeling, FWIT was not identified as a predictor of kidney graft outcome.

3.4. Restricted cubic spline modeling and asystolic time

Restricted cubic spline modeling of graft loss as a function of TTD did not reveal a nonlinear relationship (Fig. 2). However, a nonlinear relationship was observed when modeling graft loss as a function of asystolic time (Fig. 3). In this model, the relationship was sigmoidal. Pancreas graft survival was significantly higher in recipients of grafts with an asystolic time <13 minutes compared with recipients of grafts with an asystolic time ≥13 minutes ($P = .024$, Fig. 4). Pancreas graft survival at 1-, 3-, and 5-years was 92.8%, 89.2% and 87.3%, respectively, in the asystolic time ≥13 minutes group and 86.8%, 82.2% and 71.0%, respectively, in the asystolic time >13 minutes group. There was no significant difference (Supplementary Fig. S4, $P = .700$) in kidney graft survival. One-, 3-, and 5-year kidney graft survival was 96.8%, 94.5%, and 92.6%, respectively, in the asystolic time <13 minutes group and 96.0%, 92.1%, and 92.1%, respectively, in the asystolic time ≥13 minutes group.

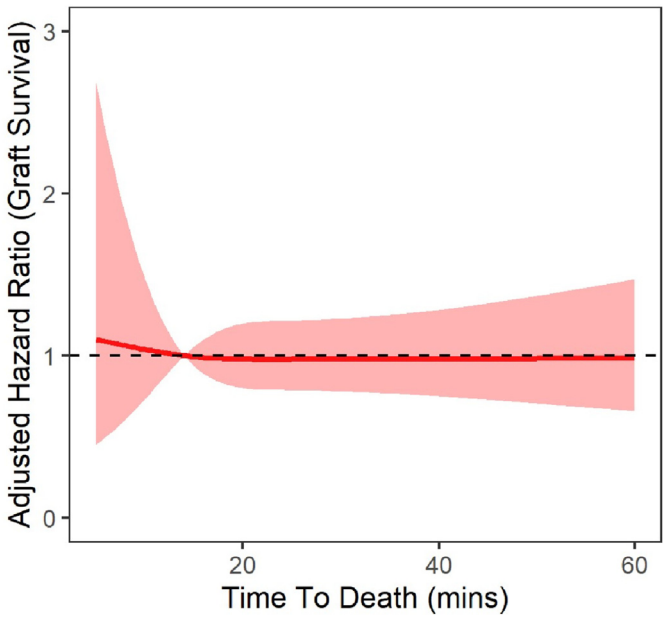

Figure 2. Restricted cubic spline modeling: the adjusted hazard ratio of graft survival as a function of time to death.

4. Discussion

In this study, there was no relationship between TTD and death-censored pancreas graft survival after DCD SPK transplantation. This suggests that from the time of treatment withdrawal to cold aortic perfusion, the pancreas graft is relatively protected from ischemic injury that may impact the posttransplant outcome during the agonal phase. FWIT and asystolic time were

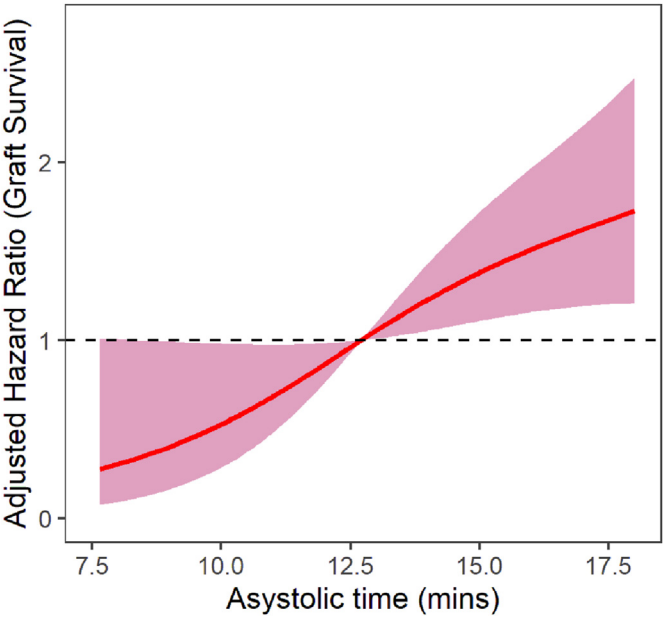

Figure 3. Restricted cubic spline of the adjusted hazard ratio of graft survival as a function of asystolic time.

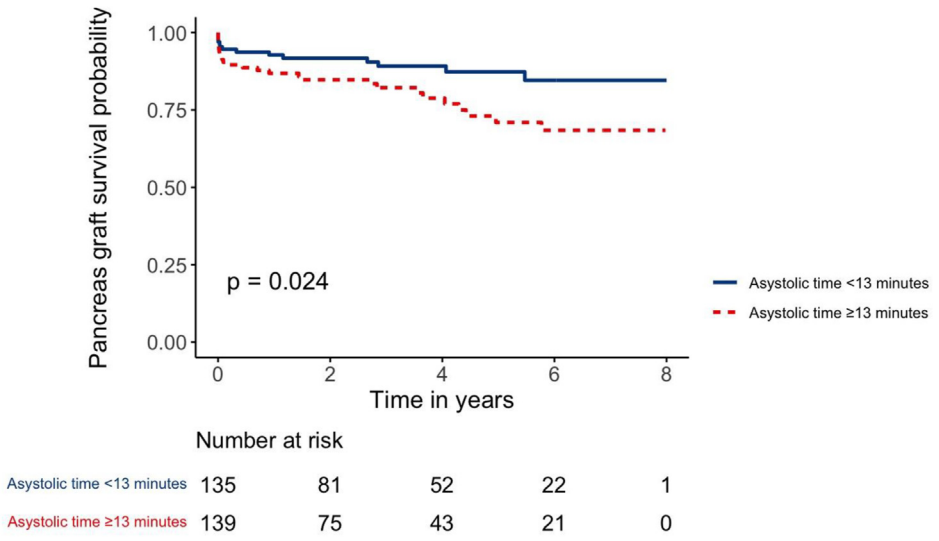

Figure 4. Kaplan-Meier curve of pancreas graft survival, comparing asystolic time <13 minutes with asystolic time ≥13 minutes.

separately identified as significant predictors of graft outcome, with a sigmoidal relationship identified between asystolic time and pancreas graft outcome. A further exploratory survival analysis around the median asystolic time in the cohort confirmed this finding for pancreas grafts but not kidney grafts. Therefore, pancreas graft injury was found to occur once donor systolic blood pressure and/or SaO_2 dropped below 50 mmHg and 70%, respectively, with the relative resistance of the kidney graft.

Ideally, keeping asystolic time to a minimum would benefit DCD SPK transplant recipients. However, efforts from procurement teams to reduce asystolic time are not straightforward. In contrast to the US, no preprocurement interventions (such as systemic heparinization, insertion of NRP cannulae, or prearrest prepping/draping of the donor) are implemented to potentially optimize[11,13,26,27] and speed up organ donation. We accept that the location of treatment withdrawal in relation to the distance to the operating theater is variable, with some donor hospitals withdrawing in the intensive care unit, observing the 5-minute "no-touch" period, and then transferring to the operating theater, potentially adding to the asystolic time and impacting outcome. Our data suggests that treatment withdrawal within the anesthetic room in the operating theater complex may reduce transfer time and therefore asystolic time. This has been recognized as a "donation action likely to be in a patient's best interest" in the Donation Actions Framework,[28] which seeks to address ethical questions in organ donation in order to remove barriers to decision-making during organ donation. Given the impact of asystolic time on pancreas graft outcome, the legality of prearrest interventions will require further consideration in the UK.

In 2021 and 2022, 46% of DCD pancreas graft offers were declined by implanting centers.[29] In a retrospective study of pancreas graft utilization in the UK, out of 1879 pancreas grafts declined for retrieval, 317 grafts (16.9%) were due to "prolonged donor asystole" from 2005 to 2015.[30] However, decisions regarding the utilization of a pancreas graft are multifactorial, and a prolonged asystolic time, TTD, and/or FWIT in addition to the recorded reason for decline (eg, donor past medical history) may have contributed to the decision to decline a pancreas graft, confounding any analysis into the reasons for the decline in donors where the pancreas graft was not procured. Therefore, the precise number of donor pancreatic grafts that do not proceed to procurement due to prolonged TTD, FWIT, or asystolic time contributing to the decision to decline a graft in the UK is unknown. This demonstrates a need to optimize procurement (potentially through reducing asystolic time during donation) and utilization (through more informed decision-making) given that diabetic uremic patients still die while waiting. UK practice is for procurement teams to wait at least 3 hours for the onset of FWIT (and then 30 minutes from the onset of FWIT for asystole to occur) prior to standing down. TTD exceeded 30 minutes in 20 donors in our cohort, with a maximum value of 407 minutes in 1 donor.

We are unable to comment on whether extending the stand-down time for procurement teams beyond 3 hours could be achieved without impairing the posttransplant outcome. While this may improve utilization, the disadvantages would include resource utilization and cost (surgical team on standby, operating theater in use, and others). In the US, there is no formal stand-down time for procurement teams following the withdrawal of treatment. A single-center retrospective study examined the impact of extending the stand-down time from 1 hour posttreatment withdrawal to 2 hours and demonstrated that this resulted in up to 10% more kidney grafts being procured and transplanted with no observed adverse effect on outcome.[31]

FWIT has been previously associated with an increased risk of graft loss and posttransplant complications after liver transplantation.[18,32-34] There is limited data exploring the relationship between FWIT and pancreatic graft outcome. Although we identified FWIT as a predictor of graft outcome, the current definition may not entirely reflect the total ischemic injury experienced by the abdominal viscera following withdrawal of treatment. A retrospective study of DCD liver transplantation in the United States explored the relationship between the length of donor hypoxia (defined as SaO_2 ≤80%) and graft survival. The

authors identified that increasing hypoxic time led to worse outcomes up to 16 minutes with no increase in effect thereafter, suggesting that an overreliance on FWIT may be detrimental to graft utilization. Based on tissue perfusion studies in sepsis, there has been some suggestion that FWIT should be redefined as the time SaO_2 falls below 80% and/or systolic blood pressure falls below 60 mmHg.[35-37] With NRP gaining considerable traction as a method to reduce ischemic injury during DCD organ procurement,[12,26,38] further reevaluation of definitions will be necessary. Although we did not identify NRP as a significant predictor of graft outcome, this may have been due to the small number of NRP-procured pancreas grafts[12] and the lack of any previously reported large multicenter studies. A preclinical porcine model of pancreas transplantation following NRP demonstrated that extended preservation could be achieved with minimal graft edema and immediate graft function.[39]

The interaction between warm and cold ischemia has not been explored in this study. Cold ischemic time was not found to be a significant predictor of graft outcome, which is surprising.[14,40] An early preclinical study of pancreas transplantation in rats evaluated islet function after 2 hours of warm ischemia and after 24 hours of cold ischemia separately.[41] The authors found that a combination of 60-minute warm ischemia followed by 12-hour cold ischemia was well tolerated; however, any expansion of either ischemic time beyond these thresholds led to nonfunctioning grafts. In our study, 20% of pancreas grafts had a cold ischemic time exceeding 12 hours; however, the median FWIT for these grafts was 22.8 minutes (range 9 to 58 minutes), which may have mitigated some of the deleterious effects of cold ischemic time.

Novel preservation technologies are likely to have a future impact on the utilization of pancreas grafts by enabling real-time assessment of the graft and potentially ameliorating the ischemic injury associated with preservation.[11] This has been achieved successfully in liver[6,42,43] and kidney transplantation[44,45] with ex-situ machine perfusion and with NRP.[12] Pancreas grafts have not demonstrated as much enthusiasm with initial trials of ex-situ perfusion observing graft damage following reperfusion.[46] More recently, normothermic machine perfusion of pancreas grafts has been demonstrated, with perfusate amylase correlated with fatty infiltration and the exocrine function of the graft.[47,48] Normothermic machine perfusion may also be used as a platform for delivering therapeutics to grafts to recondition them prior to implantation.[49-51] Recently, a preclinical model of cellular therapy delivered via normothermic machine perfusion to kidney grafts demonstrated improved urine output and reduced inflammatory injury.[52] In the future, pancreas and kidney grafts may simultaneously undergo ex-situ perfusion for viability assessment and reconditioning prior to SPK transplantation.

We acknowledge the following limitations for this study: missing data are inevitable in any retrospective study and could impact analyses; however, we believe that data were missing at random and employed multiple imputations to address this. Variations in blood pressure, heart rate, and oxygen saturation following withdrawal of life-sustaining treatment were also not available from our registry. A detailed analysis of changes in hemodynamic parameters following withdrawal of life-sustaining treatment may have provided additional granularity to our analyses and allowed for the identification of patterns of decline and what association (if any) they may have with post-SPK transplant outcome. Implantation technique and immunosuppression protocols were determined by centers, and variation was not captured in our analyses. Finally, inherent to the retrospective nature of the study, an element of selection bias is likely to be present, and this may be reflected by the narrow IQR for TTD, asystolic time, and FWIT. For obvious reasons, it would not be possible to explore posttransplant outcomes of grafts that declined due to prolonged TTD, asystolic time, or FWIT. However, further prospective evaluation of agonal times and their impact on outcome in pancreas transplantation (both SPK and pancreas-alone), particularly of grafts declined by one center but accepted and transplanted by another center, would be very informative on the decision-making process surrounding graft assessment.

Our analyses demonstrated that TTD did not impact recipient outcomes following DCD SPK transplantation. FWIT and asystolic time were found to be significant predictors of outcome, with longer asystolic time associated with poorer graft survival at 5 years. Our data confirms that procurement teams should therefore not emphasize the duration of TTD while FWIT has not been achieved.

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Data availability

The data used in this manuscript is managed by the United Kingdom Transplant Registry through NHS Blood and Transplant (NHSBT). The authors are not able to provide the raw data, however this may be requested from NHS BT through written request.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose, as described by the American Journal of Transplantation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2024.02.008.

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