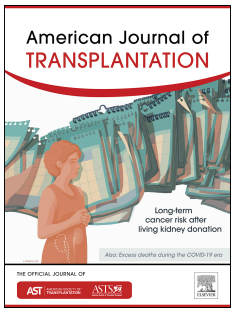
The impact of time to death in donors after circulatory death on recipient outcome in simultaneous pancreas-kidney transplantation



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

Abdullah K. Malik, Samuel J. Tingle, Nicholas Chung, Ruth Owen, Balaji Mahendran, Claire Counter, Sanjay Sinha, Anand Muthasamy, Andrew Sutherland, John Casey, Martin Drage, David van Dellen, Chris J. Callaghan, Doruk Elker, Derek M. Manas, Gavin J. Pettigrew, Colin H. Wilson, Steven A. White, On behalf of the NHSBT Pancreas Advisory Group

PII: S1600-6135(24)00134-5

DOI: https://doi.org/10.1016/j.ajt.2024.02.008

Reference: AJT 434

To appear in: *American Journal of Transplantation*

Received Date: 27 November 2023

Revised Date: 27 January 2024

Accepted Date: 7 February 2024

Please cite this article as: Malik AK, Tingle SJ, Chung N, Owen R, Mahendran B, Counter C, Sinha S, Muthasamy A, Sutherland A, Casey J, Drage M, van Dellen D, Callaghan CJ, Elker D, Manas DM, Pettigrew GJ, Wilson CH, White SA, On behalf of the NHSBT Pancreas Advisory Group, The impact of time to death in donors after circulatory death on recipient outcome in simultaneous pancreas-kidney transplantation, *American Journal of Transplantation*, https://doi.org/10.1016/j.ajt.2024.02.008.

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

Abdullah K. Malik*[1,2], Samuel J. Tingle*[1,2], Nicholas Chung[3], Ruth Owen[4], Balaji Mahendran[2], Claire Counter[5], Sanjay Sinha[6], Anand Muthasamy[7], Andrew Sutherland[8], John Casey[8], Martin Drage[9], David van Dellen[4], Chris J. Callaghan[5,9], Doruk Elker[10], Derek M. Manas[1,2,5], Gavin J. Pettigrew[2,11], Colin H. Wilson[1,2], Steven A. White[1,2,5] On behalf of the NHSBT Pancreas Advisory Group

***Joint first authors**

1 – Institute of Transplantation, Freeman Hospital, Newcastle upon Tyne

2 – NIHR Blood and Transplant Research Unit, Newcastle University and Cambridge University

3 – Northumbria Healthcare NHS Foundation Trust, Cramlington

4 – Manchester University NHS Foundation Trust, Manchester

5 – NHS Blood and Transplant, Bristol

6 – Oxford University Hospitals NHS Foundation Trust

7 – Imperial College Healthcare NHS Trust

8 – Edinburgh Royal Infirmary

9 – Guy's and St Thomas' NHS Foundation Trust

10 – Cardiff and Vale University Health Board

11 – Cambridge University Hospitals NHS Foundation Trust

Corresponding author: Mr Abdullah K. Malik (abdullah.malik@nhs.net)

Abbreviations

DBD – Donation after brainstem death

DCD – Donation after circulatory death

FWIT – Functional warm ischaemia time

IQR – Interquartile range

NHSBT – NHS Blood and Transplant

NPOS – National pancreas offering scheme

NRP – Normothermic regional perfusion

RCS – Restricted cubic spline

SPK – Simultaneous pancreas-kidney transplantation

TTD – Time to death

UKTR – United Kingdom Transplant Registry

Word count (excl. abstract, figure legends, tables, references): 3,725

Abstract word count: 200

Abstract

Time to arrest in donors after circulatory death is unpredictable and can vary. This leads to variable periods of warm ischaemic 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 DCD SPK transplantation. Data were extracted from the UK transplant registry from 2014 to 2022. Predictors of graft loss were evaluated by a Cox proportional hazards model. Adjusted restricted cubic spline (RCS) models 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 (aHR 0.98, 95% CI 0.68-1.41, P=0.901). Increasing asystolic time worsened graft survival (aHR 2.51, 95% CI 1.16-5.43, P=0.020). RCS modelling revealed a non-linear relationship was demonstrated between asystolic time and graft survival, and no relationship between TTD and graft survival. We found no evidence that TTD impacts on pancreas graft survival after DCD SPK transplantation, however increasing asystolic time was a significant predictor of graft loss. Procurement teams should attempt to minimise asystolic time to optimize pancreas graft survival rather than focus on the duration of TTD.

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 number of patients on the waiting list limits access to SPK transplantation. So far during 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 optimise utilisation. In the UK pancreas grafts from donors after circulatory death[6] have been used to good effect in order to improve access to beta cell replacement therapy[6,7].

Some centres, however, remain reluctant to use pancreas grafts from donors after circulatory death (DCD)[6], because of historical reports suggesting that these grafts have higher failure rates than pancreas grafts from donors after brainstem death (DBD)[8-10]. Nevertheless improving the utilisation 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 DBD grafts[4,7,14-16]. Indeed some studies even suggest the outcomes are even better for DCD SPK[14].

Following withdrawal of life-sustaining treatment, time to death (TTD) can vary with fluctuations in haemodynamic parameters leading to variable periods of warm ischaemia to the abdominal viscera. Donors may decline rapidly, gradually or demonstrate a period of relative stability followed by 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 unecessarily. Hypotension, hypoxia and vascular shunting towards the brain and heart may also lead to organ injury that is not fully reflected in the donor systolic blood pressure or oxygen saturations[18]. It is accepted that reducing stand down times for procurement teams leads to less ischaemic injury in grafts, however this will have significant implications on the number of grafts available, waiting list management along with a poorer utilisation rate. With this in mind there is no national or international consensus on what is accepted practise on 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 hypothesise that a prolonged time to death is associated with an increased risk of pancreas graft loss.

Methods

Setting

We performed a retrospective review of adult (≥18-years) DCD SPK graft recipients in the UK from 1st January 2014 to 31st December 2022. Data were extracted from the UK Transplant Registry (UKTR) maintained by NHS Blood and Transplant following approval from the UK Pancreas Advisory Group. The common closure date of the study was 1st April 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 a National Pancreas Offering Scheme (NPOS)[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 deescribed[22], but must have an estimated glomerular filtration rate ≤20mL/min and insulin-treated diabetes mellitus. SPK transplantation is performed by eight transplant units in the UK; all data was anonymised, including transplant centre.

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 (e.g. systemic heparinisation 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 centres generally decline pancreas grafts after 1 hour. Pancreas and kidney grafts are placed into static cold storage boxes for transportation to implanting centres. Normothermic regional perfusion (NRP) was used variably by the organ procurement teams. Transplantation and post-operative immunosuppression protocols were determined by the implanting centre.

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) (Figure 1). Asystolic time was from asystole until cold aortic perfusion. Functional warm ischaemia time (FWIT) was the time from donor systolic blood pressure <50mmHg and/or 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 death 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 onwards. Death-censored kidney graft failure was defined as a return to dialysis or re-transplantation, whichever occurred first. Patient survival was calculated from the time of transplantation to death.

Statistical analyses

Continuous variables are presented as means/medians with standard deviations/interquartile ranges (IQR). Missing explanatory data were imputed with multiple imputation using the fully conditional specification technique, applied to generate five imputed datasets. Supplementary table 1 summarises 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 Fishers' 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 have 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 five 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 $P<0.05$ level). 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.

Ischaemic times were kept as continuous variables, and those which were right-skewed (all except cold ischaemic time) were log-transformed (base 2) prior to fitting into our main Cox regression models. TTD, time to FWIT and FWIT all overlap (figure 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 (three knots located at the 10^{th}, 50^{th} and 90^{th} percentile) 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. Non-imputed data was used for this exploratory analysis. For all statistical tests, significance was set at $P<0.05$. All analyses were performed using SPSS™ version 26 (IBM corp, Armonk, New York, USA), and figures were generated using R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Donor, recipient, and organ procurement characteristics

From 1st January 2014 to 31st December 2022, 375 adult patients underwent DCD SPK transplantation (first pancreas graft in 371 patients, 98.9%) ,189 patients transplanted from 2014 to 2017 and 186 from 2018 to 2022. TTD was not available in 20.5% patients. A summary of missing data given in Supplementary table 1, and the patterns of missing data are

shown in Supplementary figure 1. Donor and recipient characteristics are described in table 1. Hypoxic brain injury was the commonest cause of death (46.9%). Forty-three SPK transplants were from grafts procured from donors who underwent NRP. Mean waiting time to 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. Median TTD was 13-minutes (IQR 10-16 minutes), median FWIT was 27-minutes (IQR 23-31 minutes), and median asystolic time was 13-minutes (IQR 11-15 minutes). TTD was greater than 30 minutes in 20 donors (5.3%) and greater than 60 minutes in 9 donors (2.4%), with a maximum value of 407 minutes in one donor. Overall cold ischaemic time was >12 hours in 75 grafts (20%). Demographic variables comparing TTD ≤60 minutes with TTD >60 minutes is presented in supplementary table 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 80.7%, respectively. Pancreas graft failure occurred in 42 patients (11.2%), 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 was 96.3%, 93.3% and 93.3%.

Impact of donor time to death on recipient outcome

Multivariable analysis of potential predictors of graft failure (including TTD) is presented in table 4. Donor BMI, recipient age, year of transplant, diabetes cause and asystolic time were retained as significant predictors, with NRP, donor age, 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 (aHR 0.98, 95% CI 0.68-1.41, P=0.901), however

asystolic time was significantly associated with pancreas graft loss (aHR 2.51, 95% CI 1.16-5.43, P=0.020). These aHR relate to changes on the Log_2 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 post-transplantation.

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 time to death and asystolic time may be different in donors undergoing NRP. This hypothesis was tested by the addition of interaction terms to the model shown in table 4. There was no evidence that the impact of time to death or asystolic time on pancreas graft survival was different in donors receiving NRP (interaction P=0.167 and P=0.553 respectively). In addition, sensitivity analysis was performed 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 a predictor of kidney graft survival in separate modelling (*analysis not shown*). The majority of DCD SPK transplants from grafts with a donor TTD exceeding 60 minutes were performed by a single centre (supplementary figure 3). A

sensitivity analysis was performed including this implanting centre as a confounder in the model with no impact on the results (*analysis not shown*).

Impact of functional warm ischaemia time on recipient outcome

Multivariable analysis 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=0.035). 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.

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=0.607). 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 modelling, FWIT was not identified as a predictor of kidney graft outcome.

Restricted cubic spline modelling and asystolic time

Restricted cubic spline modelling of graft loss as a function of TTD did not reveal a non-linear relationship (figure 2). However, a non-linear relationship was observed when modelling graft loss as a function of asystolic time (figure 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 to recipients of a grafts with an asystolic time ≥13 minutes (P=0.024, figure 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 figure 4, P=0.700) 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.

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 ischaemic injury that may impact on post-transplant outcome during the agonal phase. FWIT and asystolic time were 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 SaO2 drop below 50mmHg and 70%, respectively, with 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 is not straightforward. In contrast to the US, no pre-procurement interventions (such as systemic heparinization, insertion of NRP cannulae or pre-arrest prepping/draping of the donor) are implemented to potentially optimise [11,13,26,27] and speed up organ donation. We accept that location of treatment withdrawal in relation to the distance to the operating theatre 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 theatre, potentially adding to the asystolic time

and impacting outcome. Our data suggests that treatment withdrawal within the anaesthetic room in the operating theatre complex may reduce transfer time and therefore asystolic time. This has been recognised 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 pre-arrest interventions will require further consideration in the UK.

In 2021-22, 46% of DCD pancreas graft offers were declined by implanting centres[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 2005-15[30]. However decisions regarding utilization of a pancreas graft are multifactorial, and a prolonged asystolic time, TTD and/or FWIT in addition to the recorded reason for decline (e.g. donor past medical history) may have contributed to the decision to decline a pancreas graft, confounding any analysis into the reasons for decline in donors where the pancreas graft was not procured. Therefore the precise number of donor pancreas grafts that do not proceed to procurement due to prolonged TTD, fWIT or asystoltic time contributing to the decision to decline a graft in the UK is unknown. This demonstrates a need to optimise procurement (potentially through reducing asystolic time during donation) and utilisation (through more informed decision-making) given that diabetic uraemic patients still die whilst 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 one donor.

We are unable to comment on whether extending the stand down time for procurement teams beyond 3-hours could be achieved without impairing post-transplant outcome. Whilst this may improve utilisation the disadvantages would include resource utilisation and cost (surgical team on standby, operating theatre in use, etc). In the US, there is no formal stand down time for procurement teams following withdrawal of treatment. A single-centre retrospective study examined the impact of extending the stand down time from 1 hour post-treatment 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 previously been associated with an increased risk of graft loss and post-transplant complications after liver transplantation[18,32-34]. There is limited data exploring the relationship between FWIT and pancreas graft outcome. Although we identified FWIT as a predictor of graft outcome, the current definition may not entirely reflect the total ischaemic 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 SaO2 ≤80%) and graft survival. The authors identified that increasing hypoxic time led to worse outcome up to 16 minutes with no increase in effect thereafter, suggesting that an over-reliance on FWIT may be detrimental to graft utilisation. Based on tissue perfusion studies in sepsis, there has been some suggestion that FWIT should be redefined as the time SaO2 falls below 80% and/or systolic blood pressure falls below 60mmHg[35-37]. With NRP gaining considerable traction as a method to reduce ischaemic injury during DCD organ procurement[12,26,38], further re-evaluation 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 multi-centre studies A pre-clinical

porcine model of pancreas transplantation following NRP demonstrated that extended preservation could be achieved with minimal graft oedema and immediate graft function[39].

The interaction between warm and cold ischaemia has not been explored in this study. Cold ischaemic 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 ischaemia and after 24-hours of cold ischaemia separately[41]. The authors found that a combination of 60-minutes warm ischaemia followed by 12-hours cold ischaemia was well tolerated, however any expansion of either ischaemic time beyond these thresholds led to non-functioning grafts. In our study, 20% of pancreas grafts had a cold ischaemic time exceeding 12-hours, however the median FWIT for these grafts was 22.8-minutes (range 9-minutes to 58-minutes), which may have mitigated against some of the deleterious effect of cold ischaemic time.

Novel preservation technologies are likely to have a future impact on utilisation of pancreas grafts, through enabling real-time assessment of the graft and potentially ameliorating ischaemic 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 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 pre-clinical 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. Missing data are inevitable in any retrospective study and could impact analyses, however we believe that data were missing at random and employed multiple imputation to address this. Variations in blood pressure, heart rate and oxygen saturations following withdrawal of life-sustaining treatment were also not available from our registry. Detailed analysis of changes in haemodynamic parameters following withdrawal of life-sustaining treatment may have provided additional granularity to our analyses, and allow for 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 centres, 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 post-transplant outcomes of grafts 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 centre but accepted and transplanted by another centre would be very informative on the decision-making process surrounding graft assessment.

Our analyses had demonstrated that TTD did not impact recipient outcome 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

362 confirms that procurement teams should therefore place no emphasis on the duration of TTD
363 whilst FWIT has not been achieved.
364
365 **Disclosures: The authors have no conflicts of interest to declare**
366
367 **Acknowledgements:** This study is funded by the National Institute of Health and Care
368 Research (NIHR) Blood and Transplant Research Unit in Organ Donation and
369 Transplantation (NIHR203332), a partnership between NHS Blood and Transplant,
370 University of Cambridge and Newcastle University. The views expressed are those of the
371 authors and not necessarily those of NIHR, NHS Blood and Transplant or the Department of
372 Health and Social Care.
373
374 **Data availability statement:** The data used in this manuscript is managed by the UKTR
375 through NHSBT. The authors are not able to provide the raw data, however this may be
376 requested from NHSBT through written request.

List of tables and figures

Supplementary table 1 – Summary of missing data

Supplementary table 2 – Demographic variables in the donors and recipients presented by time to death category

Supplementary figure 1 – missing values map to show pattern of missing data. Participants span the x axis and light blue represents missing data.

Supplementary figure 2 – Kaplan-Meier graph of A) pancreas graft survival and B) patient survival, comparing time to death ≤30 minutes, time to death 30-60 minutes and time to death >60 minutes.

Supplementary figure 3 – Distribition of time to death (minutes) across the anonymised eight UK pancreas transplant units. All points above the dashed line represent grafts with a donor time to death exceeding 60 minutes.

Supplementary figure 4 – Kaplan-Meier graph of kidney graft survival, comparing asystolic time <13-minutes with asystolic time ≥13-minutes

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

Variable	Value	Percentage
Donor		
Age (years)	30.7±12.8	
Sex		
Male	231	61.6%
Female	144	38.4%
Cause of death		
Hypoxic brain injury	176	46.9%
Intracranial haemorrhage	100	26.7%
Trauma	46	12.3%
CVA	14	3.7%
Other cause	39	10.4%
NRP	43	11.5%
Recipient		
Age (years)	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 (days)	371.8±289	
Dialysis	213	56.8%
Pre-transplant HbA1c (%)	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%

Table 2 – Donor procurement times

Variable	Median	Interquartile range	Range
Cold ischaemic time (hours)	10	9-12	6-18
Warm ischaemic time (minutes)	27	23-31	12-66
Functional warm ischaemia time (minutes)	21	17-25	9-58
Asystolic time (minutes)	13	11-14	3-33
Time to death (minutes)	13	10-16	0-407
Donor pancreatectomy time (minutes)	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 non-function	1	2.4%
Unknown/other	16	38.1%

Table 4 – Multivariable Cox regression analysis of potential predictors of pancreas graft loss, modelling 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	0.901
Asystolic time*	2.51	1.16-5.43	0.020
Pancreatectomy time*	0.98	0.49-1.97	0.947
Cold ischaemic time (hours)	0.93	0.80-1.08	0.354
Donor age (years)	0.99	0.96-1.02	0.315
Donor BMI (per unit)	1.17	1.07-1.27	<0.001
Cause of death			
Hypoxic brain injury	Ref	-	-
CVA	1.07	0.47-2.41	0.880
Trauma	0.90	0.35-2.30	0.825
Other	0.90	0.30-2.72	0.847
Year of transplant	0.79	0.65-0.95	0.012
NRP	0.27	0.04-1.82	0.181
Recipient age (years)	0.91	0.87-0.95	<0.001
Diabetes			
Type 1	Ref	-	-
Type 2	5.62	1.47-23.50	0.013

*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); i.e. the adjusted hazard ratio associated with a doubling of the respective time.

Table 5 – Multivariable cox regression analysis of potential predictors of pancreas graft loss, modelling functional warm ischaemia time. Pooled data from 5 imputed datasets.

Variable	**Adjusted HR**	**95% CI**	**P-value**
Functional warm ischaemia time*	2.21	1.06-4.61	0.035
Pancreatectomy time*	0.97	0.46-2.04	0.930
Cold ischaemia time (hours)	0.96	0.82-1.13	0.594
Donor age (years)	0.98	0.95-1.01	0.236
Donor BMI (units)	1.17	1.07-1.27	<0.001
Cause of death			
Hypoxic brain injury	Ref	-	-
CVA	1.10	0.49-2.46	0.826
Trauma	0.87	0.35-2.18	0.770
Other	0.81	0.26-2.51	0.717
Year of transplant	0.77	0.64-0.93	0.006
NRP	0.30	0.04-2.34	0.249
Recipient age (years)	0.91	0.87-0.94	<0.001
Diabetes			
Type 1	Ref	-	-
Type 2	3.54	1.07-11.74	0.039

*Functional warm ischaemia 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.

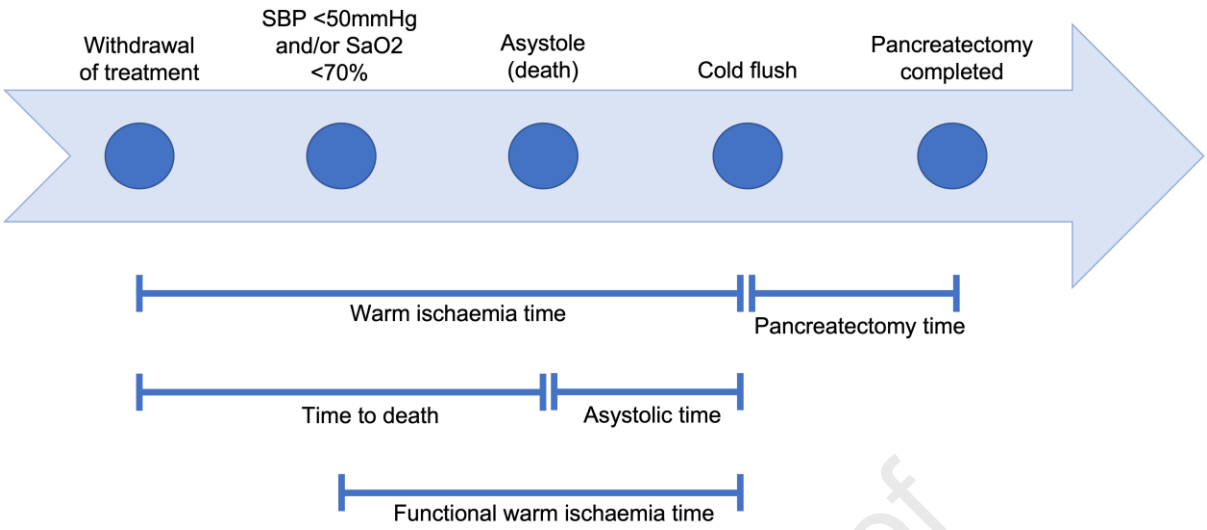


Figure 1 – Timeline of events following withdrawal of life-sustaining treatment in a donor after circulatory death

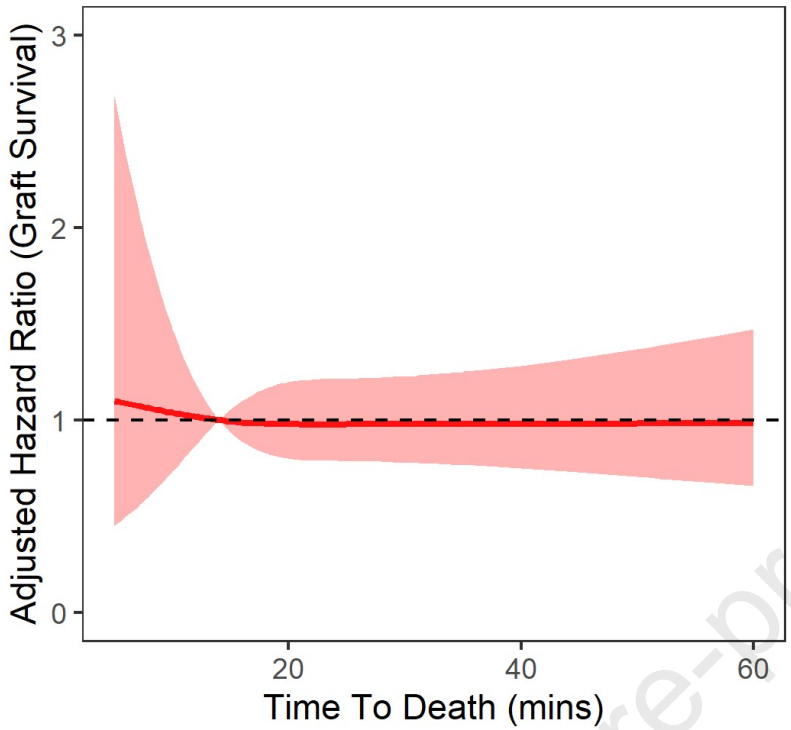


Figure 2 – Restricted cubic spline modelling adjusted hazard ratio of graft survival as a function of time to death

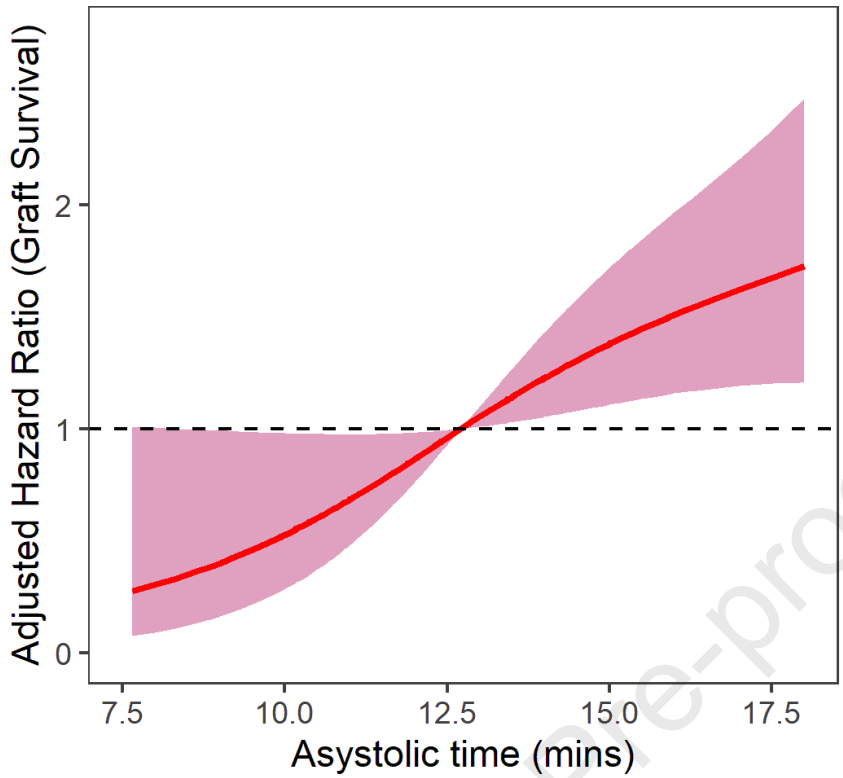


Figure 3 – Restricted cubic spline of adjusted hazard ratio of graft survival as a function of asystolic time

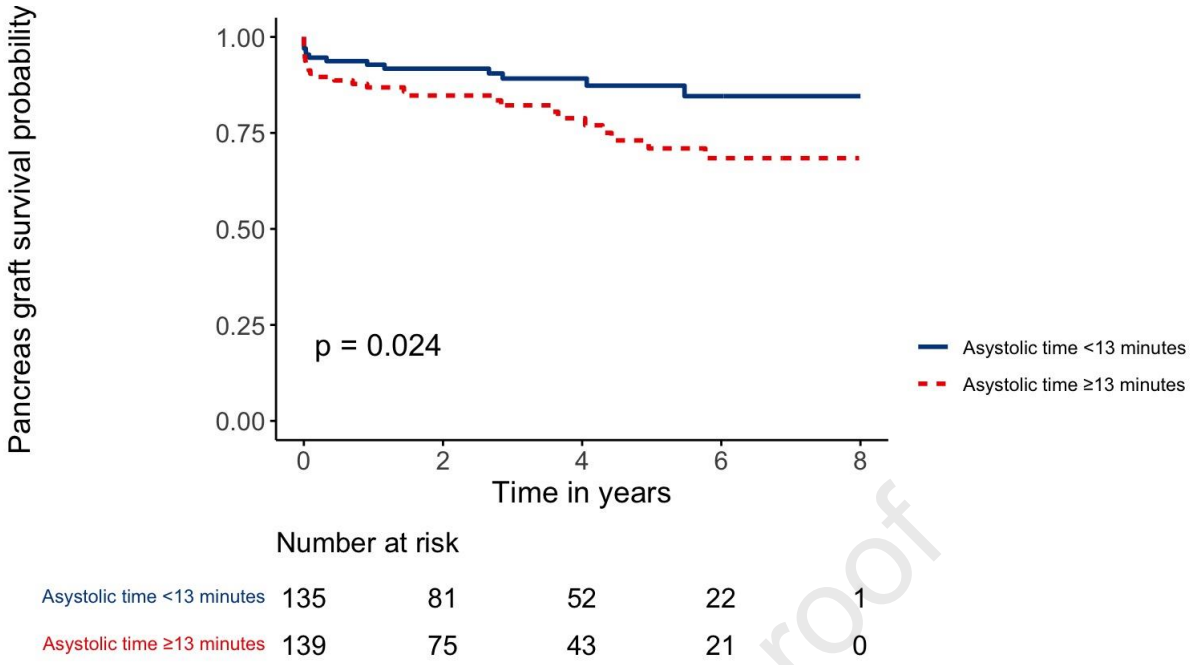


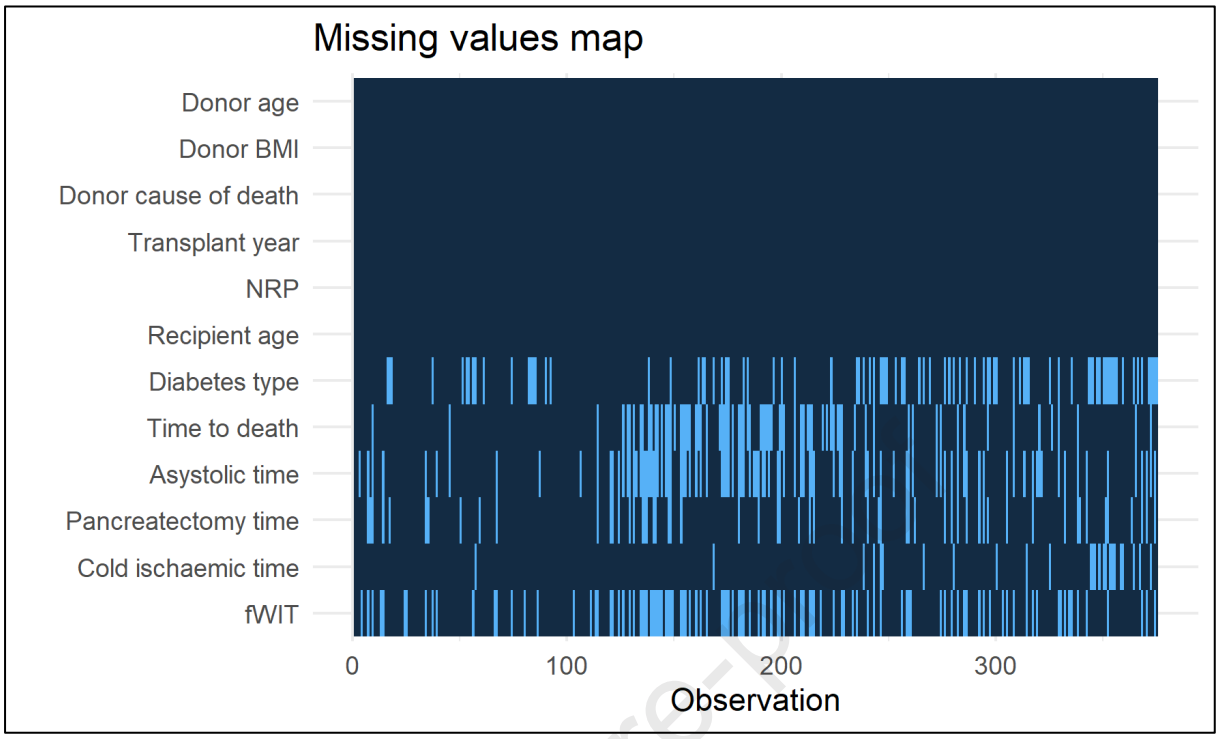
Figure 4 – Kaplan-Meier curve of pancreas graft survival, comparing asystolic time ≤13-minutes with asystolic time >13-minutes

1 *Supplementary table 1 – Summary of missing data*

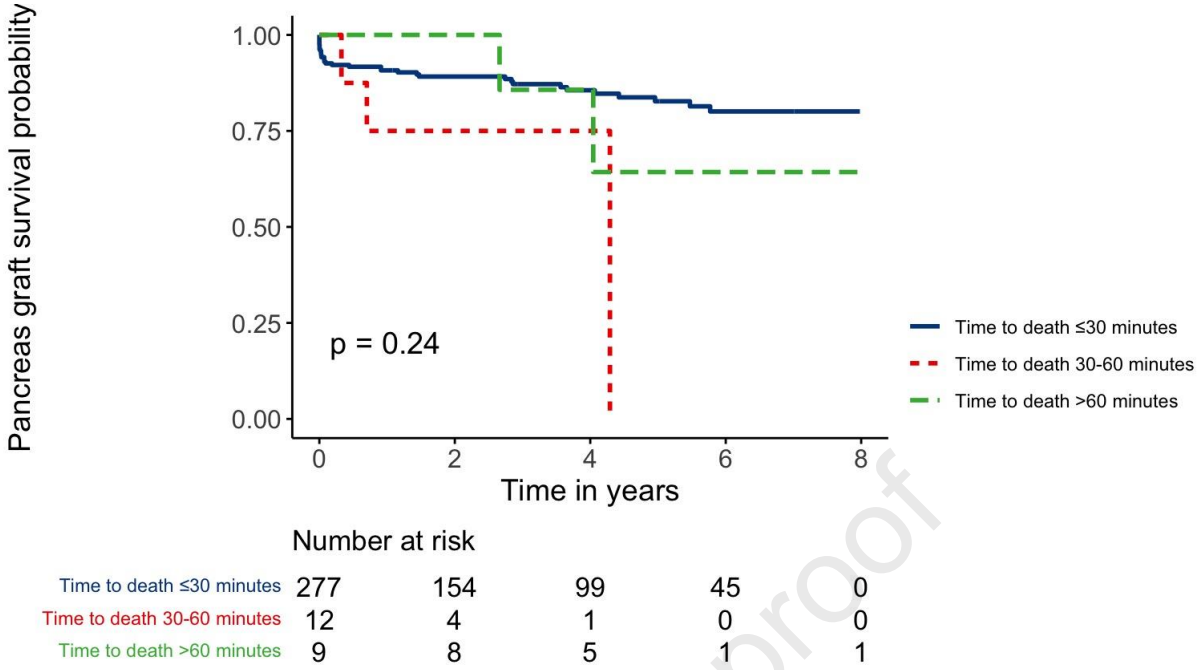
	Number missing	Percent missing (%)
Donor age	0	0
Donor BMI	0	0
Donor cause of death	0	0
Transplant year	0	0
NRP	0	0
Recipient age	0	0
Diabetes type	87	23.2
Time to death	77	20.5
Asystolic time	101	26.9
Pancreatectomy time	58	15.5
Cold ischaemic time	25	6.7
fWIT	108	28.8

Supplementary table 2 – Demographic variables in the donors and recipients presented by time to death category

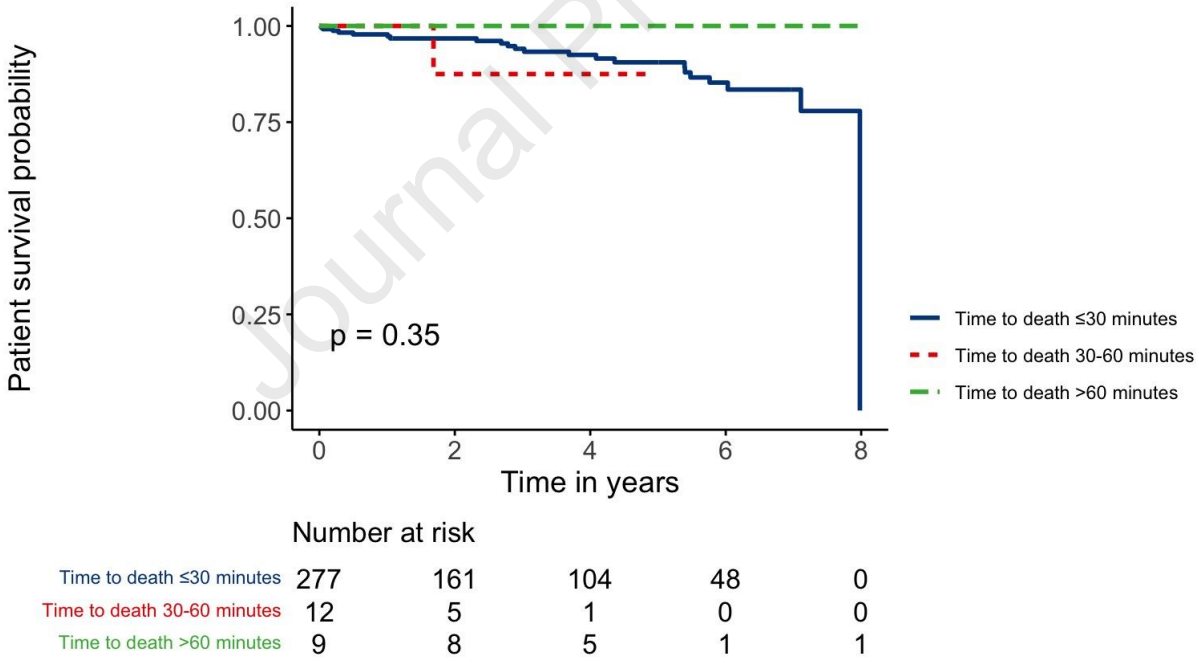
Variable	Time to death ≤60 minutes (IQR)	Time to death >60 minutes (IQR)	P-value
Donor			
Donor age (years)	30.5±12.8	38.0±8.8	0.035
Sex			
Male	226 (61.7%)	5 (55.6%)	0.976
Female	140 (38.3%)	4 (44.4%)	
Cause of death			
Hypoxic brain injury	173 (47.3%)	3 (33.3%)	0.638
Intracranial haemorrhage	98 (26.8%)	2 (22.2%)	
Trauma	45 (12.3%)		
CVA	14 (3.8%)	1 (11.1%)	
Other cause	36 (9.8%)	0	
		3 (33.3%)	
NRP	42 (11.5%)	1 (11.1%)	1.00
Recipient			
Age (years)	41.5±8.7	40.8±10.0	0.828
Sex			
Male	215	8	0.090
Female	151	1	
BMI (kg/m^2)	25.3±3.6	22.9±4.0	0.264
Waiting time (days)	373±291	332±168	0.503
Pre-transplant HbA1C (%)	35.5±12.0	36.6±9.4	0.785



Supplementary figure 1 – missing values map to show pattern of missing data. Participants span the x axis and light blue represents missing data.

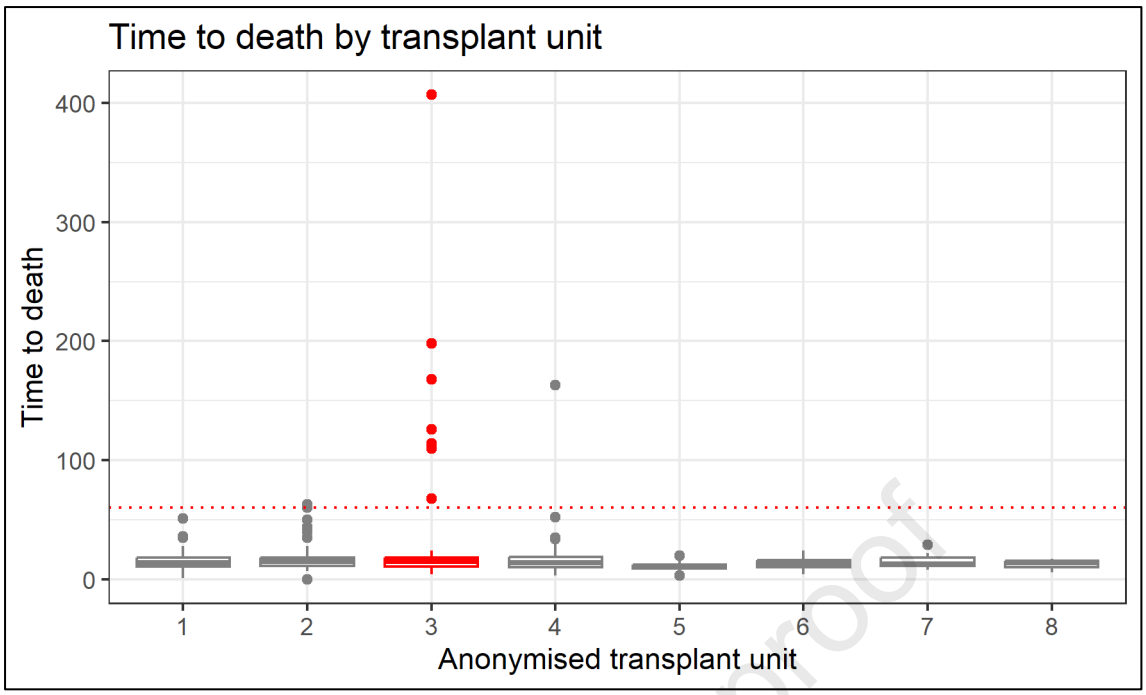


A

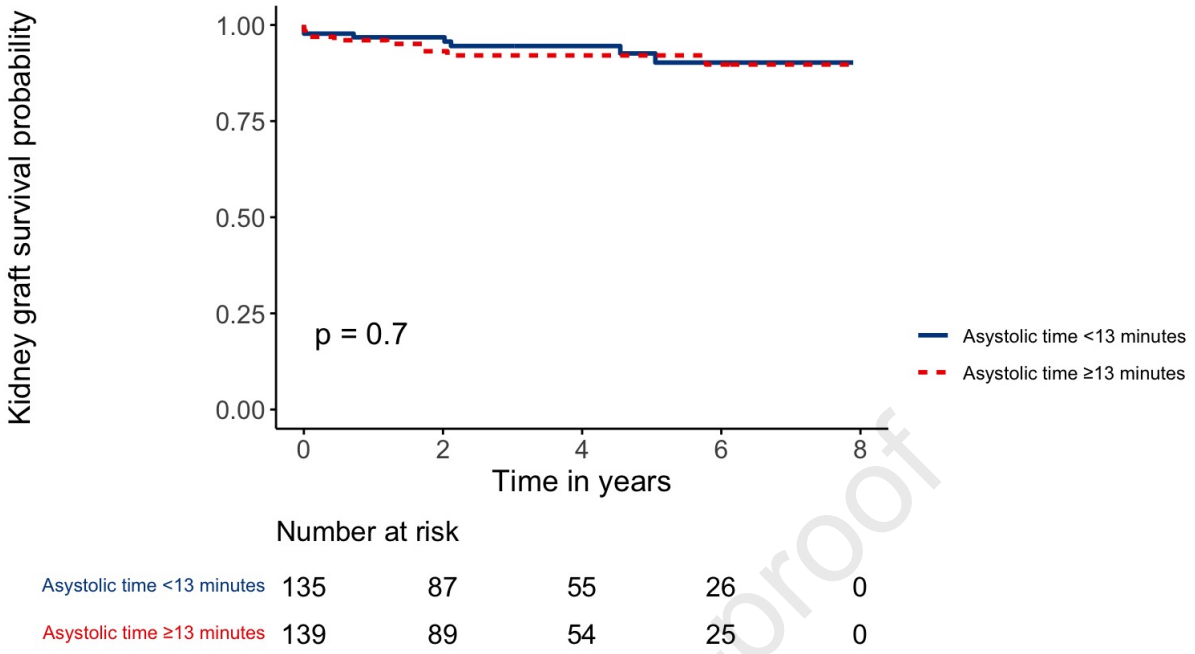


B

Supplementary figure 2 – Kaplan-Meier graph of A) pancreas graft survival and B) patient survival, comparing time to death ≤30 minutes, time to death 30-60 minutes and time to death >60 minutes.



Supplementary figure 3 – Distribition of time to death (minutes) across the anonymised eight UK pancreas transplant units. All points above the dashed line represent grafts with a donor time to death exceeding 60 minutes.



Supplementary figure 4 – Kaplan-Meier graph of kidney graft survival, comparing asystolic time <13-minutes with asystolic time ≥13-minutes

References

1. van Dellen D, Worthington J, Mitu-Pretorian OM, et al. Mortality in diabetes: pancreas transplantation is associated with significant survival benefit. *Nephrol Dial Transplant.* 2013;28(5):1315-1322.
2. Lindahl JP, Jenssen T, Hartmann A. Long-term outcomes after organ transplantation in diabetic end-stage renal disease. *Diabetes Res Clin Pract.* 2014;105(1):14-21.
3. Khairoun M, de Koning EJ, van den Berg BM, et al. Microvascular damage in type 1 diabetic patients is reversed in the first year after simultaneous pancreas-kidney transplantation. *Am J Transplant.* 2013;13(5):1272-1281.
4. Ollinger R, Margreiter C, Bosmuller C, et al. Evolution of pancreas transplantation: long-term results and perspectives from a high-volume center. *Ann Surg.* 2012;256(5):780-786; discussion 786-787.
5. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet.* 2009;373(9677):1808-1817.
6. van Rijn R, Schurink IJ, de Vries Y, et al. Hypothermic Machine Perfusion in Liver Transplantation - A Randomized Trial. *N Engl J Med.* 2021;384(15):1391-1401.
7. Fernandez LA, Di Carlo A, Odorico JS, et al. Simultaneous pancreas-kidney transplantation from donation after cardiac death: successful long-term outcomes. *Ann Surg.* 2005;242(5):716-723.
8. Kandaswamy R, Stock PG, Gustafson SK, et al. OPTN/SRTR 2018 Annual Data Report: Pancreas. *Am J Transplant.* 2020;20 Suppl s1:131-192.
9. Axelrod DA, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant.* 2010;10(4):837-845.
10. Leemkuil M, Leuvenink HGD, Pol RA. Pancreas Transplantation from Donors after Circulatory Death: an Irrational Reluctance? *Curr Diab Rep.* 2019;19(11):129.
11. Joana Ferrer-Fàbrega BM, Franka Messner, Jason B. Doppenberg , Cinthia Drachenberg, Marten A. Engelse, Paul R. V. Johnson, Henri G. D. Leuvenink, Gabriel C. Oniscu, Vassilios Papalois, Rutger J. Ploeg, Trevor W. Reichman,, WE 3rd Scott FV, Thierry Berney, Daniel Jacobs-Tulleneers-Thevissen, Nicos Kessaris, Annemarie Weissenbacher, Ann Etohan Ogbemudia, Steven White and Julien Branchereau on behalf of the ESOT Guidelines Taskforce. European Society for Organ Transplantation (ESOT) Consensus Statement on the Role of Pancreas Machine Perfusion to Increase the Donor Pool for Beta Cell Replacement Therapy. *Transpl Int.* 2023;In Press.
12. Oniscu GC, Mehew J, Butler AJ, et al. Improved Organ Utilization and Better Transplant Outcomes With In Situ Normothermic Regional Perfusion in Controlled Donation After Circulatory Death. *Transplantation.* 2023;107(2):438-448.
13. Richards JA, Roberts JL, Fedotovs A, et al. Outcomes for circulatory death and brainstem death pancreas transplantation with or without use of normothermic regional perfusion. *Br J Surg.* 2021;108(12):1406-1408.
14. Callaghan CJ, Ibrahim M, Counter C, et al. Outcomes after simultaneous pancreas-kidney transplantation from donation after circulatory death donors: A UK registry analysis. *Am J Transplant.* 2021;21(11):3673-3683.
15. Sollinger HW, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg.* 2009;250(4):618-630.

16. Qureshi MS, Callaghan CJ, Bradley JA, Watson CJ, Pettigrew GJ. Outcomes of simultaneous pancreas-kidney transplantation from brain-dead and controlled circulatory death donors. *Br J Surg.* 2012;99(6):831-838.
17. Firl DJ, Hashimoto K, O'Rourke C, et al. Role of donor hemodynamic trajectory in determining graft survival in liver transplantation from donation after circulatory death donors. *Liver Transpl.* 2016;22(11):1469-1481.
18. Kalisvaart M, de Haan JE, Polak WG, et al. Onset of Donor Warm Ischemia Time in Donation After Circulatory Death Liver Transplantation: Hypotension or Hypoxia? *Liver Transpl.* 2018;24(8):1001-1010.
19. Hudson A, Bradbury L, Johnson R, et al. The UK Pancreas Allocation Scheme for Whole Organ and Islet Transplantation. *Am J Transplant.* 2015;15(9):2443-2455.
20. Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential improvements. *Transplantation.* 2014;97(3):258-264.
21. Society BT. UK Guidelines on Pancreas and Islet Transplantation. 2019.
22. NHSBT. Pancreas transplantation: Patient selection. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17326/pancreas-selection-policy-pol185.pdf. Published 2019. Accessed 19/05/2023.
23. Andrews PA, Burnapp L, Manas D, British Transplantation S. Summary of the British Transplantation Society guidelines for transplantation from donors after deceased circulatory death. *Transplantation.* 2014;97(3):265-270.
24. Reid AW, Harper S, Jackson CH, et al. Expansion of the kidney donor pool by using cardiac death donors with prolonged time to cardiorespiratory arrest. *Am J Transplant.* 2011;11(5):995-1005.
25. Rickels MR, Stock PG, de Koning EJP, et al. Defining outcomes for beta-cell replacement therapy in the treatment of diabetes: a consensus report on the Igls criteria from the IPITA/EPITA opinion leaders workshop. *Transpl Int.* 2018;31(4):343-352.
26. Bekki Y, Croome KP, Myers B, Sasaki K, Tomiyama K. Normothermic Regional Perfusion Can Improve Both Utilization and Outcomes in DCD Liver, Kidney, and Pancreas Transplantation. *Transplant Direct.* 2023;9(3):e1450.
27. Shahrestani S, Webster AC, Lam VW, et al. Outcomes From Pancreatic Transplantation in Donation After Cardiac Death: A Systematic Review and Meta-Analysis. *Transplantation.* 2017;101(1):122-130.
28. Committee UDE. *Donation Actions Framework.* 2022.
29. NHSBT. *Annual Report on Pancreas and Islet Transplantation.* 2022.
30. Cornateanu SM, O'Neill S, Dholakia S, et al. Pancreas utilization rates in the UK - an 11-year analysis. *Transpl Int.* 2021;34(7):1306-1318.
31. Scalea JR, Redfield RR, Arpali E, et al. Does DCD Donor Time-to-Death Affect Recipient Outcomes? Implications of Time-to-Death at a High-Volume Center in the United States. *Am J Transplant.* 2017;17(1):191-200.
32. Coffey JC, Wanis KN, Monbaliu D, et al. The influence of functional warm ischemia time on DCD liver transplant recipients' outcomes. *Clin Transplant.* 2017;31(10).
33. Du Z, Dong S, Lin P, et al. Warm ischemia may damage peribiliary vascular plexus during DCD liver transplantation. *Int J Clin Exp Med.* 2015;8(1):758-763.

34. Taner CB, Bulatao IG, Perry DK, et al. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. *Transpl Int.* 2012;25(8):838-846.
35. Kalisvaart M, Croome KP, Hernandez-Alejandro R, et al. Donor Warm Ischemia Time in DCD Liver Transplantation-Working Group Report From the ILTS DCD, Liver Preservation, and Machine Perfusion Consensus Conference. *Transplantation.* 2021;105(6):1156-1164.
36. Kato R, Pinsky MR. Personalizing blood pressure management in septic shock. *Ann Intensive Care.* 2015;5(1):41.
37. Dunser MW, Takala J, Ulmer H, et al. Arterial blood pressure during early sepsis and outcome. *Intensive Care Med.* 2009;35(7):1225-1233.
38. Johnston CJC, Sherif AE, Oniscu GC. Transplantation of discarded livers: the complementary role of normothermic regional perfusion. *Nat Commun.* 2021;12(1):4471.
39. Mazilescu LI, Parmentier C, Kalimuthu SN, et al. Normothermic ex situ pancreas perfusion for the preservation of porcine pancreas grafts. *Am J Transplant.* 2022;22(5):1339-1349.
40. Rudolph EN, Dunn TB, Sutherland DER, Kandaswamy R, Finger EB. Optimizing outcomes in pancreas transplantation: Impact of organ preservation time. *Clin Transplant.* 2017;31(9).
41. Schulak JA, Kisthard J. The effect of warm ischemia and cold-storage preservation on rat pancreas transplantation. *J Surg Res.* 1984;36(2):134-139.
42. Mergental H, Laing RW, Kirkham AJ, et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun.* 2020;11(1):2939.
43. Nasralla D, Coussios CC, Mergental H, et al. A randomized trial of normothermic preservation in liver transplantation. *Nature.* 2018;557(7703):50-56.
44. Mazilescu LI, Urbanellis P, Kim SJ, et al. Normothermic Ex Vivo Kidney Perfusion for Human Kidney Transplantation: First North American Results. *Transplantation.* 2022;106(9):1852-1859.
45. Hosgood SA, Thompson E, Moore T, Wilson CH, Nicholson ML. Normothermic machine perfusion for the assessment and transplantation of declined human kidneys from donation after circulatory death donors. *Br J Surg.* 2018;105(4):388-394.
46. Prudhomme T, Mulvey JF, Young LAJ, et al. Ischemia-Reperfusion Injuries Assessment during Pancreas Preservation. *Int J Mol Sci.* 2021;22(10).
47. Nassar A, Liu Q, Walsh M, Quintini C. Normothermic Ex Vivo Perfusion of Discarded Human Pancreas. *Artif Organs.* 2018;42(3):334-335.
48. Barlow AD, Hamed MO, Mallon DH, et al. Use of Ex Vivo Normothermic Perfusion for Quality Assessment of Discarded Human Donor Pancreases. *Am J Transplant.* 2015;15(9):2475-2482.
49. Tingle SJ, Thompson ER, Bates L, et al. Pharmacological testing of therapeutics using normothermic machine perfusion: A pilot study of 2,4-dinitrophenol delivery to steatotic human livers. *Artif Organs.* 2022;46(11):2201-2214.
50. Thompson ER, Sewpaul A, Figuereido R, et al. MicroRNA antagonist therapy during normothermic machine perfusion of donor kidneys. *Am J Transplant.* 2022;22(4):1088-1100.

51. DiRito JR, Hosgood SA, Tietjen GT, Nicholson ML. The future of marginal kidney repair in the context of normothermic machine perfusion. *Am J Transplant.* 2018;18(10):2400-2408.
52. Thompson ER, Bates L, Ibrahim IK, et al. Novel delivery of cellular therapy to reduce ischemia reperfusion injury in kidney transplantation. *Am J Transplant.* 2021;21(4):1402-1414.

1

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: