Improved Organ Utilization and Better Transplant Outcomes With In Situ Normothermic Regional Perfusion in Controlled Donation After Circulatory Death

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Background. We evaluated whether the use of normothermic regional perfusion (NRP) was associated with increased organ recovery and improved transplant outcomes from controlled donation after circulatory death (cDCD). **Methods**. This is a retrospective analysis of UK adult cDCD donors, where at least 1 abdominal organ was accepted for transplantation between January 1, 2011, and December 31, 2019. **Results**. A mean of 3.3 organs was transplanted when NRP was used compared with 2.6 organs per donor when NRP was not used. When adjusting for organ-specific donor risk profiles, the use of NRP increased the odds of all abdominal organs being transplanted by 3-fold for liver ($P < 0.0001$; 95% confidence interval [CI], 2.20-4.29), 1.5-fold for kidney ($P = 0.12$; 95% CI, 0.87-2.58), and 1.6-fold for pancreas ($P = 0.0611$; 95% CI, 0.98-2.64). Twelve-mo liver transplant survival was superior for recipients of a cDCD NRP graft with a 51% lower risk-adjusted hazard of transplant failure (HR = 0.494). In risk-adjusted analyses, NRP kidneys had a 35% lower chance of developing delayed graft function than non-NRP kidneys (odds ratio, 0.65; 95% CI, 0.465-0.901), and the expected 12-mo estimated glomerular filtration rate was 6.3 mL/min/1.73 m^2 better if abdominal NRP was used ($P < 0.0001$). **Conclusions**. The use of NRP during DCD organ recovery leads to increased organ utilization and improved transplant outcomes compared with conventional organ recovery.

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Deidentified data for the purpose of meta-analyses, statistical analysis plans, and data dictionary are available on request, which should be sent to the corresponding author (gabriel.oniscu@ed.ac.uk). Data requestors will need to sign a data access agreement.

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INTRODUCTION

Transplantation as a lifesaving procedure is severely limited by a shortage of suitable donor organs. In recent years in the United Kingdom, there has been a substantial increase in the number of donors, mostly in controlled donation after circulatory death (cDCD), which currently contributes 40% of all deceased donors.[1] However, fewer organs are recovered from cDCD donors (2.7/donor) than from donation after brain death (DBD) donors (3.6/donor)[1] because of the highly subjective assessment of organ quality and concerns about organ function. There is a high attrition rate from the number of organs offered for transplantation to those actually transplanted, particularly for liver and pancreas, with only 29% and 20% of the respective offered cDCD organs being transplanted.[1] Likewise, in the United States, 1.9 organs are recovered and transplanted from cDCD donors compared with 3.3 for DBD donors, with substantial discard rates for liver and pancreas.[2]

Although organ-specific donor risk scores may inform the risk of graft failure[3-5] and guide organ acceptance, transplantation of cDCD organs remains associated with higher complication rates and inferior outcomes. The combination of warm and cold ischemia that characterizes cDCD procurement may account for the suboptimal nature of many livers and pancreases.[6] Controlled donation after circulatory death kidney transplantation appears to be the notable exception, yielding comparable outcomes to DBD kidney transplants,[7] and, as such, has been the primary driver for increasing cDCD utilization in the United Kingdom.

The use of in situ normothermic regional perfusion (NRP) during cDCD retrieval restores an oxygenated blood supply to the organs before cold perfusion. NRP is now the primary approach to cDCD organ recovery in Spain, is mandated in France, Italy, and Norway for liver procurement, and is increasingly used in the United Kingdom.[8-11]

Excellent outcomes for NRP cDCD liver transplantation have been reported, with better graft survival and a reduced incidence of ischemic cholangiopathy.[8-10,12] To date, there has been no in-depth analysis of how NRP impacts the utilization of abdominal organs from cDCD donors, with a single registry report[13] and isolated small series suggesting a potentially improved function following kidney transplantation.[14,15]

This article describes the impact of NRP on the utilization of abdominal organs offered from cDCD donors and reports the outcomes of these transplants in the United Kingdom.

MATERIALS AND METHODS

This retrospective study used data from the UK Transplant Registry held by NHS Blood and Transplant (NHSBT) on all cDCD donor organs offered for transplantation, their utilization and outcomes according to the recovery modality—with and without NRP. The conduct of the study was approved by the NHSBT Implementation of Novel Technologies Board. NRP was undertaken when a trained team was available and at least 1 abdominal organ had been accepted for transplant.

Study Cohort

Patient Cohort for the Organ Utilization Analysis

The cohort consisted of UK adult (≥16) cDCD donors with consent for donation between January 1, 2011, and December 31, 2019, where at least 1 abdominal organ was accepted for transplantation preretrieval. Donors who had any organ stood down because of prolonged time to asystole, donors where abdominal NRP (A-NRP) was performed by a team that was not Edinburgh or Cambridge (n = 12), donors that were HIV positive, and donors who had no abdominal organ accepted for transplant before retrieval were excluded from analysis. This cohort was separated into 3 (overlapping) datasets: 1 where the liver was offered, 1 where at least 1 kidney was offered, and 1 where the pancreas was offered. An organ-specific analysis was performed on each dataset. For organ-specific analyses, additional exclusion criteria were applied (**Table S1, SDC,** http://links.lww.com/TP/C505).

Patient Cohort for the Transplant Outcome Analysis

All UK first adult (≥18) transplant recipients of organs from cDCD donors aged ≥16 between January 1, 2011, and December 31, 2019, were included in this analysis, with a follow-up period of 1-y (December 31, 2020) (data extracted on September 9, 2021, with 92% completion rate for kidney, 95% for liver, and 93% for pancreas). The donors considered were those defined in the utilization analysis. The kidney analysis considered patients who received a kidney-only transplant, and the pancreas analysis considered only those who received a simultaneous pancreas and kidney (SPK) transplant because no NRP pancreases were transplanted as isolated grafts. The liver analysis considered patients who received a liver-only transplant.

Statistical Methods

Whether or not A-NRP was undertaken was added as a binary indicator to the utilization and outcome models described below. All models have been validated for organ utilization and organ outcomes analyses in the United Kingdom. NRP was considered to significantly impact utilization or transplant outcomes if it reduced the model deviance significantly ($P < 0.05$) according to the likelihood ratio test (LRT).

Utilization Analysis

Multivariable Logistic Regression models were used for liver, kidney, and pancreas utilization using each of the datasets described in section 2.1.1. For kidneys, donors were included if at least 1 kidney was offered, and they were counted as transplanted if at least 1 kidney was transplanted. For pancreases, any pancreas offered solely for islet use was counted as an offered pancreas, and any islet transplants counted as a pancreas utilized for transplant, given the combined organ offering system in place in the United Kingdom for solid pancreas and islet transplantation.[16] Validated organ-specific donor risk indices[3-5] were calculated for donors in each dataset, and donors were grouped into quartiles based on the resulting risk score (Q1 representing the best quality/least risk donors and Q4

the worst quality/most risk donors). The "risk index quartile" was used as a 4-level categorical variable in the logistic regression to model organ utilization. The definitions of individual risk indices, the variables considered, and the handling of missing data are detailed in Appendix 1 (**Tables S2–S4, SDC,** http://links.lww.com/TP/C505). Each model was assessed and deemed to be a reasonable fit for the data.

Graft and Transplant Survival Analysis

Multivariable Cox Proportional Hazard Regression models were used to model the time from transplant to graft failure, censored at 1 y, for kidney transplants and pancreas transplants separately, using the datasets described in Section 2.1.2. Patients with unknown graft survival information were excluded. The statistical models applied to each organ were taken from the NHSBT organ-specific annual reports,[1] which have been validated on a UK cohort and are detailed in **Appendix 2** (**SDC,** http://links.lww.com/TP/C505). Missing continuous variables were imputed with mean observed value from the cohort; missing categorical variables were imputed with the most common observed value from the cohort (detailed in **Tables S5–S7, SDC,** http://links.lww.com/TP/C505). For the liver transplant outcomes, a previously published Cox Proportional Hazard Regression model[17] was used to model the time from transplant to either graft failure or patient death, both censored at 1 y (referred to as transplant survival). Each model was assessed and deemed to be a reasonable fit for the data.

One-y Estimated Glomerular Filtration Rate Postkidney Transplant

A General Linear Model was used to model estimated glomerular filtration rate (eGFR) at 1-y posttransplant, with eGFR calculated using the Modification of Diet in Renal Disease method.[18] If the graft failed within 1 y, the eGFR value was set to the average value on dialysis as quoted in the UK Renal Registry annual report[19] (8.5 mL/min/1.73 m^2). If the patient died with a functioning graft within 12 mo of transplant, eGFR was set to the mean value (45.9 mL/min/1.73 m^2). The risk factors considered are taken from NHSBT annual reporting, which has been validated on a UK cohort, and the handling of missing values is detailed in **Table S8** (**SDC,** http://links.lww.com/TP/C505). The model was assessed and deemed to be a reasonable fit for the data.

Graft Function Postkidney Transplant

The proportion of kidney grafts that had (1) immediate function, (2) delayed graft function (DGF, defined as at least 1 dialysis treatment being required during the first postoperative wk), or (3) primary nonfunction was compared between the NRP group and non-NRP and tested using Fisher exact test. Patients with unknown graft function were removed from the analysis.

A Multivariable Logistic Regression model was developed for DGF using the cohort for the 1-y graft survival analysis, restricted to those who experienced immediate graft function and DGF only, and was assessed for goodness-of-fit. The factors used in the 1-y graft survival model were considered **Table S9, SDC,** http://links.lww.com/TP/C505), restricted to those reducing the model deviance at a borderline significance level ($P < 0.1$) according to the LRT to adjust for any potential factors associate with DGF. Missing values were imputed using the mean imputation values used for the 1-y graft survival analysis.

NRP Procedure

The details of the NRP procedure have been published previously.[9,14] In brief, A-NRP was undertaken for 2 h with postmortem cannulation of abdominal vena cava and aorta (or iliac vein and artery) with an endovascular or external clamp occluding the descending thoracic aorta. The perfusion was stopped after 30 to 60 min when thoraco-abdominal NRP (TA-NRP) was undertaken and the heart allowed support to the limited thoraco-abdominal circulation while its function was evaluated; otherwise, perfusion continued for 2 h. NRP was considered to have failed when a circulation could not be established or maintained for at least 30 min to allow the initial set of blood tests to be collected and analyzed (n = 8). All bar 1 case yielded transplantable organs, and these donors were included in the NRP group in an intention to treat analysis.

In the United Kingdom, the national organ retrieval service involves 10 abdominal and 6 cardiothoracic teams that have primary retrieval zones but could be deployed anywhere in the country. All retrieval teams are led by highly trained surgeons who have completed a national training curriculum and are certified as competent before being allowed to lead the team. Four of the 10 abdominal teams are consultant-led (including the 2 NRP teams), whereas the other 5 are led by a mix of consultants and senior transplant fellows. The teams are regularly audited for outcomes to ensure comparable expertise and outcomes are maintained, which is critical in the setting of a national organ sharing system. At the time of organ offering and acceptance, it is unknown to the accepting center which team will undertake the retrieval and whether or not NRP will be used, as the retrieval team (with/without NRP) is mobilized only once organs have been accepted by centers for transplantation. The use of NRP (yes/no) was assumed to be driven solely by the availability of a trained surgeon and perfusion practitioner, as during the conduct of this study, the service was not fully funded to ensure 100% coverage of all donors. NRP was also undertaken mainly in the primary retrieval zones of the 2 centers—Scotland, Northern Ireland, and East Anglia (according to the National Organ Retrieval System rules) and deployment was not influenced by any other donor or recipient-specific characteristics.

The effect of A-NRP upon liver outcomes may be confounded with the effects of liver machine perfusion; however, these data are not available for the full national cohort, and the use of ex situ machine perfusion has been limited during the duration of this study (approximately 90–100 cases) to the non-NRP arm. Although some kidney machine perfusion data were captured, it was felt that no adjustment would be made for machine perfusion. Also, because of the small number of A-NRP cases, only A-NRP cases performed by Edinburgh and Cambridge have been analyzed. Therefore, all donors in

the NRP group will have been attended by 1 of these 2 retrieval teams, whereas donors in the non-NRP group will have been attended by any of the 10 UK abdominal retrieval teams. There have been 12 NRP cases performed by Oxford and Birmingham; however, these are excluded from the analysis because of the haphazard/discontinued activity of these NRP programs over the duration of the study.

RESULTS

Impact of NRP on Organ Utilization

Nine-thousand nine-hundred one adult DCD donors consented for donation in the period considered, of which 2587 (26%) were excluded because of prolonged time to asystole, and 12 NRP cases were removed as detailed above, giving 7302 donors. Of these 7302 donors, 6440 had at least 1 organ (abdominal or cardiothoracic) offered for transplantation and 4716 had at least 1 abdominal organ accepted for transplantation before retrieval and were considered in the subsequent analyses. The demographics for the study cohort are illustrated in Table 1.

Four-thousand four-hundred ninety-three donors proceeded and had at least 1 organ retrieved. A-NRP was undertaken in 163 (3%) of the 4716 donors considered. The mean number of organs retrieved from the 163 NRP donors was 3.3 compared with 2.6 organs for the 4553 non-NRP donors (*t* test $P < 0.0001$).

When applying organ-specific criteria, 4276 donors had the liver offered, 1906 donors had the pancreas offered, and 4622 donors had at least 1 kidney offered for transplantation before retrieval (9223 kidneys offered in total).

Of the 4716 donors considered, there were 1862 donors who had at least 1 lung offered for transplantation. Of the 1862 donors, 90 underwent A-NRP (11% were transplanted), and 1772 did not (14% were transplanted). There were 379 donors who had their heart offered for transplantation, of which 42 underwent A-NRP (48% were transplanted) and 336 did not undergo NRP (23% were transplanted). The UK DCD Heart program began in February 2015 and was only in operation at certain transplant centers during the period considered.

Of the 4553 donors who did not undergo NRP, Edinburgh and Cambridge attended 971 (21%) of these cases. For the NRP cohort, all were attended by the 2 centers.

The use of NRP (not adjusted for differences in donor risk profile) was associated with improved organ utilization rates for liver, kidney, and pancreas from the total number of organ offers as illustrated in Figure 1A. We also undertook a comparison of the number of organs accepted that were retrieved and transplanted (Figure 1B) and found a significant increase in transplantation rates for livers ($P = 0.006$, chi-square) and kidneys ($P = 0.03$, chi-square) if NRP was used. The outcome of the offering process for each organ in the study cohort according to the use of NRP is illustrated in Figure 2A–C and compared with the utilization rates of the UK DBD donor cohort using equivalent donor inclusion criteria. Utilization rates, unadjusted for donor risk profile, were similar for donors who underwent A-NRP or TA-NRP, despite the TA-NRP donors being significantly younger (median age 40 y old versus 54 y old for A-NRP donors), but the numbers are rather small to draw definitive conclusions **Table S10, SDC,** http://links.lww.com/TP/C505). The use of NRP (A-NRP and TA-NRP) during the study period is illustrated in Figure 3.

Risk-adjusted Organ Utilization

Liver

Four-thousand two-hundred seventy-six donors in the cohort had their liver offered and met criteria to be included in the analysis; 1512 (35%) proceeded to

TABLE 1.

Demographics for the 4716 donors considered in this analysis

Variable	Non-NRP, n = 4553 (%)	NRP, n = 163 (%)	*P*	Total, N = 4716 (%)
Median donor age (y) (IQR)	57 (46–67)	51 (38–61)	<0.0001	57 (46–67)
Donor sex				
Male	2828 (62)	105 (64)	0.6073	2933 (62)
Female	1725 (38)	58 (36)		1783 (38)
Median donor BMI (kg/m^2) (IQR)	26.5 (23.4–30.4)	25.8 (22.8–29.7)	0.0869	26.4 (23.4–30.4)
Donor cause of death				
CVA	2059 (45)	77 (47)	0.0782	2136 (45)
RTA	103 (2)	8 (5)		111 (2)
Other trauma	114 (3)	6 (4)		120 (3)
Other	2277 (50)	72 (44)		2349 (50)
Proceeded to donate at least 1 organ				
No	222 (5)	1 (1)	0.0197	223 (5)
Yes	4331 (95)	162 (99)		4493 (95)
Median TWIT (min) (IQR)	29 (23–37)	31 (26–41)	0.0006	29 (23–37)
Median FWIT (min) (IQR)	18 (12–22)	23 (18–28)	<0.0001	18 (14–22)

TWIT is defined as the time from treatment withdrawal to the start of NRP/start of in situ cold perfusion for non-NRP group (missing data: 613 [13%] for non-NRP group and 3 [2%] for NRP group).
FWIT is defined as the time from systolic BP reaching 50 mm Hg to the start of NRP/start of in situ cold perfusion for non-NRP group (missing data: 1435 [32%] for non-NRP and 46 [28%] for NRP group).
BMI, body mass index; BP, blood pressure; FWIT, functional warm ischemic time; IQR, interquartile range; NRP, normothermic regional perfusion; TWIT, total warm ischemic time.

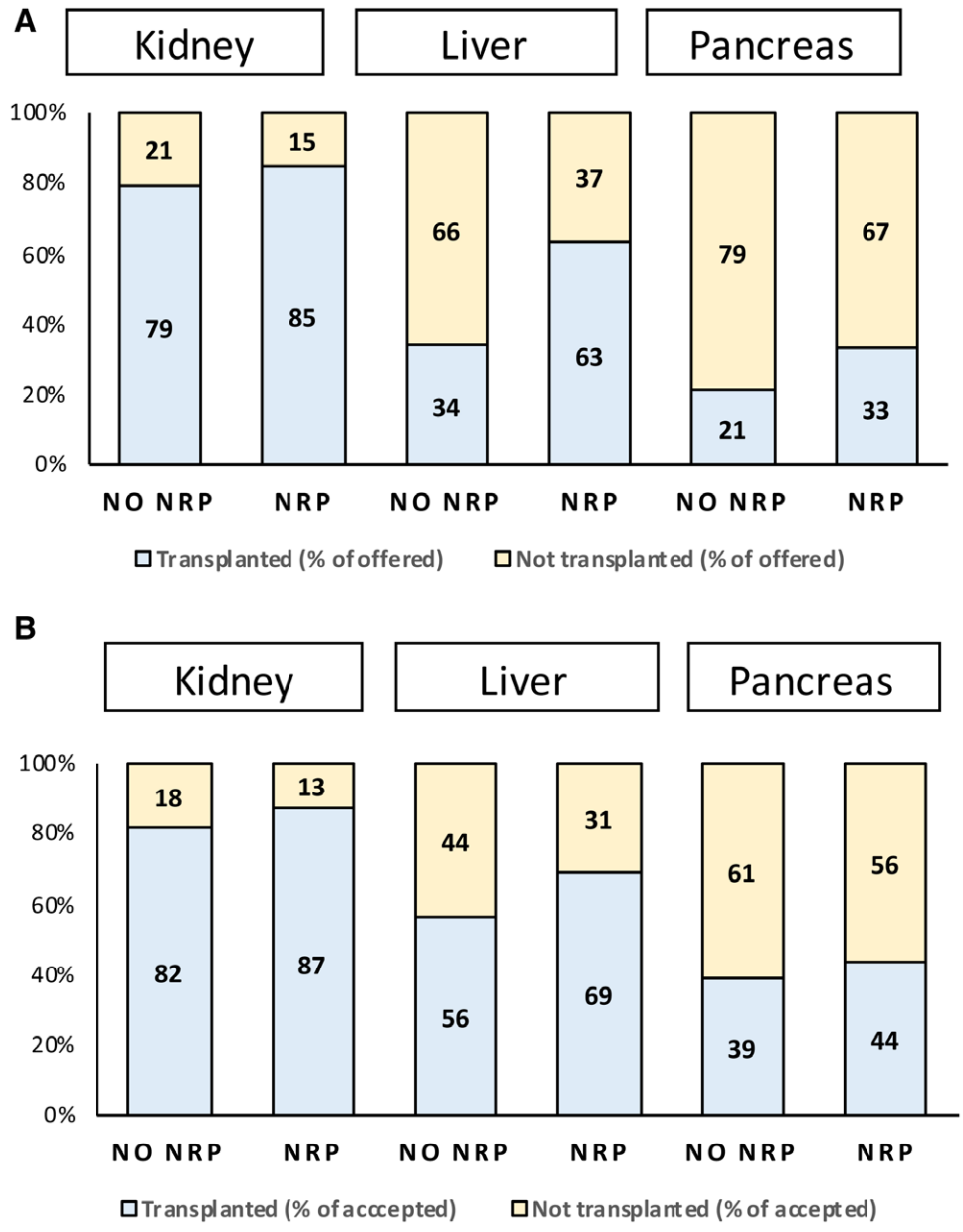


FIGURE 1. Individual organ utilization according to the use of NRP. A, Percentage of organs transplanted of those offered. B, Percentage of organs transplanted of those retrieved. NRP, normothermic regional perfusion.

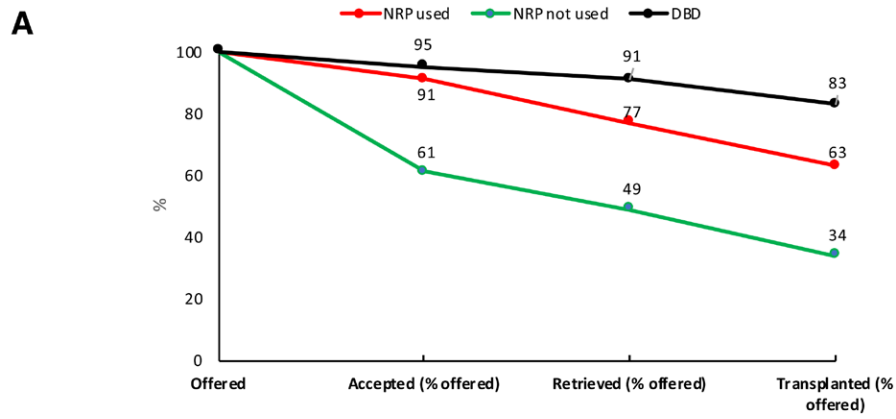
transplant. When adjusting for the donor indices of Feng et al[5] (US Donor Risk Index) or Collett et al[4] (UK Donor Liver Index), the use of A-NRP significantly influenced the probability of a liver transplant resulting from a liver offer (LRT $P < 0.001$). The odds of a liver transplant being undertaken was approximately 3 times higher for donors who underwent NRP than for those who did not (Table 2).

Kidney

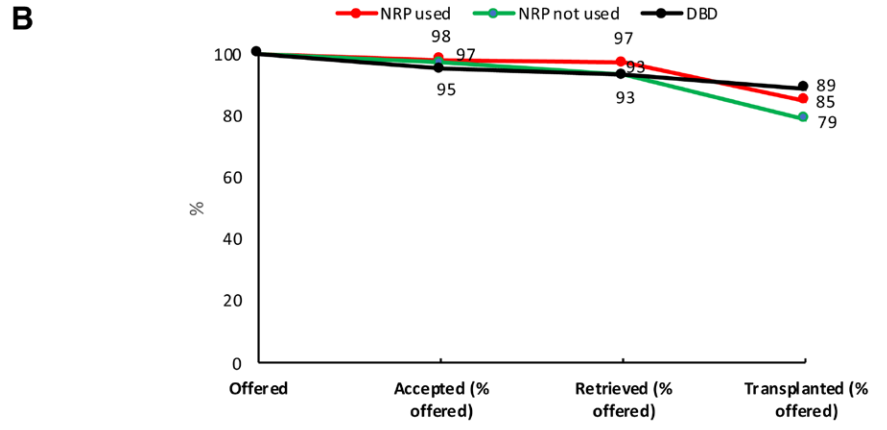
Four-thousand six-hundred twenty-two donors had at least 1 kidney offered and met criteria for inclusion in the analysis; 3901 (84%) had at least 1 kidney transplanted. The use of NRP was associated with 50% higher odds of kidney transplantation (where at least 1 kidney was offered), but this was not significant (LRT $P = 0.1240$) (Table 3).

Pancreas

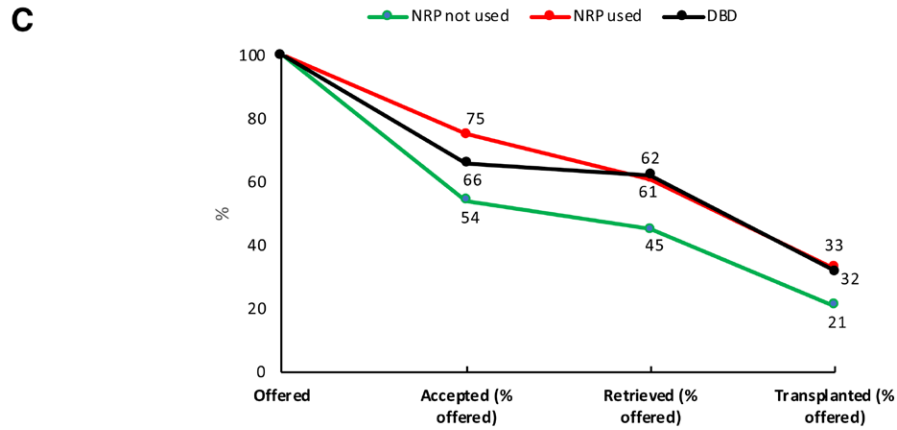
There were 1906 donors who had their pancreas offered, of which 413 (22%) proceeded to transplant. Thirty-one NRP pancreases were transplanted (28 as SPK, 1 as kidney and pancreas islets, and 2 as pancreas islets). Three-hundred eighty-two non-NRP pancreases were transplanted (312 as SKP, 3 as kidney and pancreas islet, 41 as pancreas alone, and 26 as pancreas islets). The use of NRP influenced the probability of pancreas transplantation (SPK) with a 1.6 odds ratio for donors undergoing NRP compared with those who did not (LRT $P = 0.0611$) (Table 4).



NRP cDCD	163	148	126	103
Non NRP cDCD	4113	2491	2007	1412
DBD donors	7008	6682	6395	5796



NRP cDCD	324	318	315	276
Non NRP cDCD	8899	8613	8302	7066
DBD donors	7038	6666	6580	6266



NRP cDCD	93	70	57	31
Non NRP cDCD	1813	975	808	382
DBD donors	4900	3228	3019	1546

FIGURE 2. Outcome of offering process (accepted, retrieved, and transplanted) for all cDCD donors in the study cohort where the organ was offered, according to the use of NRP and compared with the utilization rates for DBD organs offered during the study period (A, liver; B, kidney; C, pancreas). (DBD and DCD donors in the analysis are matched for the inclusion criteria detailed in the methods and **Table 1, SDC**, http://links.lww.com/TP/C505). A, Liver utilization rates with number in the analysis at each stage. DBD and DCD donors in the analysis are matched for the inclusion criteria detailed in the methods and **Table 1** (**SDC,** http://links.lww.com/TP/C505). B, Kidney utilization rates with number in the analysis at each stage. DBD and DCD donors in the analysis are matched for the inclusion criteria detailed in the methods and **Table 1** (**SDC,** http://links.lww.com/TP/C505). C, Pancreas utilization with number in the analysis at each stage. DBD and DCD donors in the analysis are matched for the inclusion criteria detailed in the methods and **Table 1** (**SDC,** http://links.lww.com/TP/C505). cDCD, controlled donation after circulatory death; DBD, donation after brain death; DCD, donation after circulatory death; NRP, normothermic regional perfusion.

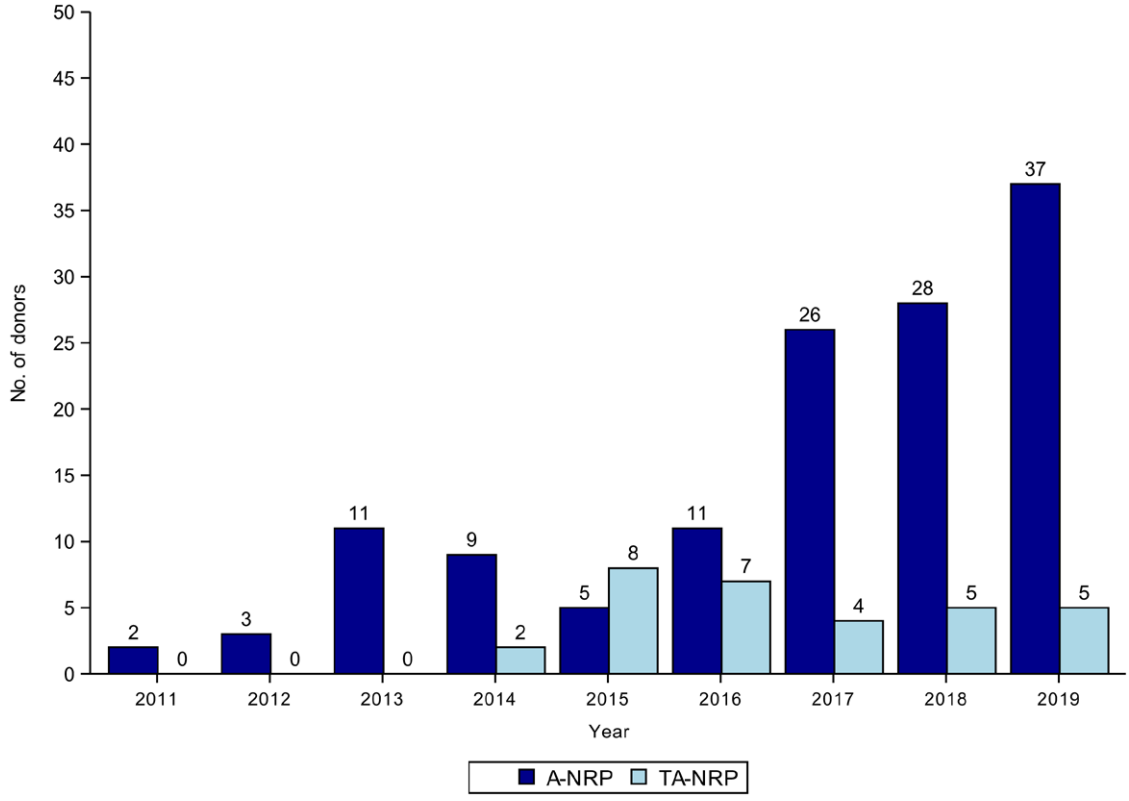


FIGURE 3. NRP use during the study period (2011–2019) by y and whether A-NRP or TA-NRP was used. A-NRP, abdominal normothermic regional perfusion; NRP, normothermic regional perfusion; TA-NRP, thoraco-abdominal normothermic regional perfusion.

Impact of NRP on Transplant Outcomes

Liver

One-thousand four-hundred seventy cDCD first whole liver transplants were undertaken, of which 94 (6%) used cDCD NRP grafts. In the NRP group, 7% of patients experienced transplant failure (patient death or graft loss) within 12 mo, compared with 13% in the non-NRP group. In a Cox Proportional Hazard Regression analysis adjusted for the risk factors listed in **Table S5** (**SDC,** http://links.lww.com/TP/C505), 12-mo transplant survival was superior for recipients who received a cDCD NRP graft compared with those who did not ($P = 0.0534$). The risk-adjusted hazard of transplant failure occurring was 51% lower for recipients of cDCD NRP livers (HR, 0.49; 95% confidence interval [CI], 0.225-1.084) (Table 5). The demographics of the liver transplant cohort are illustrated

TABLE 2.

The effect of NRP on the probability of liver transplantation resulting from a DCD liver offer adjusted for the liver donor risk indices

	N	Odds ratio (95% CI)	*P*
UK DLI quartile			**<0.0001**
Q1 (highest quality)	1069	3.749 (3.106-4.524)	
Q2	1069	2.029 (1.677-2.454)	
Q3	1069	1.410 (1.159-1.715)	
Q4 (lowest quality)	1069	1.000	
NRP use			**<0.0001**
Yes	**163**	**3.072 (2.200-4.289)**	
No	4113	1.000	
US DRI quartile			**<0.0001**
Q1 (highest quality)	1060	3.157 (2.621-3.802)	
Q2	1079	1.846 (1.530-2.227)	
Q3	1068	1.349 (1.112-1.635)	
Q4 (lowest quality)	1069	1.000	
NRP use			**<0.0001**
Yes	**163**	**2.904 (2.083-4.048)**	
No	4113	1.000	

Two separate models were built for the UK DLI3 and US DRI4. *P* for likelihood ratio test. An interaction term was considered between NRP and risk index quartile but was not significant ($P = 0.0614$ for Collett et al[4] [DRI] and $P = 0.0859$ for Feng et al[5] [DRI]), suggesting that the effect of NRP upon utilization does not depend on the "quality" of the donor, although an influence of donor quality on utilization after NRP cannot be ruled out with the size of this cohort (type 2 error).
CI, confidence interval; DCD, donation after circulatory death; DLI, Donor Liver Index; DRI, Donor Risk Index; NRP, normothermic regional perfusion.

TABLE 3.

The effect of NRP on the probability of kidney transplantation resulting from a DCD kidney offer adjusted for the 2017 Mumford UK Kidney Offering Scheme Donor Risk Index (*P* for likelihood ratio test)

	N	Odds ratio (95% CI)	*P*
KDRI quartile			<0.0001
Q1 (highest quality)	1155	3.333 (2.609-4.258)	
Q2	1156	2.175 (1.749-2.706)	
Q3	1156	1.659 (1.350-2.038)	
Q4 (lowest quality)	1155	1.000	
NRP use			0.1240
Yes	163	1.499 (0.871-2.579)	
No	4459	1.000	

An interaction term was considered between NRP and risk index quartile but was not significant ($P = 0.0933$), suggesting that the effect of NRP (upon utilization) does not depend on the "quality" of the donor.
CI, confidence interval; DCD, donation after circulatory death; KDRI, Kidney Donor Risk Index; NRP, normothermic regional perfusion.

TABLE 4.

The effect of NRP on the probability of pancreas transplantation resulting from a DCD pancreas offer adjusted for the PDRI (*P* for likelihood ratio test)

	N	Odds ratio (95% CI)	*P*
PDRI quartile			<0.0001
Q1 (highest quality)	476	21.106 (13.025-34.201)	
Q2	477	6.297 (3.827-10.361)	
Q3	477	3.217 (1.904-5.434)	
Q4 (lowest quality)	476	1.000	
NRP use			0.0611
Yes	93	1.614 (1.0986-2.641)	
No	1813	1.000	

CI, confidence interval; DCD, donation after circulatory death; NRP, normothermic regional perfusion; PDRI, Pancreas Donor Risk Index.

TABLE 5.

Number of transplant failures within 12-mo post-DCD liver transplant, split by use of abdominal NRP and risk-adjusted hazard ratios

NRP use	Liver transplants (N)	Transplant failures within 12 mo, N (%)	Risk-adjusted hazard ratio (95% CI)
Yes	94	7 (7)	0.494 (0.225-1.084)
No	1376	185 (13)	1 (baseline)

Multivariable analysis adjusted for duration of cold ischemia, donor and recipient age and ethnicity, y of transplant, indication for transplant, need for renal support at time of transplant, presence of TIPSS, ventilated in ICU status, in-patient status at the time of transplant, sepsis at the time of transplant, previous abdominal surgery, donor organ appearance, presence of esophageal varices, and acute liver failure status.
CI, confidence interval; DCD, donation after circulatory death; ICU, intensive care unit; NRP, normothermic regional perfusion.

in **Table S11** (**SDC,** http://links.lww.com/TP/C505). An additional analysis adding the effect of functional warm ischemia time (from systolic blood pressure 50 mm Hg to in situ perfusion) to these models showed a significant risk-adjusted increase in the hazard of transplant failure of 1% for each minute increase (*P* = 0.0442; HR, 1.01; 95% CI, 1.003-1.023), and the hazard of failure for recipients of cDCD NRP livers was reduced further to 55% lower after accounting for this (*P* = 0.0251; HR, 0.45; 95% CI, 0.202-0.978).

Kidney

Five-thousand nine-hundred fifty-four first kidney-only transplants were undertaken during the study period, of which 210 (4%) used cDCD NRP kidneys. In the A-NRP group, 3% of the grafts failed within 12 mo, compared with 6% in the non-NRP group (Table 6). In a risk-adjusted Cox Proportional Hazard Regression (**Table S7** (**SDC,** http://links.lww.com/TP/C505), this difference was borderline significant (*P* = 0.0932). The demographics of the kidney transplant cohort are illustrated in **Table S12** (**SDC,** http://links.lww.com/TP/C505). The addition of functional warm ischemia time to the model led to a borderline risk-adjusted difference in graft survival for each min increase (*P* = 0.0521). There was evidence (*P* = 0.0045) to suggest a difference in immediate function (74.8% for NRP and 66.8% for the non-NRP) and DGF between the 2 groups (Table 6). In a risk-adjusted model (**Table S9, SDC,** http://links.lww.com/TP/C505), NRP kidney transplants had a 35% lower chance of developing DGF (odds ratio, 0.648; 95% CI, 0.465-0.901; *P* = 0.008) than non-NRP kidneys.

TABLE 6.

Graft outcomes at 12-mo posttransplant, split by the use of abdominal NRP

Graft outcomes	NRP kidney transplants (N = 210)	Non-NRP kidney transplants (N = 5744)
12-mo graft failure, N (%)[a]	7 (3)	368 (6)
Immediate function, N (%)	155 (73.8)	3413 (59.4)
Delayed graft function, N (%)[b]	49 (23.3)	1793 (31.2)
Primary nonfunction, N (%)	4 (1.9)	175 (3.1)
Mean eGFR at 1 y (mL/min/1.73 m^2)[c]	56.4	45.6
Unknown/missing data on function, N (%)	2 (1)	363 (6.3)

[a]One-y graft survival adjusted for donor age and cause of death, recipient age, ethnicity and diabetes status, waiting time to transplant, and cold ischemic time and HLA mismatch group.
[b]Delayed graft function adjusted for donor age, recipient waiting time to transplant, cold ischemic time, and recipient ethnicity and diabetic status.
[c]eGFR adjusted for recipient sex, ethnicity and age and waiting time, donor history of alcohol abuse, hypertension and diabetes, donor age and height, and cold ischemic time.
eGFR, estimated glomerular filtration rate; NRP, normothermic regional perfusion.

The mean eGFR at 12 mo in the NRP group was 54.5 mL/min/1.73 m^2 compared with 45.8 mL/min/1.73 m^2 in the non-NRP group (Table 6). When risk adjusting for the factors listed in **Table S8** (**SDC,** http://links.lww.com/TP/C505), the 12-mo expected eGFR was 6.3 mL/min/1.73 m^2 higher for transplants from cDCD NRP donors than from non-NRP donors (*P* < 0.0001).

Pancreas

Of the 331 first SPK transplants undertaken, 28 (7%) used cDCD NRP grafts; 4% of the NRP transplants failed within 12 mo, compared with 10% in the non-NRP group (**Table S13, SDC,** http://links.lww.com/TP/C505). There was no significant difference between the groups (*P* = 0.2889) in terms of risk-adjusted 12-mo graft failure. The demographics of the pancreas transplant cohort are illustrated in **Table S14** (**SDC,** http://links.lww.com/TP/C505). There was no impact of the functional warm ischemia time in the overall model with no significant difference in graft survival for each min increase (*P* = 0.826).

DISCUSSION

The use of in situ NRP before organ recovery has increased significantly in many European countries.[8-11] Recent reports have shown that the use of NRP is associated with improved liver transplantation outcomes and a substantial reduction in the incidence of ischemic biliary complications.[9,10,14] Data on the impact of NRP on organ utilization and the outcomes of renal and pancreas transplantation are scarce.[13-15] This study compared the utilization rates and clinical outcomes of organs offered for transplantation and recovered using NRP with a contemporaneous UK cohort of cDCD donors undergoing standard organ recovery over a 9-y period, where at least 1 abdominal organ was accepted for transplant. We have shown that NRP is an independent factor in increasing organ utilization for all abdominal organs. The number of organs recovered from each cDCD donor increases from

2.6 to 3.3 when NRP is used. The current organ recovery rate for all DBD donors in the United Kingdom is 3.7.[1]

There was a significant increase in the utilization rates of all abdominal organs offered for transplant. The most noteworthy increase in utilization rates was observed for liver, with an unadjusted utilization rate for NRP donors nearly double that for non-NRP donors (63% versus 34%). If we consider the number of organs accepted at the point of offering (before the start of the retrieval process), it is conceivable that, because of a better appreciation of NRP benefits in the 2 centers undertaking the procedure, more livers are likely to be accepted when NRP is planned given that cDCD liver allocation in the United Kingdom is centerbased and organs are likely to be transplanted by the retrieving center. However, when we analyzed only those livers that were accepted and eventually retrieved and transplanted, there was an increased utilization that probably reflects the added benefit of the dynamic functional liver assessment during NRP.

Controlled donation after circulatory death kidney utilization in the United Kingdom has been consistently high, driven by excellent clinical results.[20] As such, we did not expect NRP to lead to a significant increase in utilization. Nonetheless, we noted an increased utilization of the kidneys that were accepted and eventually retrieved and transplanted, which may reflect the improved in situ perfusion of the NRP kidneys compared with standard DCD procurement. This is further confirmed in **Figure S1a–c** (**SDC,** http://links.lww.com/TP/C505), which compares the NRP and non-NRP organ utilization for donors attended only by the Edinburgh and Cambridge teams illustrated against the utilization of DCD organs from donors attended by the rest of the UK teams and the DBD donors attended by the Edinburgh and Cambridge teams.

However, it is the 1-y kidney transplant outcomes that are particularly noteworthy. Our analysis has revealed that, at 1 y, the eGFR of transplanted NRP kidneys is 6 mL/min/1.73 m^2 better than that of non-NRP kidneys. This may translate into 5 additional years of graft life for the recipients.[21,22] Recent French data[13] suggest that recipients of NRP kidneys have comparable 1-y outcomes with recipients of DBD kidneys, albeit the French mandate ex situ hypothermic machine perfusion of kidneys following NRP, something that is not routine in the United Kingdom and was not done in any NRP donor kidney at the point of donation in this series. In our study, we have noted a slight reduction in the rate of primary nonfunction plus a notable decrease in DGF rate from 31% for non-NRP cDCD transplants to 23% when NRP was used. The comparable DGF rate for cDCD NRP kidneys in the 2 series is encouraging, and further studies may be needed to explore the added value of ex situ hypothermic machine perfusion after NRP.

We also report the detailed UK NRP data on pancreas utilization and outcomes. The use of NRP was associated with increased pancreas utilization with comparable outcomes to non-NRP cDCD transplants. The numbers are too low to draw any conclusions on a positive impact on function, although there appear to be a lower percentage of graft losses. Further work is needed to define this benefit and also the impact on the quality and function of islets isolated for transplantation. Although the utilization of the cardiothoracic organs was not a direct focus of this article, during this study, NRP has facilitated cDCD heart transplantation. There was no increase, however, in the utilization of cDCD lungs when A-NRP was used[23] compared with standard DCD procurement. The utilization rates are lower in both groups than in reports from other countries,[24] and the reasons for that are more complex and go beyond the use of NRP.

Recent reports suggest that ex situ machine perfusion technology may lead to comparable beneficial outcomes for individual organs (especially the liver),[25-28] but such interventions are expensive[29] and are organ specific. NRP is unique, as it provides a multiorgan benefit allowing improved outcomes for more patients. Despite the perceived benefits of NRP, the uptake has been slow. This is illustrated by the 3% to 5% utilization of NRP during this study. A number of challenges and concerns may have contributed to this slow uptake. The risk of brain perfusion during NRP has been raised, and measures have been put in place to ensure continued absence of brain perfusion.[30] Logistical challenges have often been quoted as a stumbling block. Several approaches have been developed to facilitate the implementation of NRP across a number of legal and organizational settings.[14,31] As such, the use of NRP is routine in Spain (where comparable liver and kidney outcomes have been reported[32]) and is mandated for liver recovery in France and Italy. In other countries such as the United Kingdom, Sweden, the Netherlands, and Switzerland, the use of NRP is expanding, with a clear need for a well-funded and well-designed infrastructure including establishing a dedicated Advanced Perfusion and Organ Preservation Specialist role to support the NRP and other novel perfusion technologies.

In countries where national organ sharing schemes are in place, as is the case in the United Kingdom, there is a need for buy-in from all stakeholders. The offering of NRP-recovered organs should be accompanied by a breadth of clinical and perfusion data to reassure clinicians and help them decide to accept the organs with a great deal of confidence, which will invariably help the national expansion of the NRP services.

The study has several limitations. This is a retrospective analysis of national registry data, which included all cDCD donors in the United Kingdom where an abdominal organ has been offered and accepted for transplantation over a 9-y study period. Given that organ quality and acceptance practice have changed with time, organ utilization analyses had to consider organ-specific risk indices to minimize the risk of vintage bias. The use of NRP was fitted as an independent factor in the multivariable organ utilization analyses, adjusting for the level of donor risk. Further analyses are needed to explore the effect of NRP in each of the donor risk quartiles, but there were too few cases in the higher quartiles to allow us to undertake this analysis. Given that NRP was undertaken by 2 centers, it is possible that some of the effects on organ acceptance may reflect a better appreciation of NRP benefits in the 2 centers. However, as kidneys and pancreas are shared nationally, the increased utilization of the organs retrieved may represent a technology effect rather than a center effect, especially as organs are accepted before having knowledge of whether or not NRP will be used. We acknowledge that NRP was not undertaken for all donors, although the decision to do so was driven by team

on-call availability (as the service was not fully funded to cover all DCD retrievals) rather than a donor preselection. We considered a comparative analysis of the outcomes of organs recovered with and without NRP by the 2 centers alone, but there was a very small number of events to inform the outcome analyses. The transplant outcome analyses reported herein accounted for all the risk factors known to affect graft and transplant outcome in the United Kingdom to account for any differences in cohorts and used NHSBT validated statistical models to which the use of NRP was fitted as an additional factor. Model checking was performed for all outcomes and deemed to be a reasonable fit for the data. Additional analyses were undertaken comparing the distribution of donors within each risk quartile, and subsequent NRP usage, between the national cohort and those in the zonal distribution of the 2 centers undertaking NRP to ensure that there was no center bias. We also recognize that these data are real-world registry outcomes rather than data generated from randomized control trials, and as such, there is a lack of matching of donors and inherent reporting variations. With the rapidly shifting equipoise for the use of NRP in many countries, it is difficult to see how a definitive randomized control trial could be undertaken by these centers. There is a need, therefore, for an international registry with agreed reported criteria and uniform datasets that would inform clinical practice and expand the evidence base in transplantation.[33]

In summary, the use of NRP for organ recovery in cDCD donors is associated with an increase in the utilization of abdominal organs, improved liver transplant outcomes, and better kidney function. Given the beneficial results for all abdominal organs and in concordance with recent international statements about expansion of DCD donation[34] and expert consensus statements,[35] we believe that NRP should become the standard for organ recovery in cDCD donors.

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