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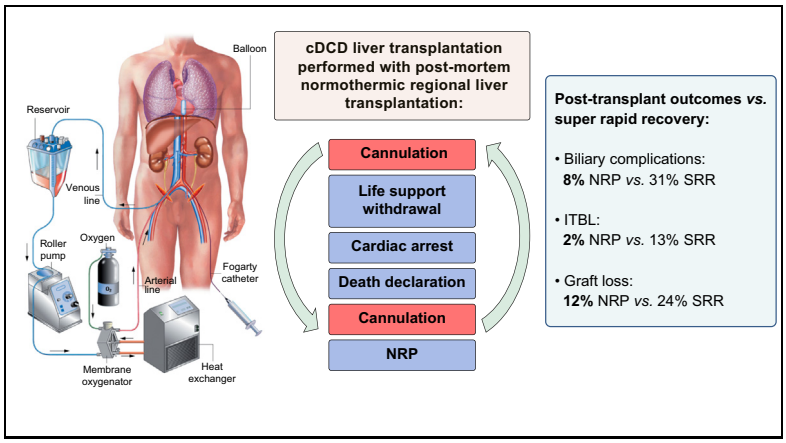
Normothermic regional perfusion *vs.* super-rapid recovery in controlled donation after circulatory death liver transplantation

Graphical abstract



Highlights

- In cDCD livers, postmortem NRP reduces biliary complications, in particular ITBL.
- Postmortem NRP helps improve cDCD liver graft survival.
- Use of postmortem NRP facilitates successful transplantation of older cDCD livers.

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Lay summary

This is a propensity-matched nationwide observational cohort study performed using livers recovered from donors undergoing cardiac arrest provoked by the intentional withdrawal of life support (controlled donation after circulatory death, cDCD). Approximately half of the livers were recovered after a period of postmortem *in situ* normothermic regional perfusion, which restored warm oxygenated blood to the abdominal organs, whereas the remainder were recovered after rapid preservation with a cold solution. The study results suggest that the use of postmortem normothermic regional perfusion helps reduce rates of post-transplant biliary complications and graft loss and allows for the successful transplantation of livers from older cDCD donors.

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Normothermic regional perfusion *vs.* super-rapid recovery in controlled donation after circulatory death liver transplantation

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Background & Aims: Although there is increasing interest in its use, definitive evidence demonstrating a benefit for postmortem normothermic regional perfusion (NRP) in controlled donation after circulatory death (cDCD) liver transplantation is lacking. The aim of this study was to compare results of cDCD liver transplants performed with postmortem NRP *vs.* super-rapid recovery (SRR), the current standard for cDCD.

Methods: This was an observational cohort study including all cDCD liver transplants performed in Spain between June 2012 and December 2016, with follow-up ending in December 2017. Each donor hospital determined whether organ recovery was performed using NRP or SRR. The propensity scores technique based on the inverse probability of treatment weighting (IPTW) was used to balance covariates across study groups; logistic and Cox regression models were used for binary and time-to-event outcomes.

Results: During the study period, there were 95 cDCD liver transplants performed with postmortem NRP and 117 with SRR. The median donor age was 56 years (interquartile range 45–65 years). After IPTW analysis, baseline covariates were balanced, with all absolute standardised differences <0.15. IPTW-adjusted risks were significantly improved among NRP livers for overall biliary complications (odds ratio 0.14; 95% CI 0.06–0.35, p <0.001), ischaemic type biliary lesions (odds ratio 0.11; 95% CI 0.02–0.57; p = 0.008), and graft loss (hazard ratio 0.39; 95% CI 0.20–0.78; p = 0.008).

Conclusions: The use of postmortem NRP in cDCD liver transplantation appears to reduce postoperative biliary complications, ischaemic type biliary lesions and graft loss, and allows for the transplantation of livers even from cDCD donors of advanced age.

Lay summary: This is a propensity-matched nationwide observational cohort study performed using livers recovered from donors undergoing cardiac arrest provoked by the intentional withdrawal of life support (controlled donation after circulatory death, cDCD). Approximately half of the livers were recovered after a period of postmortem *in situ* normothermic regional perfusion, which restored warm oxygenated blood to the abdominal organs, whereas the remainder were recovered after rapid preservation with a cold solution. The study results suggest that the use of postmortem normothermic regional perfusion helps reduce rates of post-transplant biliary complications and graft loss and allows for the successful transplantation of livers from older cDCD donors.

Keywords: Liver transplantation; Donation after circulatory death; Normothermic regional perfusion; Marginal donor; Ischaemic type biliary lesions; Non-anastomotic biliary strictures.
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Introduction

Donation after circulatory death (DCD) donors, who are declared dead following cardiorespiratory arrest, are an increasingly common source of organs. The period of donor warm ischaemia surrounding arrest can damage the quality of organs in general and the liver in particular, because biliary cells are exquisitely susceptible to warm ischaemia.[1] Thus, initial experiences with DCD liver transplantation described high rates of graft dysfunction and non-function and ischaemic type biliary lesions (ITBL). Although complication rates have improved with experience, the rate of post-transplant ITBL remains higher among recipients of DCD grafts *vs.* those receiving donation after brain death (DBD) grafts (16% *vs.* 3%, according to 2 meta-analyses[2,3]). Development of ITBL leads to repeat biliary procedures and hospitalisations; up to 70% of patients with ITBL either require retransplantation or die.[4]

Although DCD donors are typically classified among 4 categories depending on conditions surrounding cardiac arrest,[5] category III controlled DCD (cDCD) donors are the most frequent source of DCD organs for transplantation globally. These are ventilated patients with a devastating brain injury that does not meet the criteria for brain death; the decision is made to withdraw life-sustaining therapy because it is no longer beneficial. Experience gained over the years has allowed for better donor and graft selection to the point that outcomes are comparable to those achieved with livers arising through donation after brain death.[6,7] However, achieving these results has come at the cost of high liver discard rates.[8]

In contrast to most of the Western world, the initial Spanish experience with DCD was with donors suffering sudden out-of-hospital cardiac arrest who were unable to be resuscitated after repeated attempts. Category II uncontrolled DCD (uDCD) donors are declared dead in the hospital, and femoral vasculature is cannulated to establish normothermic regional perfusion (NRP) to reperfuse and reoxygenate abdominal organs while donor evaluation and preparations for organ recovery are undertaken.[9,10] Using NRP, even livers with extensive prerecovery warm ischaemic periods of up to 2.5 h have been successfully transplanted, with biliary complication and graft survival rates comparable to those seen using cDCD livers exposed to considerably shorter periods of warm ischaemia.[9–13]

In 2009, cDCD was piloted in Spain, and a legal and ethical framework for its widespread practice was established in 2012.[14,15] Unlike the rest of the world, where reports of the use of NRP in cDCD have been anecdotal,[16,17] approximately 25% of all cDCD transplants and 50% of all cDCD liver transplants performed in Spain have included postmortem NRP. Here, we report an analysis of the first years of the Spanish experience with cDCD liver transplantation, in particular regarding the hypothesis that the use of postmortem NRP improves organ utilisation rates and post-transplantation outcomes.

Patients and methods

Study design

This was an observational cohort study of all potential cDCD liver donors evaluated and the resulting transplants that took place between June 2012 and December 2016 in Spain, in accordance with the Spanish National DCD Protocol.[15] Outcomes were evaluated until the end of December 2017.

Donor selection and procedure

Potential cDCD donors are ventilated patients with devastating brain injury who do not meet brain death criteria, but in whom the decision is made to withdraw life-sustaining therapy on grounds of futility. Transplant coordination converses with next-of-kin to determine whether organ donation is consistent with the wishes and values of the patient. A decision is made regarding the location and timing of ventilator withdrawal. If any premortem intervention (i.e., heparinisation or cannulation) is considered, specific authorisation is obtained from legal representative(s). The local liver transplant team is alerted regarding the potential cDCD donor. If the local team declines the offer, it is extended to other groups, in order of geographic proximity.

Each donor hospital determines its practice regarding the process by which cDCD organs are recovered. Options include NRP with premortem vessel cannulation, NRP with postmortem cannulation, and super-rapid recovery (SRR).

NRP with premortem vessel cannulation

A bolus of heparin is administered, and cannulation of unilateral femoral vessels is performed, as described previously.[10] The contralateral femoral artery is cannulated with a deflated aortic occlusion balloon catheter, advanced into the supracoeliac aorta under radiographic control. For a visual representation of the NRP set-up, we refer readers to a previous publication depicting its use in uDCD.[9]

With cannulation complete, the physicians in charge of patient care disconnect the endotracheal tube from the ventilator, marking the start of total warm ischaemia (>90 min being a contraindication to liver recovery). The time at which systolic blood pressure drops below 60 mmHg and/or the arterial oxygen saturation drops below 80% marks the start of functional warm ischaemia (>30 min being a contraindication to liver recovery). Death is declared after 5 min of complete absence of spontaneous circulation and respiration.[14] The aortic occlusion balloon is then inflated and the NRP circuit initiated. Proper positioning of the balloon excluding the aortic arch vessels is confirmed by chest radiograph and absence of flow measured in the left radial arterial catheter.

Blood is sampled at baseline and every 30 min during NRP to determine biochemical, haematological and acid–base parameters. Pump flow is maintained >1.7 L/min/m^2, temperature at 37 °C, PaO_2 at 100–150 mmHg and haematocrit >20%. Hepatic transaminases should remain stable throughout NRP; levels more than 3 times the upper limit of normal at baseline and/or more than 4 times the upper limit of normal at the end of NRP are considered relative contraindications for liver recovery.[9,10] In general, NRP is run for 60–120 min to allow adequate reconditioning of the abdominal organs.

NRP with postmortem vessel cannulation

Once death has been declared, the surgical team performs a midline laparotomy to cannulate the abdominal aorta and infrarenal inferior vena cava, proximal to and distal to their bifurcations, respectively. The supracoeliac aorta is clamped, and NRP is initiated.

SRR

Once death has been declared, the surgical team performs a midline laparotomy to cannulate the distal abdominal aorta, clamp the supracoeliac aorta, and flush the cold preservation solution, which is vented through the inferior vena cava.

Recipient selection and procedure

Individual programs have their own policies regarding the recipients of cDCD livers, some choosing the first on the waiting

list organised according to their model for end-stage liver disease (MELD) score, whereas others opt for low-risk patients.

Outcomes

Primary non-function was defined as immediate graft failure resulting in either retransplantation or death within the first week. Early allograft dysfunction was defined according to Olthoff's definition.[18] Diagnosis of ITBL was contemplated in recipients with cholestasis and confirmed based on cholangiographic evidence (typically coming from magnetic resonance cholangiopancreatography) of diffuse non-anastomotic biliary strictures, with or without prestenotic dilatations, in the presence of a patent hepatic artery.[19] All deaths were considered graft loss, even if the patient died with a functioning liver.

Legislative, institutional and recipient approval

The legal basis for the application of NRP in cDCD in Spain was established by Royal Decree 1723/2012 and national protocols.[15] Local protocols have been approved by the institutional ethics committees in each participating centre. Patients listed for liver transplantation at each centre were informed of the possibility of receiving a DCD liver and signed their consent.

Data and statistical analysis

Categorical variables are described as frequencies and percentages, and continuous variables as mean (standard deviation) or median (25–75% interquartile range). Survival was evaluated according to the Kaplan-Meier method. The propensity score method, which simulates the effects of a randomised trial for observational data, was used to estimate study outcomes. Inverse probability of treatment weighting (IPTW) of the propensity scores was used to create a pseudo-population in which study groups were balanced across covariates using data blinded to outcomes. The weights were derived using logistic regression to estimate average treatment effects in treated patients and stabilised by treatment prevalence. The following covariates were included in the propensity models: donor age, sex, cause of death, and intensive care stay; donor total and functional warm ischaemia; cold ischaemia; cold preservation solution; recipient age, sex, laboratory MELD, and transplant indication; and liver transplant centre volume. Baseline categorical variables were compared using the chi-square test and continuous variables using ANOVA with rank-transformed data for both raw and IPTW-adjusted analyses. Raw and IPTW-adjusted logistic and Cox regression models were used to estimate risks: odds ratio (OR), and hazard ratio (HR) with 95% CIs for binary and time-to-event variables, respectively. Covariate balance was assessed using the standardised difference, which is the difference between groups divided by the pooled standard deviation, with a goal-to-achieve value <0.15. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) (see 'Supplementary CTAT Table' in the supplemental information online).

Results

During the study period, 342 potential cDCD liver donors were evaluated. Among these, postmortem NRP was used in 152 livers (43%), with premortem femoral vessel cannulation being performed in 132 livers (87%). SRR was performed in the remaining 190 livers (57%).

Postmortem NRP was run for 120 min (79–136). In total, 52 livers (34%) from cDCD donors undergoing NRP were turned down for transplantation for reasons listed in Table 1. Only 4 livers (3%) were discarded during NRP, all because of altered hepatic transaminases. There were 6 cases (4%) where NRP could not be run because of technical complications; in 5 cases, cold preservation was performed and the livers were recovered and ultimately transplanted. Given the mixed nature of organ recovery, these cases have been excluded from further analysis. Among livers undergoing immediate postmortem SRR, 73 (38%) were turned down for reasons listed in Table 1. Ultimately, 95 cDCD liver transplants performed with postmortem NRP and 117 cDCD performed with SRR were analysed.

Table 2 provides donor and graft characteristics. Given that femoral cannulae were typically in place at the moment at which death was declared, functional and total warm ischaemic times were shorter by ~3 and ~4 min, respectively, with NRP compared with SRR. When cannulation for NRP was performed post mortem, warm ischaemic times were longer: functional warm ischaemia was 19 min [14–24] for postmortem cannulation *vs.* 12 min [9–15] for premortem cannulation, and total warm ischaemia was 27 min [22–33] for postmortem cannulation *vs.* 18 min [13–22] for premortem cannulation ($p = 0.003$ for both comparisons). In addition to total and functional warm ischaemia, the use of colloid-containing cold preservation solutions (University of Wisconsin or IGL-1 [Institut Georges Lopez, SAS, Lissieu, France]) and colloid-free histidine tryptophan ketoglutarate also differed between NRP and SRR livers, with absolute values for standardised differences of >0.5. After IPTW analysis, all variables were well balanced, with absolute standardised differences of <0.15.

Table 3 provides recipient- and transplant-related characteristics. Based on a raw analysis, recipient age, sex and laboratory

Table 1. Reasons for discarding controlled donation after circulatory death livers for transplantation.

Reason	NRP (n = 52/152)	SRR (n = 73/190)	*p* value
Poor macroscopic aspect at recovery[a]	32 (21%)	51 (27%)	0.254
Technical and/or logistical problem(s) associated with recovery	4 (3%)	11 (6%)	0.190
Prolonged warm ischaemic time	4 (3%)	7 (4%)	0.761
Altered laboratory value(s)	4 (3%)	2 (1%)	0.413
Atheromatous lesion(s) of hepatic artery	2 (1%)	1 (0.5%)	0.587
Pathological biopsy	2 (1%)	1 (0.5%)	0.587
Previously undiagnosed cancer	2 (1%)	0	0.197
Active untreated infection	1 (0.7%)	0	0.444
Technical failure of NRP	1 (0.7%)	–	–

[a] Poor macroscopic aspect at recovery refers to an unfavourable visual impression of the liver as seen by the donor surgeon and includes visual impression of moderate-to-severe steatosis, heterogeneous and poor perfusion, and/or graft fibrosis. NRP, normothermic regional perfusion; SRR, super-rapid recovery.

Table 2. Donor- and graft-related characteristics.

Characteristic	Raw analysis				IPTW analysis		
	NRP (n = 95)	SRR (n = 117)	*p* value	Standardised difference[a]	NRP	SRR	Standardised difference[a]
Age (yr)	53.8 (15.2) 57 (45–65)	54.5 (12.0) 56 (47–64)	0.796	−0.050	52.8 (16.7) 58 (44–65)	53.9 (13.3) 56 (46–64)	−0.068
Sex male	63 (66.3%)	77 (65.8%)	0.939	0.011	61 (62.0%)	79 (69.0%)	−0.148
Cause of death							
CVA	42 (44.2%)	49 (41.9%)	0.733	0.047	39 (39.7%)	48 (41.2%)	−0.031
Anoxic brain injury	38 (40.0%)	47 (40.2%)	0.980	−0.004	48 (48.2%)	48 (42.0%)	0.125
Traumatic brain injury	8 (8.4%)	13 (11.1%)	0.514	−0.091	7 (7.4%)	13 (11.0%)	−0.126
Other	7 (7.4%)	8 (6.8%)	0.881	0.021	5 (4.7%)	7 (5.7%)	−0.048
ICU stay (days)	9.2 (9.9) 7 (4–12)	9.5 (8.5) 7 (5–11)	0.460	−0.033	9.7 (9.5) 7 (5–13)	8.7 (7.8) 7 (5–11)	0.117
Total WIT[b] (min)	19.2 (8.2) 18 (13–23)	23.1 (6.7) 22 (19–26)	<0.001	**−0.515**	22.8 (11.9) 20 (15–30)	21.9 (6.3) 21 (17–25)	0.092
Functional WIT[c] (min)	13.3 (5.3) 12 (9–16)	16.1 (5.3) 15 (12–20)	<0.001	**−0.541**	15.7 (7.2) 14 (11–20)	15.0 (4.9) 13 (11–19)	0.102
CIT (min)	333.1 (109.8) 315 (265–365)	340.7 (94.2) 340 (285–383)	0.141	−0.075	349.4 (123.3) 315 (280–375)	341.4 (89.5) 340 (287–390)	0.074
Preservation solution							
UW or IGL-1	37 (38.9%)	15 (12.8%)	<0.001	**0.625**	23 (23.6%)	27 (23.6%)	0.000
HTK	1 (1.1%)	27 (23.1%)	<0.001	**−0.719**	11 (11.4%)	15 (13.4%)	−0.062
Celsior	57 (60.0%)	75 (64.1%)	0.540	−0.085	64 (65.0%)	72 (62.9%)	0.043

Descriptive statistics are frequencies (%) for categorical variables and mean (standardised difference) and median (25–75% interquartile range).
[a] Bold marked figures are greater in absolute value than 0.15.
[b] Withdrawal of life support to start of NRP or cold preservation.
[c] SBP <60 mmHg to start of NRP or cold preservation. CIT, cold ischaemia time; CVA, cerebrovascular accident; HTK, histidine tryptophan ketoglutarate; ICU, intensive care unit; NRP, normothermic regional perfusion; SBP, systolic blood pressure; SRR, super-rapid recovery; UW, University of Wisconsin; WIT, warm ischaemia time.

Table 3. Recipient- and transplant-related characteristics.

Characteristic	Raw analysis				IPTW analysis		
	NRP (n = 95)	SRR (n = 117)	*p* value	Standardised difference[a]	NRP	SRR	Standardised difference[a]
Age (yr)	54.8 (11.9) 56 (52–61)	57.7 (7.1) 59 (53–63)	0.119	**−0.294**	55.8 (9.8) 58 (52–60)	56.7 (7.4) 58 (52–62)	−0.092
Sex male	74 (77.9%)	99 (84.6%)	0.209	**−0.173**	82 (82.6%)	92 (79.9%)	0.069
Laboratory MELD score[b]	15.1 (6.2) 15 (11–19)	14.1 (6.2) 13 (9–18)	0.182	**0.170**	14.6 (5.8) 15 (10–17)	14.6 (6.7) 14 (9–21)	0.009
High-volume transplant centre[c]	69 (72.6%)	88 (75.2%)	0.670	−0.059	73 (74.0%)	85 (73.8%)	0.004
Transplant indication							
Cirrhosis	53 (55.8%)	75 (64.1%)	0.218	**−0.170**	66 (66.9%)	72 (62.5%)	0.094
Hepatocellular carcinoma	35 (36.8%)	38 (32.5%)	0.506	0.092	28 (28.4%)	39 (33.7%)	−0.116
Retransplantation or fulminant liver failure	2 (2.1%)	2 (1.7%)	0.833	0.029	2 (1.9%)	2 (2.1%)	−0.011
Other	5 (5.3%)	2 (1.7%)	0.150	**0.195**	3 (2.8%)	2 (1.7%)	0.070

Descriptive statistics are frequencies (%) for categorical variables and mean (standardised difference) and median (25–75% interquartile range).
[a] Bold marked figures are greater in absolute value than 0.15.
[b] Excluding patients with HCC, laboratory MELD scores were 16 (12–22) and 15 (12–19) among NRP and SRR recipients, respectively ($p = 0.123$).
[c] Defined as >50 liver transplants per year. IPTW, inverse probability of treatment weighting; MELD, model for end-stage liver disease; NRP, normothermic regional perfusion; SRR, super-rapid recovery.

Table 4. Post-transplantation complications and outcomes.

Complication	NRP (n = 95)	SRR (n = 117)	Raw analysis		IPTW analysis	
			Risk estimate (95% CI)[a]	*p* value	Risk estimate (95% CI)[a]	*p* value
Early allograft dysfunction	21 (22%)	32 (27%)	0.75 (0.40–1.42)	0.381	0.97 (0.53–1.80)	0.931
Primary non-function	2 (2%)	3 (3%)	0.82 (0.13–4.99)	0.827	0.24 (0.04–1.56)	0.135
Hepatic artery thrombosis	4 (4%)	3 (3%)	1.67 (0.36–7.65)	0.509	0.79 (0.16–3.85)	0.770
All biliary complications[b]	8 (8%)	36 (31%)	**0.21 (0.09–0.47)**	**<0.001**	**0.14 (0.06–0.35)**	**<0.001**
ITBL	2 (2%)	15 (13%)	**0.15 (0.03–0.66)**	**0.012**	**0.11 (0.02–0.57)**	**0.008**
Retransplantation	5 (5%)	11 (9%)	0.54 (0.18–1.60)	0.263	**0.24 (0.07–0.78)**	**0.018**
Patient death	7 (7%)	20 (17%)	0.44 (0.19–1.05)	0.064	0.53 (0.23–1.22)	0.135
Graft loss	11 (12%)	28 (24%)	**0.49 (0.24–0.98)**	**0.043**	**0.39 [0.20–0.78]**	**0.008**

Figures in bold are statistically significant.
[a] Risk estimates are odds ratios from logistic regression models for all variables except for patient death and graft loss, where hazard ratios from Cox models are shown.
[b] Including 5 and 16 cases of anastomotic biliary strictures arising among recipients of cDCD livers recovered with NRP and SRR, respectively ($p = 0.041$). CI, confidence interval; IPTW, inverse probability of treatment weighting; ITBL, ischaemic type biliary lesions; NRP, normothermic regional perfusion; SRR, super-rapid recovery.

Table 5. Causes of graft loss.

Recovery method	Case	Cause of graft loss	Outcome
NRP			
	1	Bacterial infection	Death within first month
	2	HCV recurrence	Death at 9 months
	3	ITBL	Retransplantation at 5 months
	4	HHV-6 infection	Death within first month
	5	Bacterial infection	Death at 2 months
	6	PNF	Immediate retransplantation
	7	HAT	Death within first month
	8	HAT	Immediate retransplantation
	9	Bacterial infection	Death at 2 months
	10	ITBL	Retransplantation at 7 months
	11	PNF	Immediate retransplantation
SRR			
	12	HCV recurrence	Death at 41 months
	13	HCC recurrence	Death at 37 months
	14	PNF	Immediate retransplantation
	15	ITBL	Retransplantation at 18 months
	16	ITBL	Retransplantation at 11 months
	17	ITBL	Death at 3 months
	18	ITBL	Retransplantation at 3 months
	19	HCC recurrence	Death at 21 months
	20	Chronic rejection	Death at 2 months
	21	PNF	Immediate retransplantation
	22	ITBL	Retransplantation at 5 months
	23	HCV recurrence	Death at 14 months
	24	ITBL	Retransplantation at 13 months
	25	Sudden cardiac death	Death within first month
	26	Bacterial infection	Death within first month
	27	Hyperacute rejection	Death within first month
	28	ITBL	Death at 4 months
	29	PNF	Immediate retransplantation
	30	Necrotising pancreatitis	Death at 7 months
	31	ITBL	Retransplantation at 17 months
	32	HAT	Death at 13 months
	33	HAT	Death within first month
	34	Refractory ventricular fibrillation following reperfusion	Intraoperative death
	35	ITBL	Death at 4 months
	36	Fungal infection	Death at 1 month
	37	*De novo* neoplasm	Death at 5 months
	38	ITBL	Retransplantation at 5 months
	39	ITBL	Death at 6 months

HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HHV-6, human herpesvirus 6; ITBL, ischaemic type biliary lesions; NRP, normothermic regional perfusion; PNF, primary non-function; SRR, super-rapid recovery.

MELD score, and the transplant indications cirrhosis and 'other' were imbalanced between NRP and SRR liver recipients. After IPTW analysis, all absolute standardised differences were <0.15.

Median intensive care unit (ICU) stays were 4 (3–6) *vs.* 3 (2–6) days, respectively ($p = 0.135$), and overall hospital stays were 15 (12–23) *vs.* 17 (11–21) days, respectively ($p = 0.818$), in NRP *vs.* SRR recipients. Table 4 details the raw and adjusted postoperative complication rates and outcomes of 212 cDCD livers that were transplanted. No differences were found in IPTW analysis for early allograft dysfunction, primary non-function or hepatic artery thrombosis. Results were improved among NRP livers for overall biliary complications (OR 0.14; 95% CI 0.06–0.35; $p < 0.001$) and ITBL (OR 0.11; 95% CI 0.02–0.57; $p = 0.008$). Among recipients of livers recovered with SRR (13%), 15 cases of ITBL were diagnosed, at a median of 83 days (47–212). Only 2 cases were diagnosed among the recipients of livers recovered with NRP (2%), at 88 and 212 days, respectively.

Table 5 details the causes of graft loss, including outcomes for individual cases of ITBL. In addition to 11 cases of ITBL in the SRR group that ended in graft loss, there were an additional 4 with ITBL that were alive with their original grafts at the end of follow-up, with follow-ups ranging from 13 to 51 months. There was significantly less graft loss (HR 0.39; 95% CI 0.20–0.78; $p = 0.008$), and fewer retransplantations among recipients of NRP livers during follow-up (OR 0.24; 95% CI 0.07–0.78; $p = 0.018$). With a median follow-up of 20 months, 1- and 3-year survival rates were both 93% for NRP recipients *vs.* 88% and 84% for SRR recipients, respectively, and both were 88% for NRP grafts *vs.* 83% and 76%, respectively, for SRR grafts (Fig. 1).

Discussion

This is the largest study published to date describing the use of postmortem NRP in cDCD liver transplantation and the first to suggest that the application of NRP reduces postoperative biliary strictures and ITBL and improves graft survival compared with SRR. At 1 year, rates of overall biliary complications, graft loss and patient death for those receiving cDCD livers with NRP were 8%, 12% and 7%, respectively. These were achieved despite a high median donor age of 57 years. Recently published benchmarks have established ≤28% biliary complications, ≤11% graft loss, and ≤9% patient death as the goals for standard DBD liver transplantation in high-volume centres.[20] The fact that this was an initial experience and that results did not vary according to centre volume support the reproducibility of these findings.

There are a few publications from centres in North America and the UK describing the transplantation of cDCD livers recovered with SRR that also report relatively low rates of overall biliary strictures (17–25%) and ITBL (0–8%). However, in those series, the donors themselves were very young, with mean or median donor ages ranging from 28 to 42 years (6, 7, 21–23). Two reports from the Mayo Clinics in Florida, Rochester and Arizona in the USA and University Hospital Birmingham in the UK described results of cDCD liver transplants performed using grafts from older donors (>50–60 years) recovered with SRR.[12,13] Rates of biliary complications in these 2 studies were similar to those we observed with SRR (overall 30–33%, ITBL 12%), as were 1-year patient and graft survival rates (~90% and 80–87%, respectively) (Table 6). Although older cDCD livers undergoing SRR can be used for transplantation, they present a

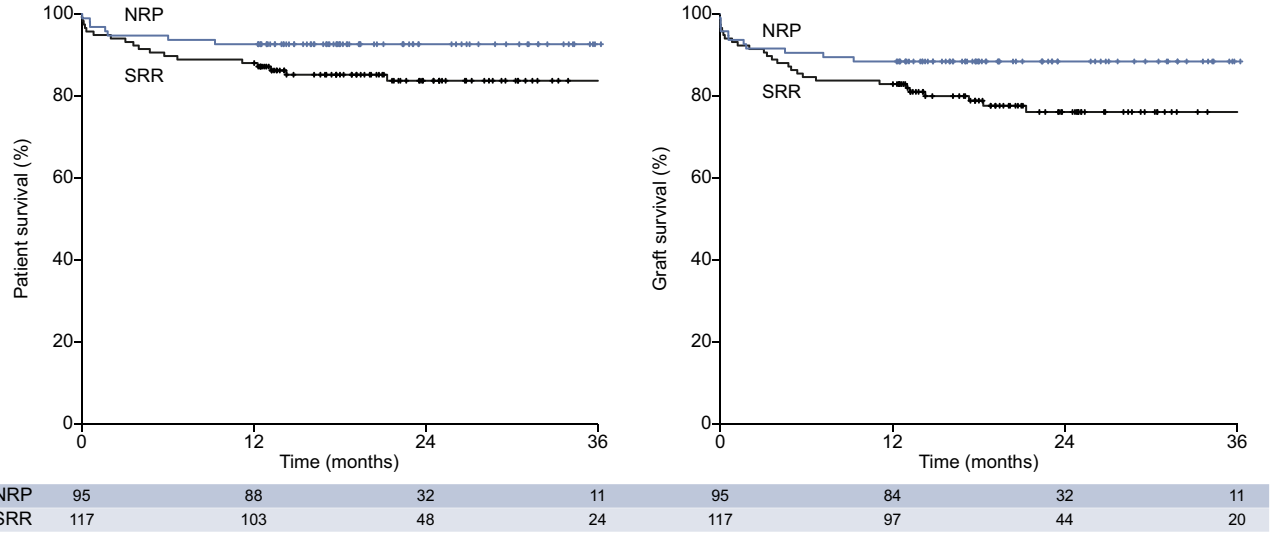

Fig. 1. Kaplan-Meier survival curves for controlled donation after circulatory death) liver recipients and grafts. The IPTW-Cox analysis hazard ratio (95% CI): patient survival 0.53 (0.23–1.22), $p = 0.135$; graft survival 0.39 (0.20–0.78), $p = 0.008$. IPTW, inverse probability of treatment weighting; NRP, normothermic regional perfusion; SRR, super-rapid recovery.

Table 6. Recent series of controlled donation after circulatory death liver transplantation performed by experienced groups.

Centre, period	n	Donor age (yr)	Functional WIT (min)	CIT (min)	All biliary complications	ITBL	1-yr patient survival	1-yr graft survival
Washington University in St Louis, 2005–2014[21]	49	28 (8–60)	12 (1–25)	318 (174–618)	20%	8%	96%	94%
Indiana University, 2011–2015[22]	30	31 (9–55)	11 (7–26)	294 (201–354)	23%	0	88%	88%
Toronto General Hospital and Ochsner Clinic Foundation, Jefferson, 2009–2013[23]	85[a]	36 (15)	21 (8) total	306 (72)	17%	4%	98%	96%
Ochsner Clinic Foundation, Jefferson, 2010–2016	100[a]	38 (15)	20 (8)[b]	304 (92)	25%	3%	93%	92%
Kings College, London, 2001–2010[8]	167	49 (0–85)	16 (5) total	420 (12)	20%	2%	>90%	>90%
Mayo Clinics Florida, Rochester and Arizona, 2002–2016[13]	316	32 (11)	19 (8) total	324 (120)	18%	8%	92%	86%
	155	56 (5)	20 (9) total	318 (84)	30%	12%	91%	87%
University Hospital Birmingham, UK, 2005–2015[12]	222	45 (27–52)	17 (14–21)	414 (342–492)	27%	11%	~92%	~85%
	93	67 (64–71)	18 (14–21)	426 (348–480)	33%	12%	~88%	~80%
Spanish multicentre, 2012–2016	117	56 (47–64)	15 (12–20)	340 (285–383)	31%	13%	88%	83%
	95[c]	57 (45–65)	12 (9–16)	315 (265–365)	8%	2%	93%	88%

[a] Include some of the same patients.
[b] Starting from SBP <80 mmHg *vs.* <55–60 mmHg, which is the more standard definition.
[c] Performed using postmortem NRP. CIT, cold ischaemia time; ITBL, ischaemic type biliary lesions; NRP, normothermic regional perfusion; SBP, systolic blood pressure; SRR, super-rapid recovery; WIT, warm ischaemia time.

greater risk for postoperative biliary complications. However, the use of postmortem NRP could help neutralise this risk and return cDCD livers closer to their prearrest state of viability.

When NRP is used, the period of warm ischaemia arising between ventilator withdrawal and the initiation of NRP is, at most, slightly longer than a period of hepatic inflow occlusion, which is frequently used in hepatic surgery. Intermittent hepatic inflow occlusion is well tolerated in this context and has even been used to achieve advantageous effects in human liver transplantation.[24] Benefits of postmortem NRP have been characterised in experimental studies and have been shown to include restoration of cellular energy substrates, reduction in nucleotide degradation products and improved concentrations of endogenous antioxidants before graft recovery.[25] It has been shown that, by blocking the A2 receptors of adenosine, the beneficial effects of NRP are abolished, indicating that NRP mediates its effects, at least in part, through adenosine.[26] Postischaemic NRP might also be useful to reduce the vasoconstrictive effects of cold graft washout with the static cold storage (SCS) solution.[27]

Considering the limitations of SCS in preserving the viability of liver grafts, especially those arising through the DCD process, the past decade has seen an incremental rise in the popularity of *ex situ* machine perfusion preservation. The limited clinical evidence available to date, most of which comes from low-level studies, suggests that machine perfusion offers advantages over SCS in the preservation of livers arising through the cDCD process.[28–32] Recently, the results of an international randomised trial were published comparing outcomes between liver transplants performed with *ex situ* normothermic machine perfusion (NMP, n = 121) and SCS (n = 101). Controlled DCD donors were included in the study at rates of 28% and 21% among grafts undergoing NMP and SCS, respectively. The major finding of the study was a significant reduction in peak aspartate amino-

transferase among NMP *vs.* SCS livers during the first postoperative week. Both post-transplantation patient and graft survival rates were similar. In terms of postoperative biliary complications, ITBL were detected at rates of 11% and 26% among cDCD livers undergoing NMP and SCS, respectively, whereas anastomotic biliary strictures were detected at rates of 48% and 58%, respectively.[33] Although NMP appears to offer promise in reducing hepatic ischaemia-reperfusion injury, it is unclear that its use can help reduce postoperative biliary complications or graft loss among cDCD livers.

In addition to being financially costly, machine perfusion preservation can also be an arduous and technically complex undertaking. Dissection, cannulation and haemostasis need to be meticulous to avoid vascular injury that would complicate, if not altogether preclude, subsequent transplantation as well as loss of volume during perfusion in a closed circuit.[29,30,33] In addition, inadequate inflow and oxygen delivery, because of loss of volume of perfusate, haemolysis, or inflow and/or outflow obstruction, result in warm ischaemia at normothermic temperatures, provoking injury that might ultimately lead to inadvertent graft loss.[30,33] At least in the context of cDCD, a period of postmortem NRP is an economically favourable option that can help reduce, if not obviate, the need for machine perfusion.

There are ethical concerns surrounding the use of NRP that might limit its widespread application in cDCD. Whereas cardiocirculatory arrest in uDCD has been proven irreversible through the futility of advanced life support manoeuvres performed over an extended period of time, the ability to declare death based on cardiocirculatory criteria in cDCD is predicated upon a condition of permanence. Permanence refers to the fact that, although cardiocirculatory arrest might not be irreversible, it will inevitably become so and, furthermore, lead to irreversible loss of brain and brain stem function (brain death) because circulation will not be restored. Concern has been raised that partially restoring circulation through the use of NRP might negate this permanence and the condition of death. Through the use of NRP, circulation is only restored to a limited region of the body, and a crucial aspect of NRP in cDCD is ensuring a lack of flow to the aortic arch vessels, thereby maintaining the permanence of circulatory arrest in the brain and brainstem. With premortem cannulation, positioning of the aortic occlusion balloon in the supradiaphragmatic aorta distal to the left subclavian artery is confirmed radiographically before the withdrawal of care. Once NRP is initiated, adequate occlusion is confirmed through the use of a left radial artery catheter demonstrating absence of flow. Regions and countries where premortem manoeuvres, such as the administration of heparin and femoral vessel cannulation, are prohibited by law might consider postmortem cannulation to establish NRP. Although total and functional warm ischaemic times were longer by ~9 and 7 min, respectively, the results we observed with NRP with postmortem cannulation were no different from those achieved with NRP with premortem cannulation (91% 1-year graft survival and no biliary complications).

There are limitations to the present study related to its observational nature and the non-random distribution of potential cDCD donors and livers between the 2 recovery methods. Although the raw differences in functional and total warm ischaemic times were marginally but statistically different between the 2 recovery methods, these differences are in fact inherent to the procedures themselves and because cannulation is typically performed premortem when NRP is used. Warm ischaemic times were longer when cannulation for NRP was performed post mortem, yet we did not detect any differences in outcomes when this approach was used, indicating that the relevant variable was the use of NRP and not warm ischaemia *per se*. In addition, there were significant variations in the cold solutions used to preserve the livers in each group. Given that cold ischaemic times in this study were rather short (in general, <6 h), the specific solution used in each case might not be as relevant. Nevertheless, IPTW analysis was applied to address these and other differences, and the adjusted analyses continue to support the raw and unadjusted findings.

In conclusion, the results of this study provide the first indication that the use of postmortem NRP in cDCD liver transplantation can help achieve improved outcomes over the use of SRR. Livers from a broader range of cDCD donors than have been used previously can be successfully transplanted, with post-transplant results that can meet current benchmarks for standard deceased donor liver transplantation.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

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Supplementary data

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