Received: 29 July 2021 | Revised: 11 November 2021 | Accepted: 11 November 2021

DOI: 10.1111/ajt.16899

ORIGINAL ARTICLE

Abdominal normothermic regional perfusion in controlled donation after circulatory determination of death liver transplantation: Outcomes and risk factors for graft loss

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Abbreviations: ALT, alanine aminotransferase; AMC, antemortem cannulation; A-NRP, abdominal normothermic regional perfusion; AST, aspartate aminotransferase; AWIT, asystolic warm ischemia time; BMI, body mass index; CD, confluence dominant; cDCD, controlled donation after circulatory determination of death; CI, confidence interval; CIT, cold ischemia time; CVA, cerebrovascular accident; DCD, donation after circulatory determination of death; D-HOPE, dual hypothermic oxygenated perfusion; DN, diffuse necrosis; EAD, early allograft dysfunction; FWIT, functional warm ischemia time; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HR, hazards ratio; HTK, histidine-tryptophan-ketoglutarate; ICU, intensive care unit; IGL, Institute Georges Lopez; ITBL, ischemic-type biliary lesions; LT, liver transplantation; MELD, model for end-stage liver disease; MF, minor form; MP, multifocal progressive; NRP, normothermic regional perfusion; ONT, Organización Nacional de Trasplantes; OR, odds ratio; PBG, peribiliary glands; PM, postmortem cannulation; PNF, primary non-function; PSC, primary sclerosing cholangitis; RETH, Registro Español de Trasplante Hepático; SETH, Sociedad Española de Trasplante Hepático; SRR, standard rapid recovery; TA-NRP, thoracoabdominal normothermic regional perfusion; TBI, traumatic brain injury; TWIT, total warm ischemia time; UK, United Kingdom; UW, University of Wisconsin; WLST, withdrawal of life-sustaining therapy.

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Postmortem normothermic regional perfusion (NRP) is a rising preservation strategy in controlled donation after circulatory determination of death (cDCD). Herein, we present results for cDCD liver transplants performed in Spain 2012–2019, with outcomes evaluated through December 31, 2020. Results were analyzed retrospectively and according to recovery technique (abdominal NRP [A-NRP] or standard rapid recovery [SRR]). During the study period, 545 cDCD liver transplants were performed with A-NRP and 258 with SRR. Median donor age was 59 years (interquartile range 49–67 years). Adjusted risk estimates were improved with A-NRP for overall biliary complications (OR 0.300, 95% CI 0.197–0.459, $p < .001$), ischemic type biliary lesions (OR 0.112, 95% CI 0.042–0.299, $p < .001$), graft loss (HR 0.371, 95% CI 0.267–0.516, $p < .001$), and patient death (HR 0.540, 95% CI 0.373–0.781, $p = .001$). Cold ischemia time (HR 1.004, 95% CI 1.001–1.007, $p = .021$) and re-transplantation indication (HR 9.552, 95% CI 3.519–25.930, $p < .001$) were significant independent predictors for graft loss among cDCD livers with A-NRP. While use of A-NRP helps overcome traditional limitations in cDCD liver transplantation, opportunity for improvement remains for cases with prolonged cold ischemia and/or technically complex recipients, indicating a potential role for complimentary *ex situ* perfusion preservation techniques.

KEYWORDS
clinical research/practice, complication: surgical/technical, donors and donation: donation after circulatory determination of death (DCD), extracorporeal membrane oxygenation (ECMO), ischemia reperfusion injury (IRI), liver transplantation/hepatology, organ procurement and allocation

1 | INTRODUCTION

Controlled donation after circulatory determination of death (cDCD) refers to donation from persons who die following withdrawal of life-sustaining therapy (WLST), based on recognized futility of continuing such measures.[1,2] Traditionally, organs from cDCD donors have been recovered with rapid *in situ* cold preservation (standard rapid recovery [SRR]) to halt warm ischemic injury as quickly as possible. By limiting risk factors (donor age, donor warm ischemia, graft cold ischemia), adequate results have been achieved using cDCD livers recovered with SRR.[3–9]

In the past 3 years, reports have come out of European countries describing series of cDCD livers[10–15] and kidneys[16] transplanted after recovery with postmortem *in situ* normothermic regional perfusion (NRP). Normothermic regional perfusion relies on placement of cannulae and occlusion balloons or clamps to isolate a region of circulation (abdomen [A-NRP] or chest and abdomen [TA-NRP]). An extracorporeal pump and membrane

oxygenator are used to recover donor arterial blood, oxygenate it, and return it to venous circulation in the region of interest.[17] *In situ* NRP may be considered "machine perfusion;" it is distinct from *ex situ* machine perfusion, however, in that it restores oxygenated blood flow to multiple cDCD organs (A-NRP: kidneys, liver, pancreas; TA-NRP: kidneys, liver, pancreas, heart, lungs), without any intervening cold ischemia. While the exact mechanism by which the beneficial effects of NRP are rendered remains unclear, evidence suggests NRP functions, at least in part, by converting the period of donor hypoperfusion and cardiac arrest into one of ischemic preconditioning, restoring energy substrates, removing waste products, and increasing endogenous antioxidants prior to cold preservation and recovery.[18–21]

In Spain, cDCD was piloted in 2009 and formally regulated in 2012.[22,23] The national protocol created a unique situation in the country, allowing for either SRR or *in situ* A-NRP to be used for abdominal organ recovery. This is contrast to other countries where use of A-NRP has been either anecdotal or compulsory.[24] In 2019, we published the results of the Spanish experience 2012–2016 transplanting 117 cDCD livers recovered with SRR and 95 recovered with A-NRP. The results of the study indicated postmortem A-NRP was superior to SRR in cDCD liver recovery and allowed for successful transplantation of cDCD livers from donors of advanced age, without increased risk for ischemic biliary complications and other adverse posttransplant events.[10]

Since the aforementioned publication, nearly 600 more cDCD liver transplants have been performed in Spain, the great majority with A-NRP. The objective of the present analysis is to describe updated data on a much larger experience in cDCD liver transplantation, evaluate dynamics and impact of different strategies for establishing A-NRP, and determine what risk factors may predispose to an adverse outcome among cDCD livers recovered with A-NRP.

2 | PATIENTS AND METHODS

2.1 | Study design

This is an observational cohort study analyzing all cDCD liver transplants performed in Spain between 2012 and 2019, with outcomes evaluated through at least December 31, 2020.

2.2 | Donor selection and procedure

Each donor hospital determined its practice for recovery of cDCD abdominal organs. Options included A-NRP or SRR with either antemortem or postmortem cannulation. Detailed techniques for each have been described previously.[10,25] If any antemortem intervention (heparinization, cannulation) was performed, specific prior authorization was obtained from the potential donor's legal representative(s).

As per Spanish Liver Transplant Society (SETH) consensus statements,[26] there was no upper age limit for considering cDCD liver donation. With SRR, liver donation was considered when donor functional warm ischemia time (FWIT) was <30 min. For cDCD liver donors recovered with postmortem A-NRP, no concise upper limit was placed on the period of donor FWIT, as long as relevant parameters measured during subsequent A-NRP were adequate (see next section).

2.3 | Abdominal normothermic regional perfusion

Postmortem A-NRP was generally run 1–4 h. Temperature was maintained 35–37°C and pump flow 2.2–2.4 L/min/m^2. Perfusate transaminases (AST, ALT) and lactate levels were measured every 30–60 min during A-NRP. Ideally, hepatic transaminase levels remained stable and <200 IU/L, and perfusate lactate trended downward. Hemoglobin was monitored and red blood cells administered to maintain hemoglobin >8–10 g/dl. Heparin was re-dosed to maintain therapeutic activated clotting time.

During A-NRP, the abdominal cavity was thoroughly explored, paying special attention to the macroscopic aspect of the liver, gallbladder, bile duct, and bowel. At the end of A-NRP, the cold preservation solution was flushed via the arterial cannula, typically with additional cannulation and flushing of a portal vein tributary. The liver was removed as quickly as possible and placed in cold storage. Neither TA-NRP nor *ex situ* machine perfusion were used in any livers included in this study.

2.4 | Recipient selection

In Spain, while cDCD livers recovered with A-NRP were considered for any recipient on the waiting list, transplantation of cDCD livers recovered with SRR into high-risk recipients (e.g., undergoing retransplantation or presenting severely decompensated liver disease) was only considered for well-selected grafts with short donor warm ischemia.[26] Livers from cDCD donors were first offered to recipients with urgent liver transplant status. If a graft was not accepted for an urgent recipient, it was offered locally and then nationally.

2.5 | Data sources, variables, and definitions

Data for this study were recovered from the Spanish Liver Transplant Registry (RETH), under the management and with the collaboration of the Organización Nacional de Trasplantes (ONT). Additionally, the ONT provided information regarding total numbers of cDCD livers offered and evaluated *in situ*.

Registry data were assessed for missing information, which was recovered after contacting individual centers. The following donor variables were recorded: age, sex, body mass, height, days intubation preceding WLST, cause of death, timing of cannulation (antemortem:

prior to WLST; postmortem: following death declaration), location of WLST (intensive care unit [ICU] or operating room), and warm ischemia times. Total warm ischemia time (TWIT) was the period in the donor between WLST and the start of organ preservation (cold flush with SRR or start A-NRP). Functional warm ischemia time started when donor systolic blood pressure dropped <60 mmHg and ended at the onset of organ preservation.[27] Asystolic warm ischemia time (AWIT) was the period between cardiac arrest and preservation; it included the 5-minute "no-touch" observation period of absence of respiration and circulation used to declare death.[23] Additional graft variables included cold ischemia time (CIT), defined as the period between the onset of cold preservation in the donor and removal from cold preservation at the time of transplantation in the recipient, and the static cold preservation solution(s) used.

The following recipient variables were recorded: age, sex, body mass, height, laboratory MELD, and transplant indication. As well, the UK DCD Risk Score was imputed. The UK DCD Risk Score stratifies cDCD liver recipients according to seven variables (donor age, donor body mass index, FWIT, CIT, recipient age, recipient MELD, and re-transplantation indication) into three risk categories (low-risk, high-risk, and futile), based on likelihood of 1-year graft loss.[7]

Intraoperative deaths were imputed as hours or minutes between graft reperfusion and recipient death declaration and were subsequently converted into days. Primary allograft non-function (PNF) was defined as graft failure resulting in re-transplantation or death within the first week. Early allograft dysfunction (EAD) was defined according to the Olthoff definition.[28] Ischemic-type biliary lesions (ITBL) were diagnosed in patients with a patent hepatic artery, signs or symptoms of cholestasis, and direct or indirect cholangiographic imaging reflecting strictures of the intra- and/or extrahepatic biliary tree proximal to the transplant anastomosis.[29] They were further classified anatomically according to the system described by Croome et al.[30]

2.6 | Legislative, institution, and recipient approval

Legal basis for performing cDCD liver transplantation in Spain was provided by Royal Decree 1723/2012[23] and national protocols.[22,27] Local protocols were additionally approved by the institutional ethics committees. Patients listed for transplantation were informed of the possibility of receiving a DCD liver and signed their consent. This analysis was additionally approved by the SETH and the Hospital Clínic Committee on Ethics in Medical Research (protocol number HCB/2021/0678).

2.7 | Statistical analysis

Categorical variables are described as frequencies and percentages and continuous variables as median [25%–75% interquartile range]. Categorical variables were compared using Pearson chi-square test and continuous variables using Mann-Whitney *U* test for independent samples. Logistic and Cox regression models were used to estimate risks: odds ratio (OR) and hazards ratio (HR), with 95% confidence intervals (CI), for binary and time-to-event outcomes, respectively. In order to identify risk factors independently associated with graft loss, multivariate Cox proportional hazards regression analysis was performed, starting with predictors with univariate $p < .2$. Backward stepwise elimination was performed, with $p > .1$ used as criterion for removal, and stratifying according to transplant center. Data were missing for ≤1.3% of all covariates; missing data were handled by case-wise deletion. A value of $p < .05$ was considered significant. Statistical analyses were performed with SPSS® Statistics version 25 (IBM®).

3 | RESULTS

During the study period, 1384 livers were offered from cDCD donors, and 1165 cDCD livers were evaluated *in situ*. Ultimately, 803 livers recovered at 86 hospitals were transplanted at 22 liver transplant centers, among which 545 were recovered with postmortem A-NRP (68%) and 258 with SRR (32%). Causes for graft discard are provided in Table 1.

Figure 1 depicts year-to-year evolution of cDCD liver transplants, separated according to recovery strategy. Considering the cut-off for high- versus low-volume centers of ≥50 liver transplants per year,[31] 80% and 20% of cDCD liver transplants performed with A-NRP were performed at high- and low-volume liver transplant centers, respectively, versus 83% and 17%, respectively, performed with SRR ($p = .358$). There were 14 combined liver-kidney transplants using organs from cDCD donors, all of which were recovered with postmortem A-NRP.

For the entire cohort, median donor age was 59 years [49–67] and body mass index (BMI) 26.3 [24.2–28.7]; 65% of cDCD donors were men. Cerebrovascular accident was the primary cause of death, followed by anoxic brain injury. Table 2 provides donor and graft characteristics for A-NRP and SRR subsets. Antemortem cannulation was performed in the majority of cases with A-NRP ($N = 506$, 93%) and a minority of cases with SRR ($N = 37$, 14%). While WLST was performed in ICU in 146 cases with A-NRP (27%), it was performed in ICU in only nine cases with SRR (3.5%). Donor warm ischemia times (TWIT, FWIT, and AWIT) were shorter in cases with A-NRP versus those with SRR by approximately 4, 2, and 2 min, respectively ($p < .001$ for all comparisons) (Figure S1). Use of different cold preservation solutions also varied significantly according to recovery technique.

Globally, recipient age was 59 years [53–63] and BMI 26.9 [23.7–29.9]; 80% of recipients were men. Cirrhosis was the most common indication for transplantation, followed by hepatocellular carcinoma (HCC). Laboratory MELD values including and excluding HCC patients were 12 [9–16] and 13 [10–17], respectively. Median UK DCD Risk Score was 5 [3–8], with 457 classified as low risk (57%), 304 as high risk (38%), and 42 as "futile" (5%). Table 3 provides characteristics associated with cDCD liver recipient and transplant procedures for

TABLE 1 Reasons for discarding controlled DCD livers for transplantation

Reason for discard	Overall (*N* = 362/1165)	A-NRP (*N* = 230/775)	SRR (*N* = 132/390)	*p* value
Poor macroscopic aspect at recovery[a]	245	151 (19%)	94 (24%)	.276
Technical problem	27	10 (1%)	17 (4%)	**.003**
Altered laboratory values	23	21 (3%)	2 (0.5%)	**.004**
Prolonged donor WIT	18	8 (1%)	10 (3%)	.084
Pathological liver biopsy	14	10 (1%)	4 (1%)	.531
Previously undiagnosed donor malignancy	13	13 (2%)	0	**.005**
Calcified hepatic artery	6	5 (0.6%)	1 (0.3%)	.310
Active untreated infection	4	2 (0.3%)	2 (0.5%)	.571
A-NRP failure	1	1 (0.1%)	—	.448
Other	11	9 (1%)	2 (0.5%)	.201

Abbreviations: A-NRP, abdominal normothermic regional perfusion; SRR, super-rapid recovery; WIT, warm ischemia time.

[a] Poor macroscopic aspect at recovery refers to an unfavorable 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/cirrhosis.

Bold indicates $p < .05$.

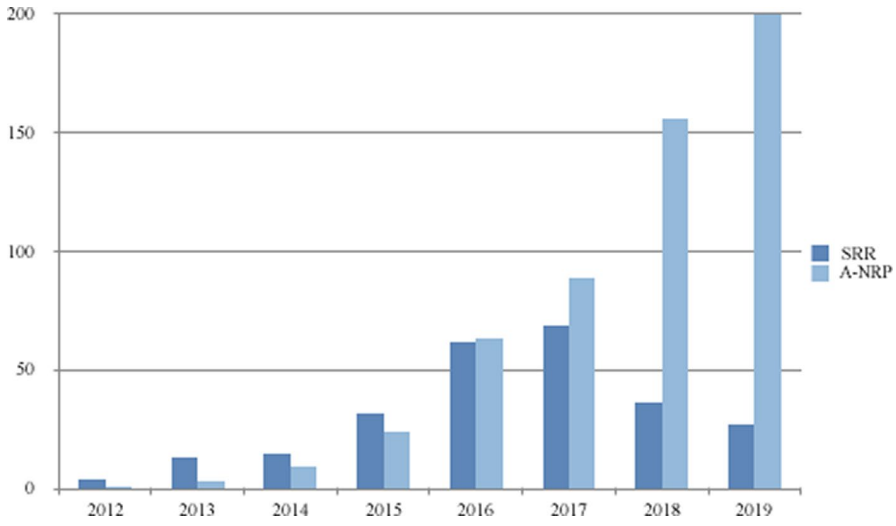


FIGURE 1 Year-to-year evolution of controlled DCD liver transplant activity in Spain, separated according to recovery method. A-NRP, abdominal normothermic regional perfusion; SRR, standard rapid recovery [Color figure can be viewed at wileyonlinelibrary.com]

A-NRP and SRR subsets. Overall UK DCD Risk Score and percentages in each risk category did not vary according to recovery method.

Rates and unadjusted and adjusted risks estimates for relevant post-operative complications and outcomes are provided in Table 4. Observed rates of EAD, PNF, hepatic artery thrombosis (HAT), overall biliary complications (including leaks and anastomotic and non-anastomotic strictures), and ITBL were 15%, 3%, 4%, 12%, and 1%, respectively, for cDCD livers recovered with A-NRP, versus 23%, 6%, 7%, 29%, and 9%, respectively, for those recovered with SRR. Among livers recovered with A-NRP, risk ratios for EAD (OR 0.562, 95% CI 0.363–0.871, $p = .010$), HAT (OR 0.452, 95% CI 0.219–0.932, $p = .032$), overall biliary complications (OR 0.320, 95% CI 0.211–0.485, $p < .001$), ITBL (OR 0.115, 95% CI 0.044–0.302, $p < .001$), re-transplantation (OR 0.258, 95% CI 0.135–0.494, $p < .001$), overall graft loss (HR 0.435, 95% CI 0.313–0.604, $p < .001$), and patient death (HR 0.517, 95% CI 0.357–0.748, $p < .001$) were improved. Table S1 provides further information regarding timing of presentation, number of hospital admissions and invasive biliary procedures, anatomical distributions, and outcomes of the 30 cDCD liver transplants that developed ITBL (6 recovered with A-NRP, 21 recovered with SRR).

Survival curves are provided for patients and grafts in Figure 2. Median follow-up was 31 months. One- and 3-year patient survival rates were 92% and 89%, respectively, for transplants performed with A-NRP, and 86% and 76%, respectively, for those performed with SRR. One- and 3-year graft survival rates (not death censored) were 90% and 87%, respectively, for A-NRP, and 79% and 68%,

TABLE 2 Controlled DCD donor- and graft-related characteristics

	A-NRP ($N = 545$)	SRR ($N = 258$)	*p* value	% Missing
Age (y)	59 [49–67]	58 [48–67]	.638	0
Sex male (%)	351 (64)	167 (65)	.928	0
BMI	26.5 [24.2–28.9]	26.2 [24.2–28.2]	.536	0.5
Intubation prior to WLST (days)	7 [4–11]	7 [4–11]	.991	0.4
Cause of death (%)				0
CVA	252 (46)	107 (42)	.205	
Cerebral anoxia	173 (32)	93 (36)	.226	
TBI	52 (9.5)	26 (10)	.811	
Other	68 (12.5)	32 (12)	.976	
Antemortem cannulation (%)	506 (93)	37 (14)	**<.001**	0
WLST location ICU (%)	146 (27)	9 (3.5)	**<.001**	0
TWIT (min)	18 [13–23]	22 [17–26]	**<.001**	0.1
FWIT (min)	12 [9–16]	14 [11–20]	**<.001**	0.1
AWIT (min)	6 [5–6]	8 [7–9]	**<.001**	0.1
A-NRP duration (min)	111 [81–126]	—	—	1.3
CIT (min)	320 [270–379]	333 [284–388]	.141	1.2
Preservation solution (%)				0
UW or IGL–1	125 (22.9)	31 (12)	**<.001**	
Celsior	329 (60.4)	156 (60.6)	.979	
HTK	73 (13.4)	61 (23.6)	**<.001**	
Other	18 (3.3)	10 (3.9)	.689	

Abbreviations: A-NRP, abdominal normothermic regional perfusion; AWIT, asystolic warm ischemia time; BMI, body mass index; CIT, cold ischemia time; CVA, cerebrovascular accident; FWIT, functional warm ischemia time; ICU, intensive care unit; SRR, standard rapid recovery; TBI, traumatic brain injury; TWIT, total warm ischemia time; WLST, withdrawal of life-sustaining therapy.

Bold indicates $p < .05$.

TABLE 3 Controlled DCD recipient- and transplant-related characteristics

	A-NRP ($N = 545$)	SRR ($N = 258$)	*p* value	% Missing
Age (y)	59 [53–63]	58 [53–63]	.701	0
Sex male (%)	431 (79)	213 (83)	.248	0
BMI	26.9 [23.8–30.1]	26.7 [23.4–29.4]	.216	0.4
Laboratory MELD score	12 [9–17]	12 [8–16]	.358	1
Transplant indication				0
Cirrhosis	349 (64)	163 (63.2)	.841	
HCC	139 (25.5)	70 (27.1)	.617	
PSC	10 (1.8)	1 (0.4)	.110	
Re-transplantation	17[a] (3.1)	3[b] (1.2)	.089	
Acute liver failure	1 (0.2)	5 (1.9)	**.007**	
Other	29 (5.3)	16 (6.2)	.617	
UK DCD Risk Score	5 [3–8]	5 [3–8]	.297	0
Low risk (%)	319 (58.5)	138 (53.5)	.194	
High risk (%)	199 (36.5)	105 (40.7)	.271	
Futile (%)	27 (5)	15 (5.8)	.617	

Abbreviations: A-NRP, abdominal normothermic regional perfusion; BMI, body mass index; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; PSC, primary sclerosing cholangitis; SRR, standard rapid recovery.

[a] Including five very early re-transplants (within 2 weeks of previous transplant), six early re-transplants (between 2 weeks and 3 months after previous transplant), and six late re-transplants (>3 months from previous transplant).[50] Of note, one late re-transplant was the patient's third liver transplant and one early re-transplant was the patient's fourth.

[b] Including one very early re-transplant and two late re-transplants; one late re-transplant was the patient's third liver transplant.

Bold indicates $p < .05$.

TABLE 4 Controlled DCD posttransplant complications and outcomes

	A-NRP ($N = 545$)	SRR ($N = 258$)	Unadjusted Risks estimate (95% CI)[b]	*p* value	Adjusted[a] Risks estimate (95% CI)[b]	*p* value
EAD (%)	81 (15)	60 (23)	0.576 (0.397–0.837)	**.004**	0.562 (0.363–0.871)	**.010**
PNF (%)	16 (3)	15 (6)	0.490 (0.238–1.007)	.052	0.573 (0.252–1.303)	.184
HAT (%)	22 (4)	19 (7)	0.529 (0.281–0.996)	**.049**	0.452 (0.219–0.932)	**.032**
All biliary complications (%)[c]	63 (12)	75 (29)	0.319 (0.219–0.464)	**<.001**	0.300 (0.197–0.459)	**<.001**
ITBL (%)	6 (1)	24 (9)	0.109 (0.044–0.269)	**<.001**	0.112 (0.042–0.299)	**<.001**
Re-transplantation (%)	19 (3.5)	31 (12)	0.265 (0.146–0.478)	**<.001**	0.279 (0.147–0.531)	**<.001**
Graft loss[d] (%)	77 (14)	88 (34)	0.422 (0.311–0.574)	**<.001**	0.371 (0.267–0.516)	**<.001**
Patient death (%)	65 (12)	66 (26)	0.494 (0.350–0.696)	**<.001**	0.540 (0.373–0.781)	**.001**

Abbreviations: A-NRP, abdominal normothermic regional perfusion; CI, confidence interval; EAD, early allograft dysfunction; HAT, hepatic artery thrombosis; ITBL, ischemic type biliary lesions; PNF, primary non-function; SRR, standard rapid recovery.

Observed rates and unadjusted and adjusted risks estimates.

[a] Adjusted for donor age, donor sex, donor body mass index, donor days of intubation prior to withdrawal of life-sustaining therapy, donor cause of death, donor asystolic warm ischemia time, cold ischemia time, cold preservation solution, recipient age, recipient sex, recipient BMI, recipient laboratory MELD score, and transplant indication. Donor total and functional warm ischemia times as well as timing of cannulation (ante- vs. postmortem) were not included in the regression models, based on collinearity.

[b] Risks estimates are odds ratios from logistic regression models for all variables except for patient death and graft loss, where hazards ratios from Cox models are shown.

[c] Including biliary leaks and anastomotic and non-anastomotic biliary strictures.

[d] Not censored for patient death.

Bold indicates $p < .05$.

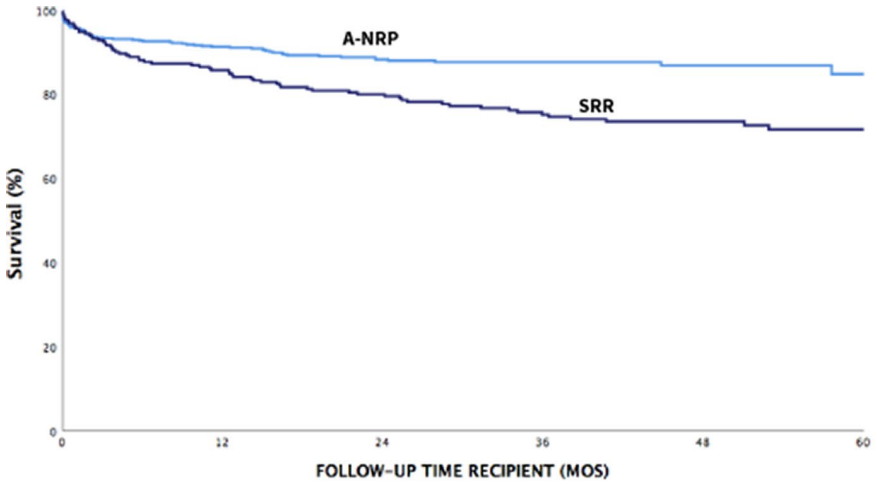
respectively, for those performed with SRR. Death-uncensored graft survival further stratified according to UK DCD Risk classification is depicted in Figure S2.

Risk factors for both death-censored and -uncensored graft loss were evaluated among the subset of cDCD livers recovered with A-NRP. Table 5 and Table S2 provide results of uni- and multivariate Cox proportional hazards models. Cold ischemia time and re-transplantation as transplant indication were the only significant independent predictors for graft loss among cDCD livers recovered with A-NRP. A potential interaction between cold preservation solution and cold ischemia time was also investigated, but none was found. Seven hours cold ischemia was determined to be the optimal cut-off point at or beyond which graft survival decreased significantly. Survival curves stratified according to CIT (<7 h vs. ≥7 h) and transplant indication (re-transplantation vs. all other indications) are provided in Figure 3.

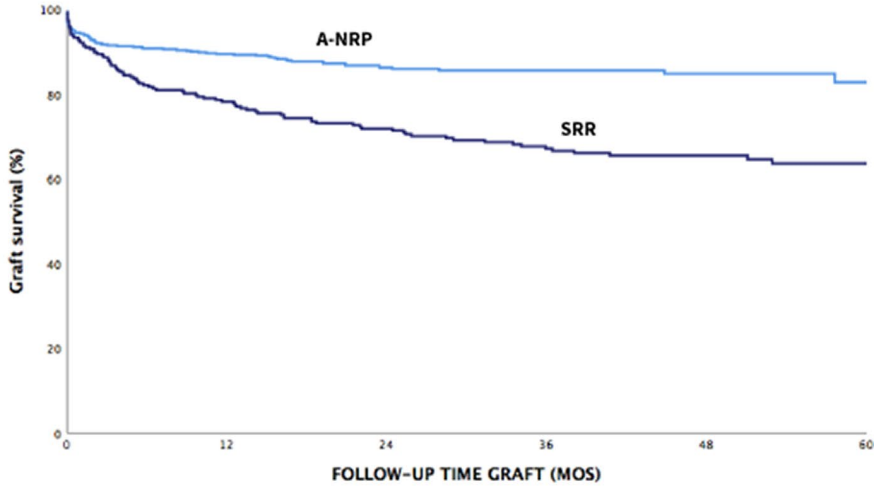
4 | DISCUSSION

Normothermic regional perfusion is a rising technology in solid organ transplantation. This is the largest experience reported to date describing results of cDCD liver transplants performed with postmortem A-NRP. Relative to SRR, significant reductions were observed in rates of all relevant posttransplant complications, including HAT, biliary complications, graft loss, and patient death. Biliary complications arose among 12% of A-NRP livers, and ITBL arose in only six cases (1%), among which three recipients are still alive with their functioning, native grafts at 23, 38, and 52 months.

While at present *ex situ* machine perfusion treats a single organ, *in situ* A-NRP offers the ability to treat up to four transplantable organs. Simultaneous treatment of multiple organs using the same device and resources is a distinct advantage of this perfusion preservation modality relative to *ex situ* machine perfusion of the individual organs. Nonetheless, the impact of *in situ* A-NRP has yet to be evaluated in the context of a randomized clinical trial (RCT). This is due, in part, to the compulsory nature of A-NRP application in DCD in several European countries (France, Italy, Norway)[24]; increasing preference for A-NRP in countries where different options for cDCD recovery are permitted (e.g., Spain)[32]; and above all difficulty in identifying clear, objective endpoints for clinical trials. *In situ* A-NRP is applied in cDCD immediately following declaration of death and prior to organ assessment. An RCT comparing A-NRP with the alternative—SRR—would require randomizing donors and organs at a point when none have been accepted. As such, any RCT on A-NRP is inherently prone to selection bias. It is impossible to blind donor surgeons to recovery method and probable that disparate numbers of organs would be accepted and donor profiles vary significantly according to the method used. Donor surgeons might be more inclined to accept organs with a "riskier" profile recovered with A-NRP, for example, as A-NRP allows for some viability assessment not offered by SRR. Even in the context of an RCT, any endpoint that might be assessed (graft or recipient complications, survival, etc.) would be conditioned by these confounding variables. Alternatively, the option of comparing *in situ* A-NRP with *ex situ* machine perfusion in the liver still does not ensure the absence of selection bias; does not adequately address risk to and potential loss of "bystander"



No. at risk	0	12	24	36	48	60
A-NRP	545	498	320	181	92	34
SRR	258	220	180	142	99	49



No. at risk	0	12	24	36	48	60
A-NRP	545	488	316	179	91	34
SRR	258	202	167	130	88	41

FIGURE 2 Kaplan-Meier survival curves for cDCD liver recipients and grafts, stratified according to recovery method. Graft survival was not censored for patient death with functioning allograft. Adjusted Cox proportional hazards ratio (95% CI): patient survival 0.517 (0.357–0.748, $p < .001$), graft survival 0.435 (0.313–0.604, $p < .001$). A-NRP, abdominal normothermic regional perfusion; SRR, standard rapid recovery [Color figure can be viewed at wileyonlinelibrary.com]

organs (kidneys, pancreas); and is, above all, illogical, given that *in situ* A-NRP and *ex situ* machine perfusion are not competitive preservation strategies and can and have been successfully applied in the same grafts.[15,33]

Median donor age in the series was 59 years and higher than that typically described in previous series of cDCD livers recovered with SRR.[3–5,9,34] Donor age has been identified as a risk factor for ischemic biliary injury in DCD liver transplantation.[35–38] Aging induces changes in choleretic function, and injury response in senescent cholangiocytes is impaired.[39,40] Cholangiocytes themselves, however, appear less implicated in the pathogenesis of ischemic biliary injury relative to peribiliary arterioles and deep peribiliary glands (PBG),[41–43] the latter acting as a progenitor cell niche in the setting of severe injury. A role for postmortem A-NRP in restoring PBG viability in the setting of DCD is plausible and warrants further investigation.

Unlike previous reports on dynamic liver preservation strategies applied at expert centers and oftentimes after considerable prior donor and graft selection,[44,45] the present analysis includes a national cohort of donors performed at over 80 centers, and the denominator for graft discard is all cDCD livers evaluated *in situ* in the country during the inclusion period. As such, it offers a rather impartial view of what can be expected from this preservation modality in real-world practice. There were more technical problems during organ recovery that resulted in liver discard when SRR was the recovery method, while more livers were discarded based on altered laboratory values (i.e., hepatic transaminases and lactate levels) measured during A-NRP. Interestingly, while 13 cDCD livers recovered with A-NRP were discarded following

TABLE 5 Univariate and multivariate Cox proportion hazards analyses evaluating risk factors for overall graft loss among cDCD livers recovered with A-NRP

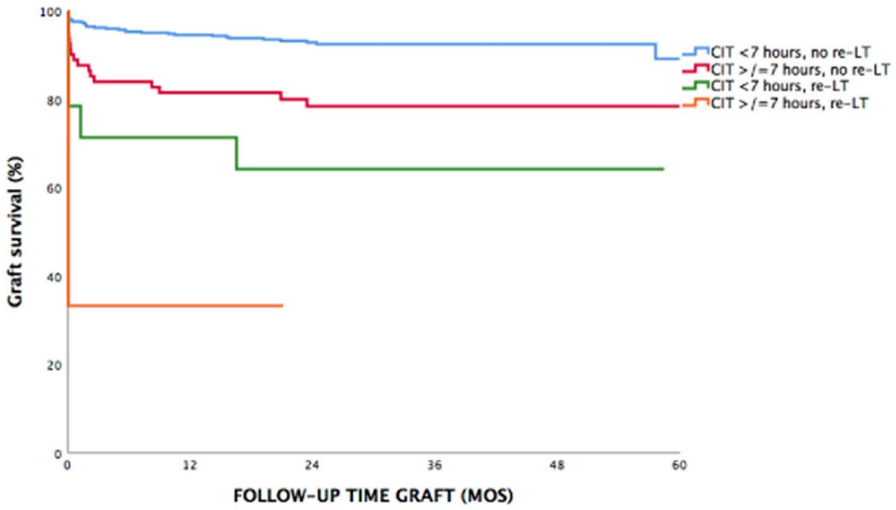
	Univariate			Multivariate		
	Hazards ratio	**95% CI**	***p* value**	**Hazards ratio**	**95% CI**	***p* value**
Donor age	1.011	0.992–1.030	.268			
Donor sex male	1.483	0.873–2.518	.145			
Donor BMI	0.982	0.926–1.042	.551			
Donor days intubation prior to WLST	0.994	0.976–1.102	.493			
Donor cause of death						
CVA	*Reference category*					
Cerebral anoxia	1.013	0.583–1.763	.962			
TBI	1.281	0.606–2.708	.517			
Other	0.645	0.283–1.469	.296			
Donor TWIT	1.010	0.983–1.036	.482			
Donor FWIT	1.005	0.966–1.047	.796			
Donor AWIT	1.040	0.989–1.094	.126			
Antemortem cannulation	0.736	0.189–2.868	.659			
WLST location ICU	1.505	0.753–3.009	.247			
A-NRP duration	0.998	0.992–1.005	.609			
CIT	1.003	1.000–1.006	.025	1.004	1.001–1.006	.015
Preservation solution						
UW or IGL–1	*Reference category*					
Celsior	0.997	0.266–3.733	.996			
HTK	1.509	0.121–18.801	.749			
Other	0.635	0.075–5.380	.677			
CIT * preservation solution[a]	1.001	1.000–1.002	.225			
Recipient age	0.982	0.958–1.007	.157			
Recipient sex male	1.095	0.624–1.922	.752			
Recipient BMI	0.982	0.937–1.030	.453			
Recipient laboratory MELD score	0.996	0.953–1.040	.845			
Recipient transplant indication						
Cirrhosis	*Reference category*					
HCC	1.126	0.649–1.952	.673			
PSC	3.405	0.766–15.133	.107			
Re-transplantation	6.214	2.469–15.641	<.001	6.449	2.548–16.325	<.001
Other	1.726	0.713–4.182	.227			

Abbreviations: A-NRP, normothermic regional perfusion; AWIT, asystolic warm ischemia time; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CVA, cerebrovascular accident; FWIT, functional warm ischemia time; HCC, hepatocellular carcinoma; ICU, intensive care unit; MELD, Model for End-stage Liver Disease; PSC, primary sclerosing cholangitis; TBI, traumatic brain injury; TWIT, total warm ischemia time; WLST, withdrawal of life-sustaining therapy.

[a] Interaction term.

discovery of previously undiagnosed malignant cancer at the time of organ recovery, no livers recovered with SRR were declined for this reason. This novel observation is important and should serve as note of caution for cDCD donor surgeons to ensure equally meticulous donor cavity explorations regardless of the recovery method.

In Spain, very few cDCD donors are turned down for liver recovery due to prolonged donor warm ischemia. Antemortem cannulation reduces donor warm ischemia, although it is currently only permitted in certain centers in Belgium and Spain.[25] The mandatory no-touch period for declaring death is 5 min in Spain, as opposed



No. at risk	0	12	24	36	48	60
CIT <7 hours, no re-LT	437	405	253	147	74	22
CIT ≥7 hours, no re-LT	82	66	50	26	14	10
CIT <7 hours, re-LT	14	10	7	2	1	0
CIT ≥7 hours, re-LT	3	1	0			

FIGURE 3 Death-censored graft survival among cDCD livers recovered with A-NRP and stratified according to cold ischemia time < versus ≥7 h and re-transplantation versus all other indications. Cox proportional hazards ratios, stratified according to transplant center, relative to CIT <7 h and no re-transplantation (reference category): CIT ≥7 h and no re-transplantation HR 2.732 (95% CI 1.301–5.740, $p = .008$), CIT <7 h and re-transplantation HR 7.604 (95% CI 2.560–22.581, $p < .001$), CIT ≥7 h and re-transplantation HR 27.141 (95% CI 4.506–163.464, $p < .001$) [Color figure can be viewed at wileyonlinelibrary.com]

to 20 min in Italy.[15,24] As well, sedo-analgesia is applied during WLST prior to cDCD in the same manner as it is applied in cases of WLST where no subsequent organ donation is contemplated. Sedo-analgesia is applied at the discretion of the physician or team of physicians managing WLST, which is entirely separate from the NRP and organ recovery team(s). In other settings, sedo-analgesia prior to or during WLST is not allowed, in order to avoid "hastening" death in the context of cDCD.[25] It remains unclear, however, whether this practice varies with respect to cases of WLST without subsequent donation and/or whether lack of sedo-analgesia during withdrawal induces undue suffering due to progressive dyspnea and asphyxia in the final moments of life.[46]

The optimal length of time for running postmortem A-NRP in cDCD has remained an issue of debate. In general, expert consensus supports maintaining A-NRP 1–4 h.[25,26,47] In our series, A-NRP lasted a median of 111 min, with most centers opting for 2 h and a few at least 1 h. On multivariate Cox proportional hazards analysis, A-NRP duration was not observed to be associated with graft loss, indicating that the typical strategy of 1–2 h postmortem A-NRP appears adequate in our setting.

In this study, apart from describing outcomes of cDCD liver transplantation performed with A-NRP, we aimed to identify specific risk factors for graft loss. On multivariate Cox proportional hazards analysis, cold ischemia and re-transplantation were the significant independent predictors that were identified. Neither of these risk factors had anything to do with the transplant graft itself but rather the logistical process and complexity of the recipient. While the UK DCD Risk Score imputes increased risk of graft loss for cold ischemia >6 h,[7] we identified CIT ≥7 h as the optimal cut-off for risk stratification in our A-NRP cohort. That said, we were not interested so much in creating our own risk score for graft loss with A-NRP livers as we were in identifying characteristics that might indicate a role for additional use of *ex situ* perfusion preservation strategies.

All *ex situ* perfusion strategies are complimentary and do not compete with *in situ* A-NRP. A recently published randomized clinical trial demonstrated that *ex situ* dual hypothermic oxygenated perfusion (D-HOPE) led to a significant reduction in ITBL detected within 6 months of transplantation among cDCD livers recovered with SRR, from 18% with static cold storage to 6% with end-ischemic D-HOPE ($p = .03$).[48] While it is unlikely that we will be able to improve rates of biliary complications or ITBL among cDCD livers recovered with A-NRP in our setting, there may be a role for *ex situ* perfusion to reduce rates of graft loss in cases with more difficult transplant logistics and/or recipients. The strategy of A-NRP followed by end-ischemic D-HOPE, in particular, is one that has offered good results in Italy. In the most recent Italian multicenter publication (Table 6), in spite of median FWIT of 40 min, the *in situ* A-NRP + end-ischemic D-HOPE strategy offered good posttransplant outcomes (98% one-year patient survival, 91% one-year graft survival, and 2% ITBL) among 44 relatively low-risk recipients (median MELD 9, 66% transplanted for HCC).[15]

The present study has limitations related to its retrospective nature and the fact that different recovery strategies were not randomized. Data for the study were recovered from a registry, and some information was missing, although this was largely overcome by contacting individual centers directly. Potential additional risk factors, such as donor hepatectomy and transplantation warm ischemia times, and specific parameters related to A-NRP (pump flows, transaminases, etc.), were not available for consideration. As well, the average degree of recipient severity at the time of liver transplantation, including MELD scores and need for intensive care and organ replacement therapy, tends to be lower

TABLE 6 Modern national/multicenter experiences using postmortem A-NRP in cDCD liver transplantation

Center, period	*N*	Donor age (y)	FWIT (min)	CIT (min)	Indication re-transplantation (%)	All biliary complications (%)	ITBL (%)	One-year patient survival (%)	One-year graft survival (%)
Spanish multicenter, 2012–2019	545	59 [53–63]	12 [9–16]	320 [270–379]	3	12	1	92	90
French multicenter, 2015–2019 (13)	132	50 [39–59]	22 [19–26]	342 [282–396]	0	17	5	95	93[a]
Italian multicenter, 2015–2019 (15)	44	59 (range 37–70)	40 (range 34–69)	394 (range 180–660)[b]	5	22	2	98	91
UK multicenter, 2011–2017 (11)	43	41 [33–57]	Total WIT 30 [26–36]	382 [303–502]	5	7	0	95	95

Abbreviations: CIT, cold ischemia time; FWIT, functional warm ischemia time; ITBL, ischemic type biliary lesions.

[a]Censored for tumor-related death.

[b]Additional end-ischemic *ex situ* dual hypothermic oxygenated perfusion (D-HOPE) applied in 37/44 cases (84%).

in Spain relative to other countries, such as the United States, and a degree of caution should be exercised when extrapolating these results to distinct settings. It is important to note that no recipient selection was performed herein based on MELD, and cDCD livers are considered the same as livers arising from DBD donors in Spain (offered to the same recipients according to the same allocation policy).[49]

In summary, in this large experience using postmortem A-NRP in cDCD liver transplantation, biliary complications were consistently low, and development of ischemic type biliary lesions was anecdotal. The use of postmortem A-NRP can help overcome many of the traditional limitations seen with cDCD liver transplantation. Nonetheless, there is still opportunity for improvement in outcomes for cases with prolonged cold ischemia ≥7 h and/or technically complex recipients, indicating a potential complimentary role for *ex situ* perfusion preservation techniques.

ACKNOWLEDGMENTS

The authors acknowledge the Spanish Liver Transplantation Society (SETH); members of the Organización Nacional de Trasplantes; and transplant coordinators, including Manuela Cid, Eduardo Miñambres, Ramón Lara, Rafael Badenes, Kepa Esnaola, Domingo Daga, Marina Pérez-Redondo, Fernando Segura, Esther Corral, Teresa Pont, Eva Oliver, Mónica Delicado, Amado Andrés, Juan Galán, Gerard Sánchez-Etayo, Carlos de Santiago, José María Manciño, Elena Gallego, José María Dueñas, Lucas Lage, Francisco Javier Gil, and Francisca Isabel Cabeza, among many others, for providing information required to prepare this manuscript as well as their ongoing efforts that make organ donation and transplantation in Spain possible.

DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. AJH and CF have received research funding and consultancy fees from Guanguong Shunde Innovative Design Institute and additional research funding from Instituto de Salud Carlos III. The other authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

AJ Hessheimer, G de la Rosa, and C Fondevila contributed to study concept and design. All authors contributed to acquisition of data. AJ Hessheimer and C Fondevila contributed to analysis and interpretation of data. AJ Hessheimer, G de la Rosa, C González-Abos, E Coll, B Domínguez-Gil, and C Fondevila contributed to drafting of the manuscript, while the remainder of authors contributed to critical revision of the manuscript for important intellectual content. All authors give their final approval of the version to be published and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Thuong M, Ruiz A, Evrard P, et al. New classification of donation after circulatory death donors definitions and terminology. *Transpl Int*. 2016;29(7):749-759.
2. Domínguez-Gil B, Delmonico FL, Shaheen FAM, et al. The critical pathway for deceased donation: Reportable uniformity in the approach to deceased donation. *Transpl Int*. 2011;24(4):373-378.
3. Paterno F, Guarrera JV, Wima K, et al. Clinical implications of donor warm and cold ischemia time in donor after circulatory death liver transplantation. *Liver Transplant*. 2019;25(9):1342-1352.
4. Kohli DR, Harrison ME, Adike AO, et al. Predictors of biliary strictures after liver transplantation among recipients of DCD (donation after cardiac death) grafts. *Dig Dis Sci*. 2019;64(7):2024-2030. 10.1007/s10620-018-5438-0
5. Farid SG, Attia MS, Vijayanand D, et al. Impact of donor hepatectomy time during organ procurement in donation after circulatory death liver transplantation: the United Kingdom experience. *Transplantation*. 2019;103(4):E79-88.
6. Croome KP, Mathur AK, Lee DD, et al. Outcomes of donation after circulatory death liver grafts from donors 50 years or older. *Transplantation*. 2018;102(7):1108-1114. http://insights.ovid.com/crossref?an=00007890-900000000-96670
7. Schlegel A, Kalisvaart M, Scalera I, et al. The UK DCD risk score: a new proposal to define futility in donation-after-circulatory-death liver transplantation. *J Hepatol*. 2018;68(3):456-464. 10.1016/j.jhep.2017.10.034
8. Schlegel A, Scalera I, Perera MTPR, et al. Impact of donor age in donation after circulatory death liver transplantation: is the cut-off "60" still of relevance? *Liver Transplant*. 2018;24(3):352-362. https://onlinelibrary.wiley.com/doi/abs/ 10.1002/lt.24865
9. Mihaylov P, Mangus R, Ekser B, et al. Expanding the donor pool with the use of extended criteria donation after circulatory death livers. *Liver Transplant*. 2019;25(8):lt.25462. https://onlinelibrary.wiley.com/doi/abs/ 10.1002/lt.25462
10. Hessheimer AJ, Coll E, Torres F, et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol*. 2019;70(4):658-665. 10.1016/j.jhep.2018.12.013
11. Watson CJE, Hunt F, Messer S, et al. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant*. 2019;19(6):1745-1758. https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.15241
12. Hagness M, Foss S, Sørensen DW, et al. Liver transplant after normothermic regional perfusion from controlled donors after circulatory death: the norwegian experience. *Transplant Proc*. 2019;51(2):475-478. 10.1016/j.transproceed.2019.01.066
13. Muller X, Mohkam K, Mueller M, et al. Hypothermic oxygenated perfusion versus normothermic regional perfusion in liver transplantation from controlled donation after circulatory death: first international comparative study. *Ann Surg*. 2020;272(5):751-758.
14. Ruiz P, Gastaca M, Bustamante FJ, et al. Favorable outcomes after liver transplantation with normothermic regional perfusion from donors after circulatory death. *Transplantation*. 2019;103(5):938-943. http://insights.ovid.com/crossref?an = 00007890-900000000-96433
15. De Carlis R, Schlegel A, Frassoni S, et al. How to preserve liver grafts from circulatory death with long warm ischemia? A retrospective Italian cohort study with normothermic regional perfusion and hypothermic oxygenated perfusion. *Transplantation*. 2021;105(11):2385-2396.
16. Padilla M, Coll E, Fernández-Pérez C, et al. Improved short-term outcomes of kidney transplants in controlled donation after the circulatory determination of death with the use of normothermic regional perfusion. *Am J Transplant*. 2021;ajt.16622. https://onlinelibrary.wiley.com/doi/ 10.1111/ajt.16622
17. Hessheimer AJ, Riquelme F, Fundora-Suárez Y, García Pérez R, Fondevila C. Normothermic perfusion and outcomes after liver transplantation. *Transplant Rev*. 2019;33:200-208.
18. Hessheimer AJ, Billault C, Barrou B, Fondevila C. Hypothermic or normothermic abdominal regional perfusion in high-risk donors with extended warm ischemia times: impact on outcomes? *Transpl Int*. 2015;28(6):700-707. http://www.ncbi.nlm.nih.gov/pubmed/24797796
19. Net M, Valero R, Almenara R, et al. Hepatic xanthine levels as viability predictor of livers procured from non-heart-beating donor pigs. *Transplantation*. 2001;71(9):1232-1237. http://www.ncbi.nlm.nih.gov/pubmed/11397955
20. Net M, Valero R, Almenara R, et al. The effect of normothermic recirculation is mediated by ischemic preconditioning in NHBD liver transplantation. *Am J Transplant*. 2005;5(10):2385-2392. http://www.ncbi.nlm.nih.gov/pubmed/16162186
21. Kerforne T, Allain G, Giraud S, et al. Defining the optimal duration for normothermic regional perfusion in the kidney donor: a porcine preclinical study. *Am J Transplant*. 2019;19(3):737-751. https://onlinelibrary.wiley.com/doi/abs/ 10.1111/ajt.15063
22. DONACIÓN EN ASISTOLIA EN ESPAÑA : SITUACIÓN ACTUAL Y RECOMENDACIONES, Documento de Consenso Nacional de la Organización Nacional de Trasplantes. http://www.ont.es/infesp/DocumentosDeConsenso/DONACI%C3%93N%20EN%20ASISTOLIA%20EN%20ESPA%C3%91A.%20SITUACI%C3%93N%20ACTUAL%20Y%20RECOMENDACIONES.pdf. Published 2012. Accessed June 1, 2021.
23. Royal Decree 1723/2012, December 28, 2012, Annex I, Section 3: diagnosis of death based on circulatory and respiratory criteria. https://www.boe.es/eli/es/rd/2012/12/28/1723/con. Published 2012. Accessed June 1, 2021.
24. Lomero M, Gardiner D, Coll E, et al. Donation after circulatory death today: an updated overview of the European landscape. *Transpl Int*. 2020;33(1):76-88. https://onlinelibrary.wiley.com/doi/abs/ 10.1111/tri.13506
25. Jochmans I, Hessheimer AJ, Neyrinck A, et al. Consensus statement on normothermic regional perfusion in donation after circulatory death: report from the european society for organ transplantation's transplant learning journey. *Transpl Int*. 2021.
26. Hessheimer AJ, Gastaca M, Miñambres E, et al. Donation after circulatory death liver transplantation: consensus statements from the Spanish liver transplantation society. *Transpl Int*. 2020;33(8):902-916.
27. Organización Nacional de Trasplantes. Protocolo Nacional de Donación y Trasplante Hepático en Donación en Asistolia Controlada. 2015.
28. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl*. 2010;16(8):943-949. http://www.ncbi.nlm.nih.gov/pubmed/20677285

29. Hessheimer AJ, Cárdenas A, García-Valdecasas JC, Fondevila C. Can we prevent ischemic-type biliary lesions in donation after circulatory determination of death liver transplantation? *Liver Transplant*. 2016;22(7):1025-1033. 10.1002/lt.24460
30. Croome KP, Mathur AK, Aqel B, et al. Classification of distinct patterns of ischemic cholangiopathy following DCD liver transplantation [published online ahead of print 2021]. *Transplantation*.
31. Muller X, Marcon F, Sapisochin G, et al. Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg*. 2018;267(3):419-425.
32. Hessheimer AJ, Coll E, Ruíz P, et al. Reply to: "Normothermic regional perfusion – What is the benefit?". *J Hepatol*. 2019;71(2):443-445. https://linkinghub.elsevier.com/retrieve/pii/S0168827819302661
33. Fondevila C, Hessheimer AJ, Maathuis M-HJ, et al. Superior preservation of DCD livers with continuous normothermic perfusion. *Ann Surg*. 2011;254(6):1000-1007. http://www.ncbi.nlm.nih.gov/pubmed/21862925
34. Doyle MBM, Collins K, Vachharajani N, et al. Outcomes using grafts from donors after cardiac death. *J Am Coll Surg*. 2015;221(1):142-152. http://www.ncbi.nlm.nih.gov/pubmed/26095563
35. de Vera ME, Lopez-Solis R, Dvorchik I, et al. Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center. *Am J Transplant*. 2009;9(4):773-781. http://www.ncbi.nlm.nih.gov/pubmed/19344466
36. Skaro AI, Jay CL, Baker TB, et al. The impact of ischemic cholangiopathy in liver transplantation using donors after cardiac death: the untold story. *Surgery*. 2009;146(4):543-553; discussion 552-3. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2790600&tool=pmcentrez&rendertype=abstract
37. Heidenhain C, Pratschke J, Puhl G, et al. Incidence of and risk factors for ischemic-type biliary lesions following orthotopic liver transplantation. *Transpl Int*. 2010;23(1):14-22.
38. Foley DP, Fernandez LA, Leverson G, et al. Biliary complications after liver transplantation from donation after cardiac death donors. *Ann Surg*. 2011;253(4):817-825. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3103075&tool=pmcentrez&rendertype=abstract
39. Maroni L, Pinto C, Giordano DM, et al. Aging-related expression of twinfilin-1 regulates cholangiocyte biological response to injury. *Hepatology*. 2019;70(3):883-898.
40. Maeso-Díaz R, Ortega-Ribera M, Fernández-Iglesias A, et al. Effects of aging on liver microcirculatory function and sinusoidal phenotype. *Aging Cell*. 2018;17(6):1-14.
41. Hansen T, Hollemann D, Pitton MB, et al. Histological examination and evaluation of donor bile ducts received during orthotopic liver transplantation—a morphological clue to ischemic-type biliary lesion? *Virchows Arch*. 2012;461(1):41-48.
42. op den Dries S, Westerkamp AC, Karimian N, et al. Injury to peribiliary glands and vascular plexus before liver transplantation predicts formation of non-anastomotic biliary strictures. *J Hepatol*. 2014;60(6):1172-1179.
43. de Jong IEM, Matton APM, van Praagh JB, et al. Peribiliary glands are key in regeneration of the human biliary epithelium after severe bile duct injury. *Hepatology*. 2019;69(4):1719-1734.
44. Mergental H, Laing RW, Kirkham AJ, et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun*. 2020. 10.1038/s41467-020-16251-3
45. Muller X, Schlegel A, Würdinger M, et al. Can hypothermic oxygenated perfusion (HOPE) rescue futile DCD liver grafts? *Hpb*. 2019;21(9):1156-1165. 10.1016/j.hpb.2019.01.004
46. Epker JL, Bakker J, Lingsma HF, Kompanje EJO. An observational study on a protocol for withdrawal of life-sustaining measures on two non-academic intensive care units in the netherlands: few signs of distress, no suffering? *J Pain Symptom Manage*. 2015;50(5):676-684. 10.1016/j.jpainsymman.2015.05.017
47. Hessheimer AJ, Polak W, Antoine C, et al. Regulations and procurement surgery in DCD liver transplantation. *Transplantation*. 2021;Publish;Ah(5):945-951.
48. van Rijn R, Schurink IJ, de Vries Y, et al. Hypothermic machine perfusion in liver transplantation - a randomized trial. *N Engl J Med*. 2021;1-11. http://www.ncbi.nlm.nih.gov/pubmed/33626248
49. Trasplantes ON De Actividad de Donación y Trasplante Hepático España 2019. http://www.ont.es/infesp/Memorias/ACTIVIDAD%20DE%20DONACI%C3%93N%20%20TRASPLANTE%20ESPA%C3%91A%202019.pdf. Published 2019. Accessed June 1, 2021.
50. Brüggenwirth IMA, Werner MJM, Adam R, et al. The liver retransplantation risk score: a prognostic model for survival after adult liver retransplantation. *Transpl Int*. 2021;34(10):1928-1937.

SUPPORTING INFORMATION

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How to cite this article: Hessheimer AJ, de la Rosa G, Gastaca M, et al. Abdominal normothermic regional perfusion in controlled donation after circulatory determination of death liver transplantation: Outcomes and risk factors for graft loss. *Am J Transplant*. 2022;22:1169–1181. doi:10.1111/ajt.16899