Similar Results in Liver Transplantation From Controlled Donation After Circulatory Death Donors With Normothermic Regional Perfusion and Donation After Brain Death Donors: A Case-Matched Single-Center Study

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Although good results have been reported with the use of normothermic regional perfusion (NRP) in controlled donation after circulatory death (cDCD) liver transplantation (LT), there is a lack of evidence to demonstrate similar results to donation after brain death (DBD). We present a single-center retrospective case-matched (1:2) study including 100 NRP cDCD LTs and 200 DBD LTs and a median follow-up of 36 months. Matching was done according to donor age, recipient Model for End-Stage Liver Disease score, and cold ischemia time. The following perioperative results were similar in both groups: alanine transaminase peaks of 909 U/L in the DBD group and 836 U/L in the cDCD group and early allograft disfunction percentages of 21% and 19.2%, respectively. The 1-year and 3-year overall graft survival for cDCD was 99% and 93%, respectively, versus 92% and 87%, respectively, for DBD ($P = 0.04$). Of note, no cases of primary nonfunction or ischemic-type biliary lesion were observed among the cDCD grafts. Our results confirm that NRP cDCD LT meets the same outcomes as those obtained with DBD LT and provides evidence to support the idea that cDCD donors per se should no longer be considered as "marginal donors" when recovered with NRP.

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Liver transplantation (LT) is limited by the shortage of organ donors available, resulting in a significant imbalance between supply and demand that has led to the use of organs with higher risks of complications and failure, the so-called "marginal donors," to expand the donor pool. Controlled donation after circulatory death (cDCD) is classically considered to be such a category.[1-6]

The use of cDCD grafts has been associated with a high incidence of ischemic type biliary lesions (ITBLs), reported in up to 34% of cases, and a consequential decrease in graft survival. These complications seem to be associated with the ischemic damage that organs suffer during warm ischemia time (WIT), which worsens organ preservation injury.[1-5] In fact, according to the donor risk index, cDCD status is considered an independent factor strongly associated with graft loss.[6]

Abbreviationso: AKI, acute kidney injury; ALT, alanine transaminase; cDCD, controlled donation after circulatory death; CIT, cold ischemia time; DBD, donation after brain death; ERT, extended-release tacrolimus; FFP, fresh frozen plasma; fWIT, functional warm ischemia time; HCC, hepatocellular carcinoma; HOPE, hypothermic oxygenated perfusion; ITBL, ischemic type biliary lesion; ITU, intensive therapy

Normothermic regional perfusion (NRP) restores the abdominal blood circulation, recovering the organs from the ischemic injury before cold storage, helping in better organ selection.[7-9] The first LT using a cDCD and NRP in Spain was carried out in 2013 following a modification of the Spanish law that allowed the use of those patients who died after withdrawal of life-sustaining therapy (WLST) as organ donors.[10] Since then, its use has exponentially grown so that today it represents the most frequent abdominal graft preservation technique performed in cDCD in Spain. Recently, good results from Spanish and UK centers have been published in LT with NRP and even its superiority over the super-rapid recovery has been reported in different studies.[7,11,12] Nevertheless, given the lack of evidence to demonstrate similar results to LT with donation after brain death (DBD), some authors still consider all cDCDs as "marginal donors."[1-4]

This article reports our experiences since the beginning of our cDCD LT program in 2015 and compares LT results with cDCD donors preserved with NRP with those obtained after a DBD LT.

unit; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NRP, normothermic regional perfusion; PMC, premortem cannulation; PSC, primary sclerosing cholangitis; RBC, red blood cell; WIT, warm ischemia time; WLST, withdrawal of life-sustaining therapy.

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Patricia Ruiz participated in the study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, manuscript writing, critical revision of the manuscript, and approval of the final version. Andres Valdivieso participated in the statistical analysis, analysis and interpretation of data, manuscript writing, critical revision of the manuscript, and approval of the final version. Ibone Palomares, Mikel Prieto, Alberto Ventoso, Patricia Salvador, Maria Senosiain, Jose Ramon Fernandez, Milagros Testillano, and Francisco Javier Bustamante participated in the acquisition of data, critical revision of the manuscript, and approval of the final version. Mikel Gastaca participated in the analysis and interpretation of data, manuscript writing, critical revision of the manuscript, and approval of the final version.

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Potential conflict of interest: nothing to report.

Patients and Methods

STUDY DESIGN

We present a single-center, retrospective, case-matched study to compare the results of LT with cDCD donors preserved with NRP and premortem cannulation (PMC) versus those obtained after DBD LT. All LTs were performed at Cruces University Hospital from January 2015 to June 2019 inclusive. Patients were followed up until January 31, 2020; thus, the minimum follow-up period was 6 months. Matching was performed on a 1:2 ratio with respect to donor age (±2 years), recipient Model for End-Stage Liver Disease (MELD) score (±2 points), and cold ischemia time (CIT; ±1 hour). cDCD donors were stratified according to the UK DCD risk score.[13]

Liver grafts were retrieved at 5 different regional centers, all of them provided with standardized NRP equipment according to institutional protocols and performed by the same surgical team, which moved to the donor hospitals. The PMC procedure, WLST, donation, and the acceptance by next of kin and signing of informed consent were conducted according to Spanish donation law (Royal Decree 1723/2012, December 28) and to the Spanish National Transplant Organization.[10,14] Our local protocols have been approved by institutional ethics committees, and all recipients signed an informed consent.

DONOR SELECTION, PROCEDURE, AND ORGAN ALLOCATION

The donor selection criteria were the same for DBD and cDCD, with no specific limit for donor age or body mass index.

Our cDCD NRP donation protocol was described previously,[7] and since then it has not been modified. In brief, PMC was performed in an interventional radiology room 2 to 3 hours prior to WLST. Following extubation, the donor was heparinized (3 mg/kg) and blood pressure was observed. Upon confirmation of death by an independent physician and after a 5-minute stand-off period, the aortic balloon was inflated, absence of radial flow in the arterial catheter was confirmed, and the NRP system was initiated. The functional WIT (fWIT) was considered as duration from systolic blood pressure lower than 60 mm Hg until NRP perfusion was initiated, including a 5-minute nontouch period. We only accepted livers with fWITs of less than 30 minutes. During NRP, alanine transaminase (ALT) and serum

lactate levels were monitored every 30 minutes, and the liver was discarded if the transaminase level exceeded more than 3 times the normal level at initiation or 4 times this level at the end of NRP. After approximately 2 hours of NRP, a dual cold organ perfusion (4°C; Celsior, Institut Georges Lopez Institut Georges Lopez - IGL Parc Tertiaire du Bois Dieu RN6, Lissieu, France) and standard procurement surgery were performed and cold stored. Routine biopsies were not performed. Because we accept up to 50% of graft steatosis, we only perform a biopsy when the procurement surgeon determines that the graft may exceed this limit. DBD liver retrieval was conducted according to the classic procurement technique and static cold storage.[15]

Organ allocation was based on the MELD system and the Child-Turcotte-Pugh score in both groups equally. The recipient surgical technique was the same in both study groups.[16] We performed a piggy-back technique without portacaval shunt, sequential reperfusion (first portal and then arterial), and an end-to-end choledochocholedochostomy with T-tube for biliary reconstruction. By protocol, wedge biopsies were performed immediately before closing. Our pathologists only consider the macrovacuolar steatosis, which is categorized as mild if fat is present in less than 30% of hepatocytes, moderate if between 31% and 60%, and severe when it involves more than 60%.[17]

A Doppler ultrasound exploration was conducted within the first 48 hours and at 1 week and 1 and 3 months after LT. Our standard immunosuppressive protocol for DBD LT was based on de novo extended-release tacrolimus (ERT) (Advagraf, Astellas Pharma Europe B.V EMEA/H/C/000712 Regulatory Affairs Europe, Leiderdorp, The Netherlands), mycophenolate mofetil, and steroids,[18] but for the cDCD, LT initially involved basiliximab (Simulect, Simulect Novartis Europharm Limited, Dublin, Ireland), mycophenolate mofetil, and steroids with a delayed introduction of ERT; however, since mid-2018, we switched to the standard protocol, initiating ERT on postoperative day 1 and restricting basiliximab and delayed ERT introduction for those patients with pretransplant renal dysfunction and those at risk or with established acute kidney injury (AKI).

ENDPOINTS

The primary endpoints were overall graft survival and death-censored graft survival, defined as graft survival censored for patient death with a functioning liver. The secondary endpoints included patient survival, the development of biliary complications (anastomotic strictures or leaks and ITBL), incidence of postreperfusion syndrome, posttransplant ALT peak (highest level within the first 7 days), early allograft dysfunction rate, and posttransplant AKI.

Postreperfusion syndrome was considered when the mean arterial blood pressure was 30% lower than the previous value, for at least 1 minute, within 5 minutes of unclamping. Early allograft dysfunction was defined according to Olthoff's criteria,[19] and AKI was diagnosed based on the Kidney Disease Improving Global Outcomes classification.[20]

BILIARY COMPLICATIONS SURVEILLANCE

ITBL was defined as the presence of a nonanastomotic biliary stricture in the presence of a patent hepatic artery and confirmed based on cholangiographic evidence (T-tube cholangiogram or magnetic resonance).[21] During the postoperative period, a routine T-tube cholangiogram was performed at 1 week and 3 months posttransplantation, before elective removal. In addition, a strict analytical monitoring (bilirubin and alkaline phosphatase) of the recipients was carried out, so a magnetic resonance cholangiography was done whenever there were clinical or laboratory abnormalities that suggested injury to the bile duct.

STATISTICAL ANALYSIS

Statistical analysis was carried out by the Bioinformatics and Statistics Platform, BioCruces Bizkaia Health Research Institute. Matching was performed with IBM SPSS version 24 (IBM Corporation, Armonk, NY), and data were analyzed with R statistical software (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are described as frequencies and percentages. Continuous variables with normal distribution are presented as mean (standard deviation); non-normal variables are reported as median (interquartile range). Differences between categorical variables were assessed with a chi-square test and between continuous variables with a Student *t* test or the Mann-Whitney U test according to the sample distribution. Cox regression models were made to analyze graft loss. The Kaplan-Meier survival curves were performed, and the differences were analyzed using the log-rank test.

Results

During the study period, 493 consented donors were evaluated (Fig. 1). Among these, 27% were cDCD, whereas 73% were DBD. During retrieval, 23 and 47 liver grafts were rejected, respectively. Thus, 83% cDCD grafts and 87% DBD grafts were accepted for LT. Because of different list management reasons, such as emergency 0 (United Network for Organ Sharing, status 1), or lack of an appropriate recipient, 66 valid grafts (16%) were sent to another transplant center in Spain (10 cDCD and 56 DBD). Finally, 100 cDCD LTs and 257 DBD LTs were performed, and of these, 200 matched controls were

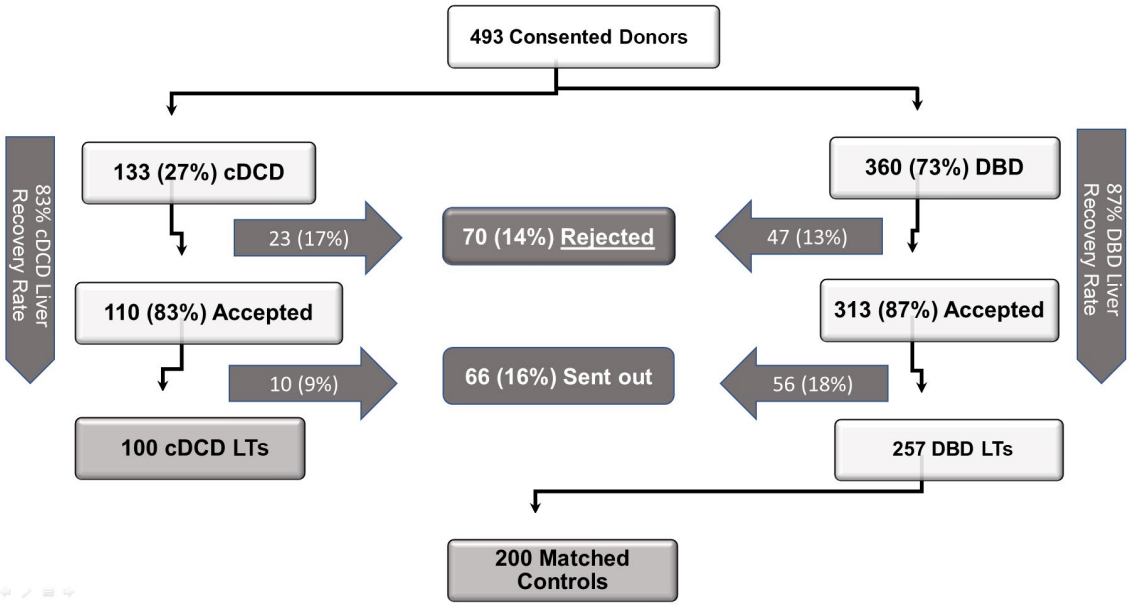

FIG. 1. Donor management and liver recovery rate during the studied period.

TABLE 1. Evolution of cDCD Donation During the Studied Period and Reasons for Liver Discarding

Year of LT	Total LT	cDCD Donors	cDCD LT (% Over Total LT)	cDCD Sent Out	cDCD Discarded	Reasons for Discarding
2015	81	15	9 (11)	–	6 (40)	• 2 exceeded ALT limit • 1 poor macroscopic aspect* • 1 technical failure of NRP • 2 undiagnosed cancer
2016	87	27	23 (26)	–	4 (15)	• 4 poor macroscopic aspect*
2017	75	27	22 (29)	1 (4)	4 (15)	• 2 poor macroscopic aspect* • 1 exceeded ALT limit • 1 moderate steatosis†
2018	75	42	30 (40)	7 (17)	5 (12)	• 2 undiagnosed cancer • 2 poor macroscopic aspect* • 1 fibrosis biopsy proven
June 2019	39	22	16 (41)	2 (9)	4 (18)	• 2 exceeded ALT limit • 1 moderate steatosis† • 1 gallbladder necrosis
	357	133	100 (28)	10 (8)	23 (17)	

NOTE: Data are provided as n or frequency (%).
*Subjective assessments of expert liver procurement surgeons.
†Biopsy: macrovacuolar steatosis more than 50%.

TABLE 2. Donor and Graft Characteristics: Univariate Analysis of cDCD and DBD

Variables	cDCD (n = 100)	DBD (n = 200)	Overall *P* Value
Age, years	62 (53-69)	62 (50.8-72)	0.67
Categorized age			0.65
≤65 years	60 (60)	113 (56.5)	
>65 years	40 (40)	87 (43.5)	
Donor sex			0.03
Male	33 (33.3)	94 (47.2)	
Female	66 (66.7)	105 (52.8)	
Body mass index (Kg/m2)	26.0 (23-29.1)	25.9 (24.2-28.1)	0.80
UK donor risk index	5.00 (2.8-6.0)	–	
Low risk	72 (72)	–	
High risk	25 (25)	–	
Futile	3 (3)	–	
Cause of death			<0.01
Cerebrovascular accident	38 (38)	147 (73.9)	
Anoxic brain injury	35 (35)	19 (9.6)	
Traumatic brain injury	8 (8)	30 (15.1)	
Respiratory failure	19 (19)	0	
ITU stay, days	7 (4-12)	2 (1-4)	<0.01
Inotropic need	43 (43)	133 (67.2)	<0.01
Sodium levels (mEq/L)	142 (140-145)	147 (143-152)	<0.01
Steatosis	11 (11.1)	51 (25.6)	<0.01
Mild/moderate	11/0	50/1	
CIT, minutes	274 (241-311)	264 (228-340)	0.89
fWIT, minutes	10 (8.5-12.2)	–	–
NRP, minutes	121 (118-128)	–	–

NOTE: Data are provided as n, frequency (%), or median (interquartile range).

selected. Reasons for rejections are listed in Table 1. It should be noted that only 1 donor was rejected as a result of technical problems during the beginning of the program.

Donor and graft characteristics are shown in Table 2. Although steatosis was higher in the DBD group (11.1% versus 25.6%; $P = 0.06$), in all cases except 1 it was mild. The main donor cause of death was anoxic brain injury (35% versus 9.6%) in the cDCD group versus mainly cerebrovascular accidents (73.9% versus 38%) in the DBD group. As a consequence, the management in the intensive therapy unit (ITU) was different with longer ITU stay (7 versus 2 days) and less inotropic need (43% versus 67.2%) in the cDCD group. In the cDCD recipients, the median UK DCD risk score was 5 (interquartile range, 2.8-6.0), with 25% of high-risk donors and 3% futile; median fWIT was 10 (interquartile range, 8.5-12.2) minutes, and the duration of NRP was 121 (interquartile range, 118-128) minutes. During the NRP, ALT and serum lactate levels remained stable (Fig. 2).

Table 3 shows that there were no differences between recipient demographics, either in the MELD score or in the indication for transplantation.

The following perioperative data and posttransplantation complications were also similar in both groups (Table 4): ALT peak 836 U/L in the cDCD group and 909 U/L in the DBD group ($P = 0.53$), early allograft dysfunction 19.2% and 21% ($P = 0.83$), and AKI 19.8% and 29.3% ($P = 0.11$), respectively. The evolution of bilirubin and alkaline phosphatase were similar during follow-up. There were also no differences in the rates of hepatic artery thrombosis (1% cDCD versus 1.5% DBD; $P = 1.00$), biliary complications (5.2% cDCD versus 6.3% DBD; $P = 0.90$), and need for retransplantation (1% cDCD versus 3.5% DBD; $P = 0.29$). Of note, no cases of primary nonfunction or ITBL were observed among the cDCD grafts, including the 28% of high-risk/futile transplants.

When analyzing variables related to graft loss (Table 5), only EAD, ALT peak, follow-up, and hepatic artery thrombosis were identified.

With a median follow-up of 36 months (interquartile range, 20.0-48.3 months), the 1-year and 3-year overall graft survival rates were significantly higher in the cDCD group: 99% and 93% for cDCD versus 92% and 87% for DBD, respectively ($P = 0.04$). We did not find differences either in the 1-year and 3-year censored graft loss (100% and 97% for cDCD versus 96% and 96% for DBD, respectively; $P = 0.28$) or in the 1-year and 3-year patient survival rates (99% and 94% for cDCD versus 96% and 90% for DBD, respectively; $P = 0.07$; Fig. 3A-C).

Discussion

In this article, we present the largest experience comparing the use of NRP cDCD donors with DBD donors in LT. With the use of NRP, we achieved excellent results compared with those obtained after DBD LT. Importantly, no cases of primary nonfunction were observed in the cDCD LT group, and biliary complications were uncommon in this group: 5.2% overall, with no cases of ITBL. Finally, the 1-year and 3-year censored graft and patient survival rates were similar in

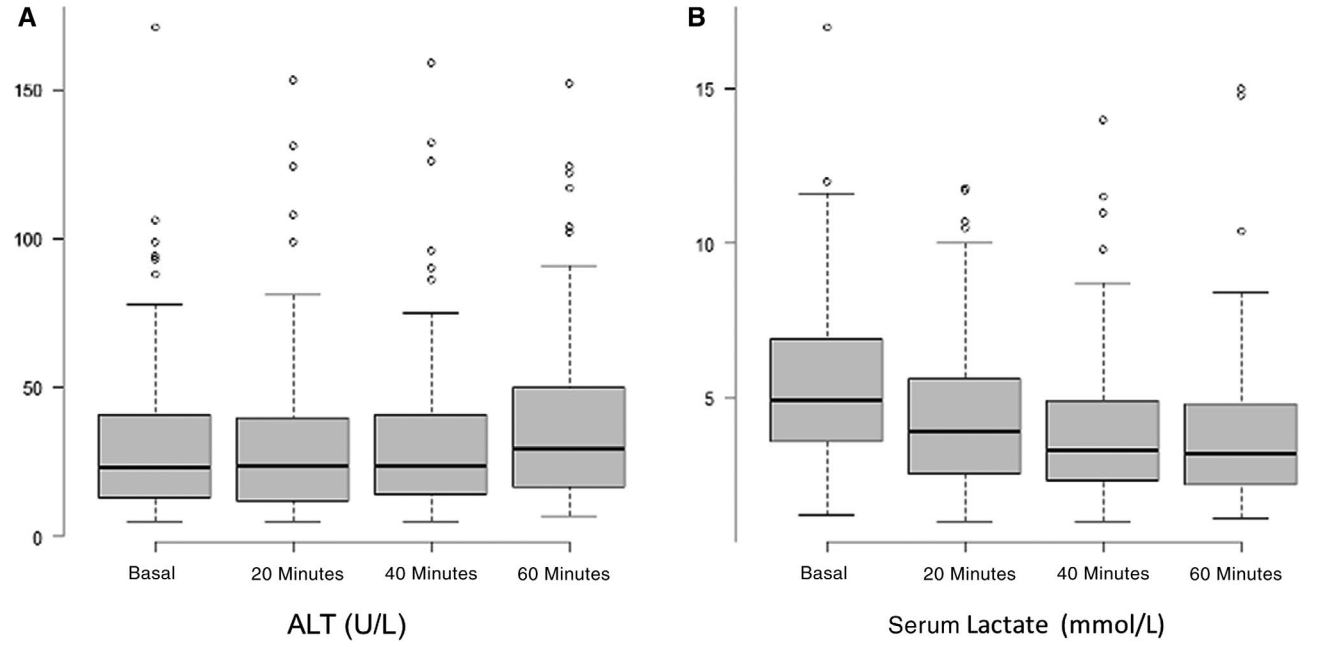

FIG. 2. Evolution of (A) ALT and (B) serum lactate during NRP.

TABLE 3. Recipient Characteristics: Univariate Analysis of cDCD and DBD

Variables	cDCD (n = 100)	DBD (n = 200)	Overall *P* Value
Age, years	59 (54-64)	58 (53-64)	0.79
Sex			0.74
Male	25 (25)	45 (22.5)	
Female	75 (75)	155 (77.5)	
MELD score	12 (9-18)	12 (9-16)	0.63
Simultaneous liver-kidney transplantation	6 (6)	6 (3)	0.35
Retransplant	3 (3)	17 (8.5)	0.12
Indication for transplantation			
Cirrhosis	36 (36)	64 (32)	0.96
PSC	3 (3)	5 (2.5)	1.00
HCC	39 (39)	98 (49)	0.13
Others	22 (22)	33 (16.5)	0.32

NOTE: Data are provided as frequency (%) or median (interquartile range).

both groups, and overall graft survival was significantly higher in the cDCD LT group.

It is important to note that donor selection criteria are the same for both groups and that our median donor age of 62 years (40% older than age 65 years) is superior to what is considered a risk factor for cDCD LT.[2,6,22,23] Recipients were also not selected, having similar recipient median age and MELD score, in both groups. In fact, we used cDCD grafts for simultaneous liver-kidney transplantations, retransplantation, or fulminant hepatic failure.

In our opinion, the use of NRP with PMC in cDCD LT has allowed us to achieve similar results to those obtained with the "gold standard" DBD donors and is clearly superior to the benchmark established in the literature,[24] without a selection of donors or recipients.

The cDCD donors represent an important source, widely established in countries with an appropriate legal

TABLE 4. Perioperative Data and Posttransplantation Complications and Outcomes: Univariate Analysis of cDCD and DBD

Variables	cDCD (n = 100)	DBD (n = 200)	Overall *P* Value
Postreperfusion fibrinolysis	13 (13.1)	27 (13.5)	1.00
Surgical time, minutes	222 (200-258)	227 (205-257)	0.59
Surgical transfusion needs			
RBCs, U	1 (0-2.3)	0 (0-2)	0.31
Platelets, U	0 (0-1)	0 (0-1)	0.79
FFP, pool	0 (0-0)	0 (0-0)	0.87
Postreperfusion syndrome	11 (11)	23 (11.5)	1.00
ALT peak, U/L	836 (573-1422)	909 (454-1725)	0.53
Bilirubin, mg/dL*	0.9 (0.6-1.5)	0.8 (0.6-1.8)	0.47
3 Months	0.6 (0.4-0.9)	0.6 (0.5-0.9)	
6 Months	0.6 (0.4-0.9)	0.5 (0.4-0.8)	
Alkaline phosphatase, U/L*	106 (70.2-154)	101 (65.8-163)	0.53
3 Months	76 (63.2-97.7)	72 (64.2-98.3)	
6 Months	78 (65-110.5)	78 (63.7-104)	
Early allograft disfunction	19 (19.2)	42 (21)	0.83
AKI	19 (19.8)	56 (29.3)	0.11
ITU stay, days	4 (3-5)	4 (3-6)	0.86
Hospital stay, days	14 (12-22.5)	15 (12-22)	0.62
Biopsy-proven rejection	5 (5.1)	8 (4.1)	0.75
Biliary complications	5 (5.2)	12 (6.3)	0.90
Peri T-tube leak	2 (2)	5 (2.5)	
Anastomotic stricture	2 (2)	6 (3)	
Biliary peritonitis	1 (1)	1 (0.5)	
ITBL	0	0	
Arterial complications	5 (5.1)	12 (6.3)	0.87
Hepatic artery thrombosis	1 (1)	3 (1.5)	1.00
Retransplantation	1 (1)	7 (3.5)	0.29
Primary nonfunction	0	2 (1)	0.56
Graft loss	2 (2)	9 (4.5)	0.37
Patient death	4 (4)	22 (11.1)	0.07
Cause of death			0.78
Cerebrovascular accident	0	2 (1)	
De novo neoplasm	1 (1)	11 (5.5)	
Graft disfunction	1 (1)	3 (1.5)	
Myocardial infarction	0	1 (0.5)	
Sepsis	2 (2)	5 (2.5)	

NOTE: Data are provided as frequency (%) or median (interquartile range).
*At 1 month of follow-up.

framework,[10-14,25] but their use is classically associated with an increase of mainly biliary complications, such as ITBL, and a decrease in graft survival. These complications seem to be associated with the ischemic damage that organs suffer during the implicit WIT related with the donor death process, exacerbated during the cold storage after the super-rapid recovery.[1-4] Multiple experimental studies have shown the benefits of NRP in the restoration of cellular energy substrates and the reduction in degradation products in liver grafts before implantation,[9] but first clinical experiences with NRP and cDCD LT are relatively recent. In 2014, Rojas-Peña et al.[26] and Oniscu et al.[27] presented their first clinical series with 13 and 11 LTs, respectively. Since then, some longer series have been published.[7,11,12,28] Our group referred 46 NRP cDCD LTs without either ITBL or graft loss after a medium follow-up period of 19 months.[7] Recently, 2 comparative studies

TABLE 5. Summary of Variables Related to Graft Loss

	Bivariate Analysis			
Variables	All (n = 300)	No (n = 289)	Yes (n = 11)	Overall *P* Value
Donor/graft factors				
Type of donor				0.04
DBD	200 (66.7)	172 (64.4)	28 (84.4)	
cDCD	100 (33.3)	98 (36.6)	2 (15.6)	
Age, years	62 (51-71)	62 (50-71)	66 (54.8-73.2)	0.13
>65 years	126 (42.1)	110 (41.2)	16 (50)	0.45
Sex, male	127 (42.8)	110 (41.5)	17 (53.1)	0.29
Body mass index (Kg/m2)	25.9 (23.7-28.5)	25.9 (23.7-28.5)	25.9 (23.9-28.5)	0.91
ITU stay, days	3 (1-7)	3.5 (2-7)	2 (1-4.5)	0.12
Inotropic need	175 (58.9)	156 (58.9)	19 (59.4)	0.12
Sodium levels (mEq/L)	145 (140-149)	145 (140-150)	141 (136-146)	0.07
CIT, minutes	265 (230-320)	263 (228-320)	287 (260-348)	0.05
Steatosis	62 (20.8)	52 (19.5)	3 (32.3)	0.15
Recipient factors				
Age	57.6 (8.7)	57.6 (8.5)	56.9 (10.8)	0.33
Sex, male	70 (23.3)	68 (23.5)	2 (18.2)	0.70
MELD	12 (9-16)	12 (9-16)	11 (6-16)	0.42
Simultaneous liver-kidney transplantation	12 (4)	12 (4.5)	0 (0)	0.37
Retransplantation	20 (6.7)	16 (5.6)	5 (15.6)	0.05
LT indication				
Cirrhosis	231 (77.3)	207 (77.5)	24 (75.0)	0.92
HCC	136 (45.5)	119 (44.6)	17 (53.1)	0.47
Others	55 (18.4)	47 (17.6)	8 (25.0)	0.43
LT outcomes				
Fibrinolysis	40 (13.4)	36(13.5)	4 (12.5)	1.00
EAD	61 (20.5)	547(17.6)	14 (45.2)	<0.01
AKI	75 (26.1)	66 (25.6)	9 (32.1)	0.60
ALT peak	902 (500-1656)	876 (482-1575)	1279 (1164-2680)	0.01
ITU stay, days	4 (3-5)	4 (3-5)	5 (3-10.8)	0.08
Hospital stay, days	15 (12-22)	15 (12-21.5)	16 (12-30)	0.09
Postreperfusion syndrome.	34 (11.4)	30 (11.2)	4 (12.5)	1.00
Biopsy-proven rejection	13 (4.4)	10 (3.8)	3 (10.3)	0.13
Follow-up, years	3.1 (1.9-4.1)	3.01 (1.7-4)	3.8 (2.8-4.8)	<0.01
Biliary complications	17 (5.9)	15 (65.7)	2 (9.1)	0.60
Hepatic artery thrombosis	4 (1.3)	0 (0.)	4 (12.5)	<0.01

NOTE: Data are provided as frequency (%) or median (interquartile range). EAD, early allograft dysunction.

demonstrated the superiority of NRP over super-rapid recovery. Hessheimer et al., in the Spanish multicenter study that compared the results of NRP cDCD LT versus super-rapid recovery, presented a significant reduction in ITBL and graft loss,[11] and afterward, Watson et al., in a similar study, concluded that NRP was an independent factor in reducing the incidence of ITBL in cDCD LT.[12] These good results may depend not only on the experimentally proven benefits of NRP but also on the fact that it allows a better assessment of the ischemic damage of the liver by monitoring the ALT and serum lactate levels during the NRP time (Fig. 2). Moreover, cDCD procurements with NRP allow for a meticulous in situ examination, similar to DBD retrievals, identifying those grafts with a gross macroscopic appearance and helping in the selection of appropriate organs. All of these factors have probably contributed to the well-performing Spanish multicenter study,

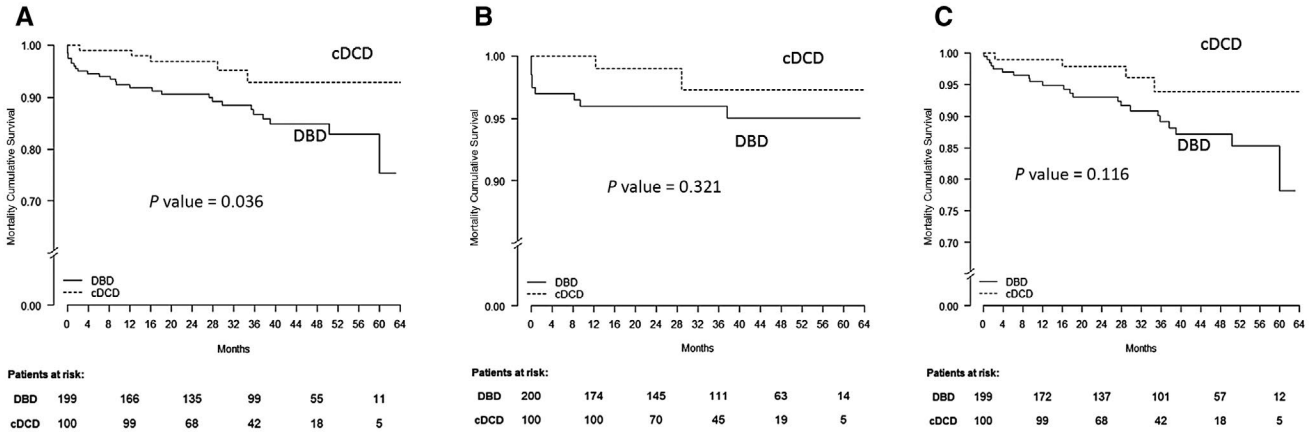

FIG. 3. (A) Overall graft survival, (B) graft survival censored for death with a functioning graft, and (C) patient survival.

regardless of the limited experience of the different participating centers.[11]

Although good outcomes have been occasionally reported with the use of old DCD grafts recovered with the super-rapid recovery technique,[29] donor age older than 60 years is still considered a risk factor in this type of LT.[13] Opposite to these experiences, we reported favorable results with cDCD donors aged older than 65 years in our initial experience,[7] comparable with those with younger donors. Moreover, in the current study, we report an extremely low biliary complication rate with 40% of donors aged older than 65 years. In our view, the use of NRP cDCD donors aged older than 65 years should not be considered a contraindication but should be assessed individually.

NRP also appears to have a benefit in renal function. The use of cDCD donors has classically been associated with an increasing rate of posttransplant AKI. Leithead et al. presented a 53.4% incidence of posttransplant AKI in cDCD LT, considering the ALT peak as a marker of ischemia reperfusion injury, and as a consequence, a predictor of renal dysfunction.[30] Based on these reports, in our first cDCD LT, we used a nephroprotective immunosuppressive therapy, but given that our rate of AKI was lower than expected (19.2%), we decided to change to our standard DBD LT protocol with the introduction of ERT on posttransplant day 1, keeping the results similar to DBD LT.

Initially emerging as an alternative to super-rapid recovery, the good results obtained with NRP have allowed its rapid expansion, becoming the most frequently used technique for liver retrieval in our country.[11] Since the implementation of our cDCD program in 2015, the use of cDCD donors has progressively increased, so that today, they account for more than 40% of our LTs (Table 1). In addition, the cDCD program has turned out to be as profitable as the DBD program with an 83% liver recovery rate (Fig. 1). Notably, NRP has recently been considered as the recovery method of choice for cDCD liver grafts in the consensus statements from the Spanish Liver Transplantation Society.[31]

An unexpected result of our study is that graft survival was significantly higher in the cDCD LTs than in the DBD LTs. However, when we analyzed the graft survival curve censored by patient death, we did not find such differences. This is because the main cause of graft loss was the death of the patient attributed to the development of de novo neoplasms (Table 4). Somehow, DBD recipients have developed more tumors. One reason that would explain this could be that the minimum follow-up of 6 months was not enough to adequately assess medium-term to long-term survival rates and that with a longer follow-up this difference would attenuate. Another factor could be the effect of the immunosuppression, considering that immunosuppression was somewhat different in the first 2 years of the study. On the other hand, when we have analyzed the factors associated with graft loss, only foreseeable factors such as graft dysfunction, hepatic artery thrombosis, and follow-up were identified.

It should be noted that short CIT and fWIT are undoubtedly part of the explanation for the good results obtained. The short CIT is partly explained by the fact that our transplant center refers to a relatively small geographic area and partly by the short surgical

times. However, the fWIT is more related to PMC and donor management in the ITU. Spanish law permits not only premortem interventions such as PMC and heparinization but also the use of palliative medical support that give comfort to the end-of-life patient, provided they are regulated by WLST protocols independent of the donation process.[10,14] However, the use of premortem interventions raises several ethical and legal concerns that might limit their application in many countries where they are considered invasive procedures that can damage body integrity.[32] Although shortening ischemia times is certainly involved in our excellent results, this should not detract from the value of NRP. The benefits of NRP itself have already been demonstrated experimentally, and good clinical results have also been reported in LT with NRP cDCD without PMC or other comfort therapies.[12,27]

Another factor that positively influences the results are the low MELD scores of our recipients, probably attributed to hepatocellular carcinoma (HCC) being the first indication and the use of the laboratory MELD score without additional MELD exception points. Nevertheless, a low MELD value is also frequently found in recent impact articles associated with DCD donation,[33,34] so more experience in patients with higher severities is needed.

In recent years, with the idea of reverting the cellular damage that cDCD grafts suffer during the WIT of super-rapid recovery, different machine perfusion strategies have emerged as an alternative to static cold storage.[35-37] Schlegel et al., in a controlled matched study that compared LT results using 3 different donor groups (DBD, cDCD, and cDCD treated by hypothermic oxygenated perfusion [HOPE]), reported 5-year outcomes of HOPE-treated cDCD LTs similar to those of DBD transplants and superior to those of untreated cDCD LTs.[33] Recently, Muller et al. compared HOPE and NRP in LTs from cDCD, concluding that both strategies achieved similar posttransplant patient and graft survival rates.[34] Seeing this emerging interest and the increasingly better results obtained, there is no doubt about the fundamental role that machine perfusion, including NRP, will play in the near future in LT. An added advantage of the NRP is that it allows the concomitant perfusion of other abdominal organs, such as the kidneys and pancreas, and the procurement of extra-abdominal grafts including the lungs and heart, contributing to making the donation process more effective.[38-40]

A considerable limitation of our study is that it is a retrospective analysis and we do not have a super-rapid recovery study group. This is because we have never used the super-rapid recovery technique in cDCD LTs. However, after analyzing our results, a randomized controlled trial comparing the super-rapid recovery technique and NRP in cDCD LTs would be unethical in our center.

Our study has also several strengths. To our knowledge, this is the largest experience comparing the use of NRP cDCD donors with DBD donors in LT performed in a short period of time and with a median follow-up of 36 months. It is important to highlight that we have not selected our recipients and that, as we routinely placed a T-tube in the biliary tract, nearly every recipient (96%) underwent a cholangiography at least 3 months after transplantation, thus increasing the diagnostic accuracy of biliary complications.

In summary, our results suggest strong evidence that LTs with NRP cDCD donors meet the same outcomes to those established in the literature for the "gold standard" DBD LTs.

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