Favorable Outcomes of Liver Transplantation from Controlled Circulatory Death Donors Using Normothermic Regional Perfusion Compared to Brain Death Donors

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Background. Liver transplantation (LT) from controlled donation after circulatory death (cDCD) was initiated in France in 2015 under a protocol based on the use of normothermic regional perfusion (NRP) before organ procurement. The aim was to compare outcomes following cDCD LT with NRP and donation after brain death (DBD) LT. **Methods.** This is a multicenter retrospective study comparing cDCD LT with NRP and DBD LT. A case-matched study (1:2) was performed using the variables such as recipient and donor age, indication of LT. **Results.** A total of 50 patients from the cDCD group were matched to 100 patients from the DBD group. From postoperative days 1–4, serum transaminase release was significantly lower in the cDCD group compared to the DBD group ($P < 0.05$). Early allograft dysfunction (cDCD: 18% versus DBD: 32%; $P = 0.11$), acute kidney injury (26% versus 33%; $P = 0.49$), 90-d graft loss (2% versus 5%; $P = 0.66$), and arterial (4% versus 12%; $P = 0.19$) and biliary (16% versus 17%; $P = 0.94$) complications were similar between the 2 groups. The 2-y graft survival was 88% for cDCD group and 85% for DBD group ($P = 0.91$). The 2-y patient survival was 90% for cDCD group and 88% for DBD group ($P = 0.68$). **Conclusions.** This study provides evidence that cDCD LT following postmortem NRP can be safely and effectively performed in selected recipients with similar graft and patient survival outcomes, without increased rates of biliary complications and early graft dysfunction compared to DBD LT.

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INTRODUCTION

The success of liver transplantation (LT) has dramatically increased demand for organs and subsequently has also increased time spent on the waiting list. This increases the risk of being removed from the waiting list because of death, deteriorating functionality of the

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liver or hepatocellular carcinoma (HCC) progression. Donation after brain death (DBD) is the standard practice in Western countries. The current organ shortage has prompted the development of donation after circulatory death (DCD) to expand the donor pool. Several reports comparing controlled DCD (cDCD) LT and DBD LT have reported that cDCD LT was associated with a higher incidence of primary nonfunction requiring retransplantation (3% versus 1%, respectively)[1,2] and ischemic cholangiopathy (6%–11% versus 0.6%–3%, respectively)[1-3] compared to DBD LT (Table 1).[1-6] However, these studies suffer from several biases, including heterogeneity in terms of recipients (primary, repeat or urgent LT),[1] donors' (young donors, prolonged cold ischemia time,[4] liver grafts with fibrosis),[5] definition of the functional warm ischemia time (FWIT), endpoint monitoring, methodology,[3] and indications for LT.[7,8]

Normothermic regional perfusion (NRP) is a technique that has been recently used to improve the outcomes of cDCD LT. In France, the program of DCD organ transplantation following NRP started in 2005 with uncontrolled DCD donors. This French initial experience of NRP of DCD organ transplantation before procurement has shown promising outcomes, initially with kidney[9] and then with liver.[10] Since the cDCD French program was implemented in 2015, all organ transplantations have included the NRP technique. To date, only 1 study[6] has compared cDCD LT with NRP and DBD LT, the current standard deceased donor LT. The aim of this study was to evaluate whether the use of NRP may limit the incidence of early allograft dysfunction and ischemic cholangiopathy following cDCD LT and may achieve at least comparable results to those of DBD LT recipients, in whom the best results might theoretically be expected.

MATERIALS AND METHODS

Study Design

This was a French multicenter retrospective matched-control study. The study population included all patients with a follow-up of at least 2 y from the 6 centers in France authorized to perform LT using cDCD grafts from February 2015 to December 2019 in accordance with the French National cDCD protocol.[11] This study was approved by *Agence de la Biomédecine* (ABM) institutional review board. The data on all transplanted cDCD recipients was collected from the ABM prospective French national database "CRISTAL". Outcomes were evaluated until the end of March 2020.

TABLE 1.

Reported series comparing cDCD LT with and without NRP and DBD LT

First author, y, country, study period	cDCD vs DBD N	Matching	cDCD vs DBD Donor age (y) FWIT (min) CIT (h)	cDCD vs DBD EAD/PNF	cDCD vs DBD AKI	cDCD vs DBD ischemic cholangiopathy	cDCD vs DBD 2-y graft survival
cDCD without NRP vs DBD							
Laing, 2016[3], UK 2004–2014	187 vs 187	PSM	49.4 vs 47.7; $P = 0.11$ 20 7.3 vs 7.4; $P = 0.094$	NA	32.6% vs 15%; $P < 0.001$	9.1% vs 1.1%; $P < 0.001$	79% vs 85%; $P = 0.519$
Blok, 2016[1], Belgium- The Netherlands, 2003–2007	126 vs 1264	No	46.8 vs 41.2; $P < 0.001$ 13 8.9 vs 7.2; $P < 0.001$	3.2% vs 0.7%; $P = 0.002$[a]	NA	6.3% vs 0.6%; $P = 0.002$	64% vs 74%; $P = 0.038$
Kalisvaart, 2017[2], The Netherlands, 2001–2015	115 vs 326	No	47 vs 54; $P < 0.001$ 17 6.5 vs 6.9; $P = 0.338$	3% vs 1%; $P = 0.018$[a]	NA	11% vs 3%; $P < 0.001$	68% vs 81%; $P = 0.002$
Kollmann, 2018[4], Canada 2009–2017	77 vs 706	No	40 vs 51; $P < 0.001$ 23 5.7 vs 7.3; $P < 0.001$	33% vs 25%; p = NA	9.1% vs 5%; $P = 0.11$	5.2% vs 3.8%; $P = 0.42$[d]	87% vs 86%; p = NA
Cascales-Campos, 2019[5], Spain 2014–2018	77 vs 77	No	65 vs 68; $P = 0.779$ 12.6 5.4 vs 6.7; $P = 0.002$	1% vs 3%; $P = 0.560$[b]	NA	6% vs 1%; $P = 0.209$	69% vs 79%; $P = 0.293$
cDCD with NRP vs DBD							
Rodriguez-Sanjuan, 2019[6], Spain 2014–2017	11 vs 51	No	49 vs 64; $P = 0.003$ 16 4 vs 6; $P = 0.009$	9.1% vs 2%; $P = 0.3$[b]	0% vs 43%; $P = 0.008$	0% vs 5.9%; $P = 0.6$[d] 13% vs 27%; $P = 0.5$[e]	NA
Present study, 2020, France 2015–2017	50 vs 100	Yes	47 vs 49; $P = 0.49$ 23 5.9 vs 6.3; $P = 0.029$	18% vs 32%; $P = 0.11$[c]	26% vs 33%; $P = 0.49$	2% vs 1%; p = NS	88% vs 85%; $P = 0.91$

[a]PNF requiring retransplantation.
[b]Primary dysfunction.
[c]EAD.
[d]Early onset biliary stricture.
[e]Delayed biliary stricture.

AKI, acute kidney injury; cDCD, controlled donation after circulatory death; CIT, cold ischemia time; DBD, donation after brain death; EAD, early allograft dysfunction; FWIT, functional warm ischemic time; LT, liver transplantation; NA, not available; NRP, normothermic regional perfusion; NS, not significant; PNF, primary nonfunction; PSM, propensity score matching.

The cohort of recipients who underwent LT using cDCD grafts (NRP cDCD group) was matched at a 1:2 ratio (1 patient from NRP cDCD group was matched to 2 patients from DBD group) to those who underwent LT using DBD grafts (DBD group serves as a control group to NRP cDCD group).

Inclusion criteria for the DBD group were as follows: recipient age ranging from 18 to 65 y, MELD score ≤25 at the time of LT, primary LT, no urgent LT for acute liver failure, donor age ranging from 18 to 65 y, serum GGT levels of the donor at baseline <50 IU/L, no circulatory arrest before organ procurement and cold ischemia time <9 h. Based on the latter inclusion criteria, 215 of 2602 patients with DBD were selected and represented the unmatched patients with DBD. Because of the donor age limit for cDCD, the inclusion period for the DBD group was extended from January 2013 to June 2017. To ensure a fair comparison, we performed a case-matched study using the following variables: recipient age, donor age, and indication of LT (decompensated cirrhosis, HCC, no HCC tumor). The endpoints were the incidence of arterial and biliary complications, rates of early allograft dysfunction (EAD), incidence of acute kidney injury (AKI), 2-y patient survival, 2-y death censored graft survival, and 2-y death noncensored graft survival. The study followed the STROBE recommendations.

NRP Technique and the French cDCD Protocol

The French cDCD protocol was as follows as previously described:[12] arterial and venous femoral lines were placed one day before the circulatory arrest. Death occurred in the intensive care unit. This was followed by the postmortem percutaneous arterial and venous femoral cannulation and NRP. Then, oxygenated normothermic in situ perfusion was started for the abdominal organs only, by introducing an endo-aortic balloon clamp in the supraceliac aorta, via the contralateral or ipsilateral femoral artery. The donor was then taken to the operating room for organ procurement. FWIT defined as the time elapsed from systolic blood pressure <45 mm Hg to the start of NRP should last ≤30 min. Agonal phase defined as the time elapsed from the withdrawal of ventilation and the absence of complete spontaneous respiration and circulation should last <3 hours. Asystolic phase should be <25 min. NRP should last >1 and <4 h. Planned cold ischemia time (CIT) should last <8 h.

During NRP, pump parameters such as temperature, flow rate, Pao_2, pH, lactic acid, haematocrit, and transaminases must be recorded and eventually adjusted to maintain them within a target range to optimize organ perfusion (eg administer bicarbonate, blood transfusion, increase O_2). Liver grafts were ultimately declined based on transaminase release and histology.

Donor selection criteria were: (1) donor age <66 y, (2) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) release < 200 IU/L during NRP, (3) macrovesicular steatosis <20% on systematic frozen-section liver graft biopsy, and (4) at least 60 min of NRP. Recipient inclusion criteria were: (1) signed informed patient consent, (2) registration on the waiting list for DBD LT, (3) no previous history of major abdominal surgery, (4) primary LT, (5) absence of portal vein thrombosis, (6) MELD score ≤25, and (7) age <66 y.

Surgical techniques for organ procurement and LT were performed according to local LT center practice. The operative strategy was to limit warm dissection before cold perfusion. As liver biopsy is a prerequisite for cDCD liver graft utilization, a surgical biopsy of the left lateral segment of the liver was performed during donor procurement. While the liver biopsy tissue was processed rapidly for histologic analysis, the retrieval surgeon continued to perform the surgical procedure. Postoperative surveillance included an assessment of liver function tests and Doppler ultrasonography every day during the first 7 d and as per the LT center's policy thereafter. All patients had a calcineurin inhibitor-based immunosuppression regimen.

Endpoints

Death noncensored graft survival was defined as the time from the date of transplantation to the date of irreversible graft failure requiring retransplantation, the date of the last follow-up or to the date of death. Here, death with graft function is treated as graft failure. Death-censored graft survival was defined as time from the date of transplantation to the date of irreversible graft failure requiring retransplantation or the date of last follow-up. In case of death with a functioning graft, the follow-up period is censored at the date of death. Patient survival was defined as time from transplantation to date of death. Primary nonfunction was defined as early graft failure resulting in either recipient death within the first week or retransplantation in the absence of any vascular problems.[13] EAD was defined according to the definition of Olthoff et al.[14] AKI was defined according to KDIGO criteria.[15]

Biliary complications included biliary strictures (regardless of the presence or the absence of arterial thrombosis or stenosis), fistula, and stones. Biliary strictures were defined according to the definition of Crome et al.[16] Briefly, biliary strictures were categorized as disseminated or localized (involving the bile duct convergence, donor bile duct or anastomotic site). Ischemic cholangiopathy was defined as the presence of any disseminated biliary stricture on magnetic resonance and endoscopic retrograde cholangiopancreatography, regardless of the presence or absence of arterial thrombosis of stenosis.

Statistical Analysis

Categorical variables were expressed as frequency and percentage, and continuous variables as medians (25%–75% interquartile range) or means (SD). Recipient and donor characteristics were compared between the NRP cDCD and DBD groups using the chi-square test or 2-sided Fisher's exact test for qualitative variables and a Student's *t*-test or Mann-Whitney U-test for quantitative variables. Data were evaluated on December 31, 2019. Survival rates were estimated via the Kaplan-Meier method and compared using the Log-rank test. All variables with $P < 0.05$ were considered statistically significant. Statistical analyses were performed using SigmaStat version 12.0 (Systat Software Inc., Erkrath, Germany).

RESULTS

Patients

From 2015 to 2019, 284 cDCD livers were proposed to the 6 centers. Of these, 159 were accepted. The reasons

why the 125 liver grafts were declined for LT are shown in Figure 1. The rate of technical failure to perform NRP was 8% (19 of 251). Reasons for failure to perform NRP included percutaneous cannulation failure (n = 7), circuit malfunction or defects (incorrect connection of the circuit, n = 1; clots in the circuit, n = 1, dysfunction, n = 4), balloon-related complications (rupture, n =3; malposition, n = 1; nonocclusive balloon, n = 1), and aortic dissection (n = 1).

At the time of data cutoff on December 31, 2019, of the 159 patients transplanted with a cDCD liver graft, 50 (who underwent LT between February 2015 and June 2017) were followed up for at least 2 y from the date of LT and represented the study population. These 50 cDCD patients were matched to 100 DBD patients (Figure 2). The remaining 109 patients who underwent cDCD LT between July 2017 and December 2019 were excluded from our analysis because of the minimum follow-up <2 y or incomplete data at the time of analysis.

Median time from treatment withdrawal to cessation of circulation was 4 (2.3–7.8) min. Median asystolic time was 17 (14–22.3) min, median FWIT was 22 (20–26.8) min, median duration of NRP was 190 (151–223) min, and median UK DCD risk score was 6 (3–6).[17]

Baseline characteristics were not significantly different between cDCD and DBD recipients (Table 2). Serum ALT (P = 0.003), AST (P = 0.03), and gGT (P < 0.001) levels were significantly higher in the cDCD group than in the DBD group. Preservation solution distributions were different between cDCD group and DBD group (P < 0.001; Table 2). CIT (P = 0.03) and warm ischemia time

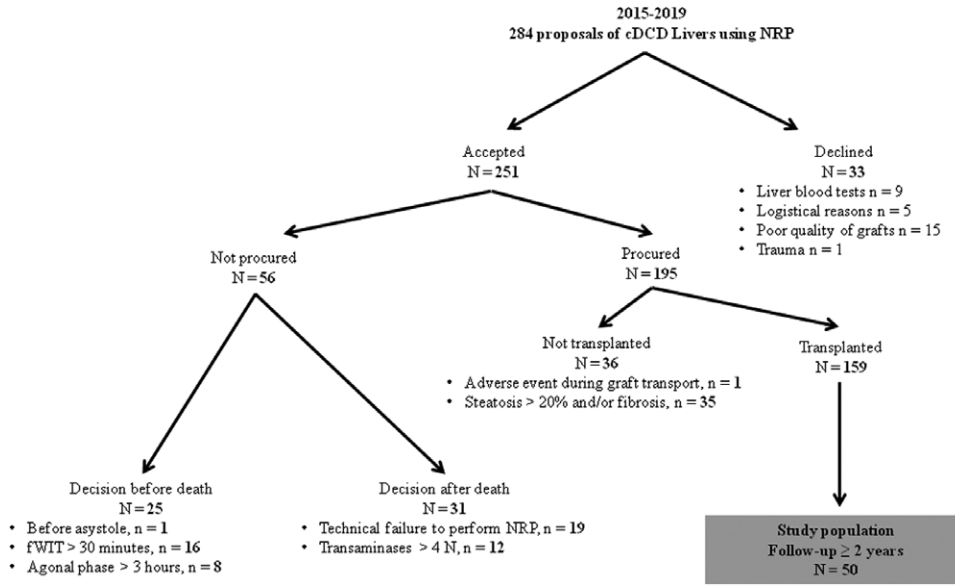

FIGURE 1. Flowchart for the cDCD Liver Offers during the study period. cDCD, controlled donation after circulatory death; fWIT, functional warm ischemic time; NRP, normothermic regional perfusion.

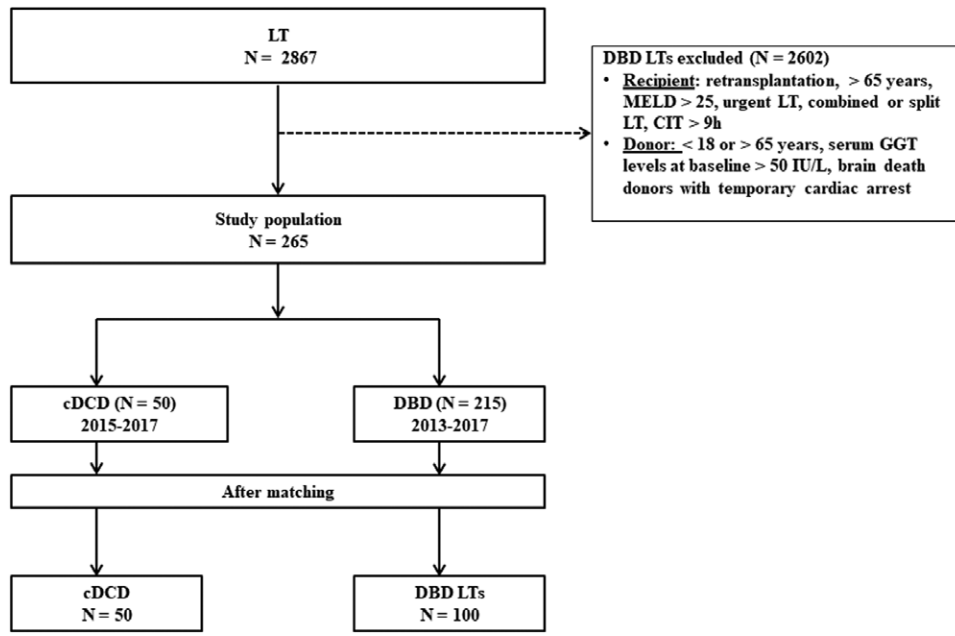

FIGURE 2. Flowchart for the case-matching process. cDCD, controlled donation after circulatory death; CIT, cold ischemia time; DBD, donation after brain death; LT, liver transplantation.

TABLE 2.

Donor and recipient characteristics

	cDCD with NRP (n = 50)	DBD (n = 100)	P
Donor			
Age (y)	50.0 (39.0–56.5)	50 (40.0–59.0)	0.49
Male gender	34 (68%)	61 (61%)	0.51
Body mass index (kg/m^2)	23.1 (21.5–25.4)	24.5 (22.2–26.9)	0.14
Umbilical perimeter (cm)	88.5 (80.8–97.8)	93.5 (81–102)	0.14
AST (IU/L) before procurement	50.0 (27.8–83.3)	34.5 (23.3–61.0)	0.03
ALT (IU/L) before procurement	39.0 (24.8–89.6)	26.0 (15.0–49.0)	0.003
GGT (IU/L) before procurement	96.0 (39.6–241.3)	22.0 (14.3–38.8)	<0.001
Steatosis >20% (biopsy)	1 (2%)	6 (6%)	0.49
Preservation solution			<0.001
SCOT 15	18 (36%)	10 (10%)	
IGL-1	23 (46%)	37 (37%)	
HTK	0 (0%)	31 (31%)	
Celsior	1 (2%)	16 (16%)	
University of Wisconsin	0 (0%)	2 (2%)	
Other	8 (16%)	4 (4%)	
Recipient			
Age (y)	59.9 (54.1–63.9)	58.4 (52.8–62.2)	0.18
MELD at LT	7 (6–12)	10 (6–14)	0.08
Status at LT			0.82
Home	47 (94%)	91 (91%)	
Hospital	2 (4%)	6 (6%)	
ICU	1 (2%)	3 (3%)	
Medical condition before LT			
Mechanical ventilation	0 (0%)	1 (1%)	0.72
Dialysis	1 (2%)	0 (0%)	0.72
Indication			0.15
Cirrhosis	11 (22%)	23 (23%)	
Malignancy	39 (78%)	70 (70%)	
Other	0 (0%)	7 (7%)	
Hepatitis C virus	16 (32%)	32 (32%)	0.85
Hepatitis B virus	11 (22%)	26 (26%)	0.74
HIV	0 (0%)	3 (3%)	0.54
Previous abdominal surgery	13 (26%)	32 (32%)	0.57
Transhepatic intrahepatic portosystemic shunt (TIPS)	3 (6%)	2 (2%)	0.42
History of portal vein thrombosis	7 (14%)	13 (13%)	0.92
Diabetes	16 (32%)	23 (23%)	0.40
Cold ischemia time (min)	348 (300–402)	378 (324–438)	0.03
Specimen analysis			
Malignant tumor[a]	38 (76%)	63 (63%)	0.16
HCC	35 (70%)	59 (59%)	0.26
Tumor size (mm)[b]	2.1 (1.4–3.0)	2.0 (1.4–3.0)	0.86
Number of nodules[b]	3 (1–4)	3 (1–5)	0.78
Vascular invasion[b]	2 (6%)	7 (12%)	0.45
Alpha score[1b]	0 (0–2)	0 (0–2)	0.65
Alpha score >2[b]	2 (6%)	5 (8%)	0.71
Within Milan criteria[2b]	21 (60%)	34 (59%)	0.89
Up to 7 score[3b]	5 (3.5–6.8)	5.0 (3.0–7.6)	0.78
Up to seven >7[3b]	8 (23%)	15 (25%)	0.98

Values are given as median and interquartile range or number and percentage.

[a]Including HCC, cholangiocarcinoma, colorectal liver metastasis from colorectal cancer, and epithelioid hemangioendothelioma.

[b]HCC.

[1]Duvoux et al. Gastroenterology, 2012:[2] Mazzaferro et al. NEJM, 1996.[3] Mazzaferro et al. Lancet Oncol 2009.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; cDCD, controlled donation after circulatory death; DBD, donation after brain death; HTK, histidine-tryptophan-ketoglutarate; HCC, hepatocellular carcinoma; ICU, intensive care unit; IGL-1, Institute Georges Lopez-1; LT, liver transplantation; MELD, model for end-stage liver disease; NRP, normothermic regional perfusion; SCOT, solution of conservation for organ transplantation; TIPS, transhepatic intrahepatic portosystemic shunt.

TABLE 3.
Perioperative outcomes

	cDCD (n = 50)	DBD (n = 100)	*P*
Biliary anastomosis			0.75
Bilio-biliary anastomosis	47 (94%)	69 (91%)	
Bilio-jejunostomy	3 (6%)	7 (9%)	
Biliary drain	24 (48%)	34 (45%)	
Early allograft dysfunction	9 (18%)	32 (32%)	0.11
Acute kidney injury	13 (26%)	33 (33%)	0.49
Arterial complications	2 (4%)	12 (12%)	0.19
Biliary complications	8 (16%)	17 (17%)	0.94
90-d graft loss	1 (2%)	5 (5%)	0.66
90-d mortality patient death <90 d	1 (2%)	1 (1%)	0.80
Graft loss <2 y			
Patient death by liver cancer recurrence	6 (12%)	3 (3%)	0.07
Patient death by de novo cancer	1 (2%)	1 (1%)	0.80

Values are given as median and interquartile range or number and percentage.
cDCD, controlled donation after circulatory death; DBD, donation after brain death.

(*P* = 0.003) was significantly shorter in the cDCD group than in the DBD group (Table 3).

Postoperative Liver Blood Tests, EAD, AKI

The serum transaminase (NRP cDCD, AST: 917 [397–1372] IU/L; DBD, AST: 1027 [532–2298] IU/L; *P* = 0.29; NRP cDCD, ALT: 702 [267–1012] IU/L; DBD, ALT: 753 [393–1509] IU/L; *P* = 0.16; Figure 3A and D) peak at postoperative (POD) 0 did not differ between the 2 groups. Serum AST/ALT levels were significantly lower from POD 1 to 4 in the cDCD group than in the DBD group (*P* < 0.05 for all comparisons). gGT levels were significantly higher from POD 4 to 8 in the NRP cDCD group than in the DBD group (Figure 3C). Serum total bilirubin, serum creatinine, and prothrombin time were similar between the 2 groups at all timepoints (*P* > 0.05 for all comparisons; Figure 3B, D, and E).

The rates of EAD and AKI were not different between the 2 groups (*P* = 0.10 and *P* = 0.49, respectively, Table 3).

Arterial and Biliary Complications and Survival

Although not statistically significant, the rate of arterial complications was higher in the DBD group than in the NRP cDCD group (12% versus 4%, *P* = 0.19; Table 4). The rate of biliary complications was not different between the 2 groups (16% in the NRP cDCD group versus 17% in the DBD group; *P* = 0.94). Among patients who developed a biliary complication, there was 1 case of ischemic cholangiopathy in each group (1 case with arterial thrombosis in the DBD group and 1 case without arterial thrombosis or stenosis in the NRP cDCD group). These 2 patients underwent retransplantation >12 mo after primary LT.

The median follow-up was 34.8 (28.6–39.8) mo in NRP cDCD group and 51.7 (34.1–61.7) mo in DBD group (*P* < 0.001). The 2-y death noncensored graft survival was 88% in the NRP cDCD group and 85% in the DBD group (*P* = 0.91; Figure 4A). The 2-y death censored graft survival was similar between the 2 groups (NRP cDCD group: 96% versus DBD: 96%; *P* = 0.79; data not shown). The 2-y patient survival was similar between the 2 groups (NRP cDCD group: 90% versus DBD: 88%; *P* = 0.68; Figure 4B). After excluding deaths due to cancer from the survival analysis, the 2-y graft survival rates were similar between the 2 groups (NRP cDCD group: 96% versus DBD group: 89%; *P* = 0.10; Figure 4C). Similarly, the 2-y patient survival was 98% and 91% in the NRP cDCD group and the DBD group, respectively (*P* = 0.15, data not shown).

DISCUSSION

To our knowledge, this is the largest matched series published to date comparing outcomes for cDCD LT using the postmortem NRP technique with those for DBD LT. Overall, this study allowed us to demonstrate the benefits of NRP when applied in the context of cDCD donors. Indeed, compared with DBD LT, in which the best results could be expected, we showed that cDCD LT achieved similar rates of (1) EAD and AKI, (2) biliary complications within the first 2 y following LT and (3) 2-y graft and patient survival rates.

The first finding of our study is that NRP allowed us to select optimal organs by evaluating the viability of the liver graft before procurement during the perfusion phase. Hence, biopsy was systematically applied and led to liver withdrawal in case of severe steatosis, fibrosis or significant necrotic lesions of the parenchyma that cannot be assessed macroscopically (35 livers not retrieved of the entire cohort). In the present study, increased value of transaminases ≥ 4 N during NRP led us to refuse 12 liver grafts.

Normothermic perfusion is a demanding procedure from a technical point of view, which requires a specific and professional surgical team. One potential concern is the technical failure of the procedure that can lead to abort organ procurement. In the present series, technical failure related to percutaneous cannulation was the most common reason for failure to perform NRP. Importantly, in the series, failure to perform NRP due to technical issues was reported in 19 donors, which represents <8% of the allocated donors. In 6 expert centers, this proportion was even less and did not exceed 5% (data not shown). Ensuring adequate heparinization at the start of NRP associated with increasing experience may help to avoid NRP dysfunction. It is important to note that open abdominal aortic cannulation is not permitted in France, and technical failure related to percutaneous cannulation would be decreased over time with the learning curve. Finally, the identification of balloon-related complications such as the presence of calcified vessels, lack of placement of over a guidewire, and forceful insertion against resistance may help us to avoid these complications. All these incidents decreased over time with senior surgeon involvement and the learning curve.

Another important benefit of NRP is to reduce primary nonfunction and ischemic cholangiopathy. This had been demonstrated in 2 previous studies comparing cDCD LT with and without NRP.[18,19] These latter studies showed that recipients in NRP group experienced an overall incidence of biliary complications of 8%,[19] an ischemic cholangiopathy rate that ranged from 0% to 2%, and an EAD reported between 12% and 22%. Interestingly, our study definitely confirms similar results since the overall biliary complications, ischemic cholangiopathy and EAD rates were 16%, 2%, and 18%, respectively.

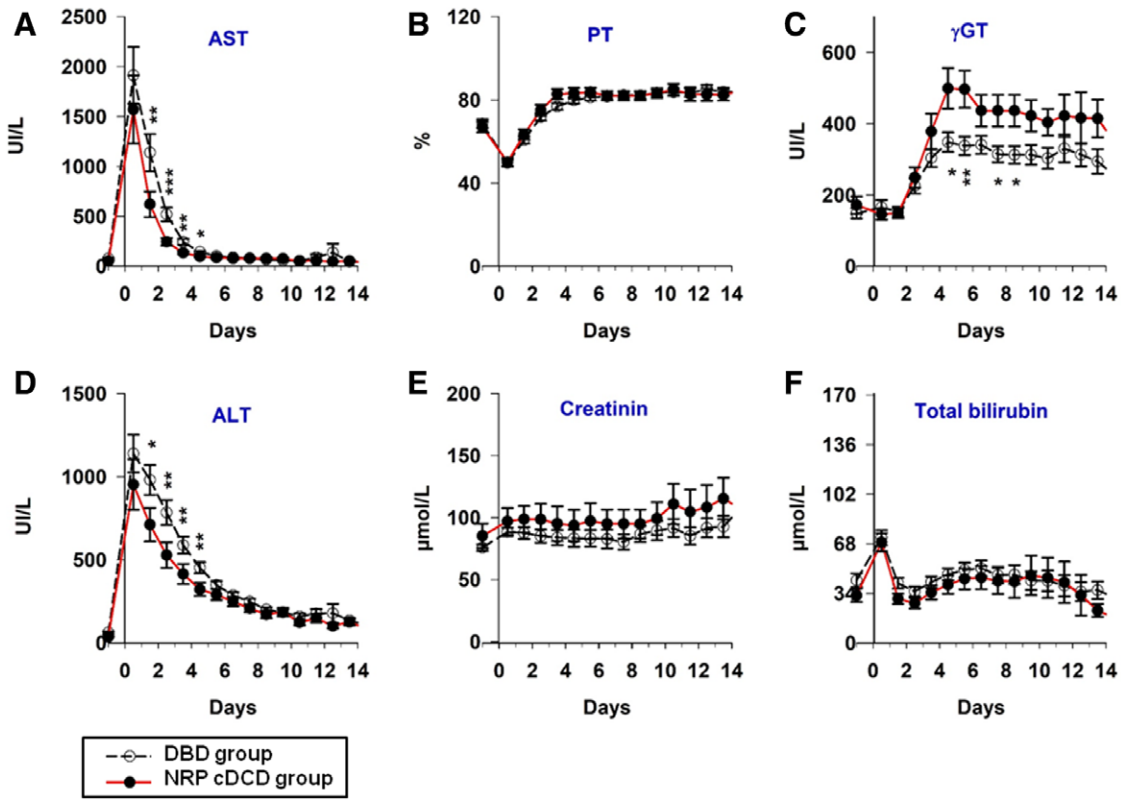

FIGURE 3. Post-LT liver blood tests.Time 0 was the date and h of portal reperfusion. A, Aspartate aminotransferase. B, Prothrombin time. C, Gamma-glutamyl transpeptidase. D, Alanine aminotransferase. E, Creatinine. F, Total bilirubin. *P < 0.05; **P < 0.01; ***P < 0.001. ALT, alanine aminotransferase; AST, aspartate aminotransferase; cDCD, controlled donation after circulatory death; DBD, donation after brain death; LT, liver transplantation; NRP, normothermic regional perfusion.

In the present study, the rate of biliary complications in NRP cDCD group and DBD group was 16% and 17%, respectively, which is consistent with the current benchmarks for standard DBD LT (≤28% biliary complications). It has been reported that cDCD was associated with higher rate of biliary complications, especially ischemia cholangiopathy ranging from 6% to 11% (Table 1).[2,3,5] In our study, NRP cDCD group showed similar rates of overall biliary complication and ischemic cholangiopathy than DBD group. This is similar to outcomes in the sole small (n = 11) existing report[6] comparing cDCD LT with NRP and DBD LT. The absence of significant difference in terms of biliary complications and ischemic cholangiopathy highlights the potential benefit of NRP in the prevention of ischemic-type biliary lesions.

However, it is interesting to note that the study by Rodriguez-Sanjuan et al.[6] reported relatively high rates of biliary strictures without accurately assessing specific ischemia type biliary lesions (13% in cDCD group and 31% in DBD group) compared to our results (2% and 1%, respectively). Their results may be explained by the fact that the donors were significantly younger in cDCD group as compared to DBD donors (P = 0.01) and probably because of the small sample size of the cDCD group (n = 11). Another important limitation of this previous study was that the minimum follow-up covered only 3 mo. Moreover, because biliary complications might appear between 6 and 12 mo after LT and given their short follow-up, the overall biliary complication rate might have been potentially much higher.

TABLE 4.
Arterial and biliary complications

	cDCD (n = 50)	DBD (n = 100)	*P*
Arterial complication	2 (4%)	12 (12%)	0.19
False aneurysm	1 (2%)	1 (1%)	
Stenosis	1 (2%)	6 (6%)	
Thrombosis	0 (0%)	5 (5%)	
Treatment			-
Medical	0 (0%)	3 (3%)	
Endovascular	1 (2%)	5 (5%)	
Surgical revision	0 (0%)	2 (2%)	
Retransplantation	0 (0%)	2 (2%)	
Biliary complication[a]	8 (16%)	17 (17%)	0.94
Localized stricture[a]	2 (4%)	9 (9%)	
Disseminated stricture[a]	1 (2%)	1 (1%)	
Fistula	5 (10%)	5 (5%)	
Stone	0 (0%)	2 (2%)	
Treatment			-
Medical	1 (2%)	0 (0%)	
Percutaneous drainage	4 (8%)	6 (6%)	
Surgical revision (hepato-jejunostomy)	0 (0%)	2 (2%)	
ERCP	3 (6%)	8 (8%)	
Retransplantation	1 (2%)	1 (1%)	

Values are given as number and percentage.
[a]According to the classification of biliary strictures published by Croome et al:[16] localized strictures are anastomotic or supra-anastomotic strictures that are reachable and treatable by endoscopic or percutaneous approaches, whereas disseminated strictures (or injury) ultimately require transplantation.
cDCD, controlled donation after circulatory death; DBD, donation after brain death; ERCP, endoscopic retrograde cholangiopancreatography stenting.

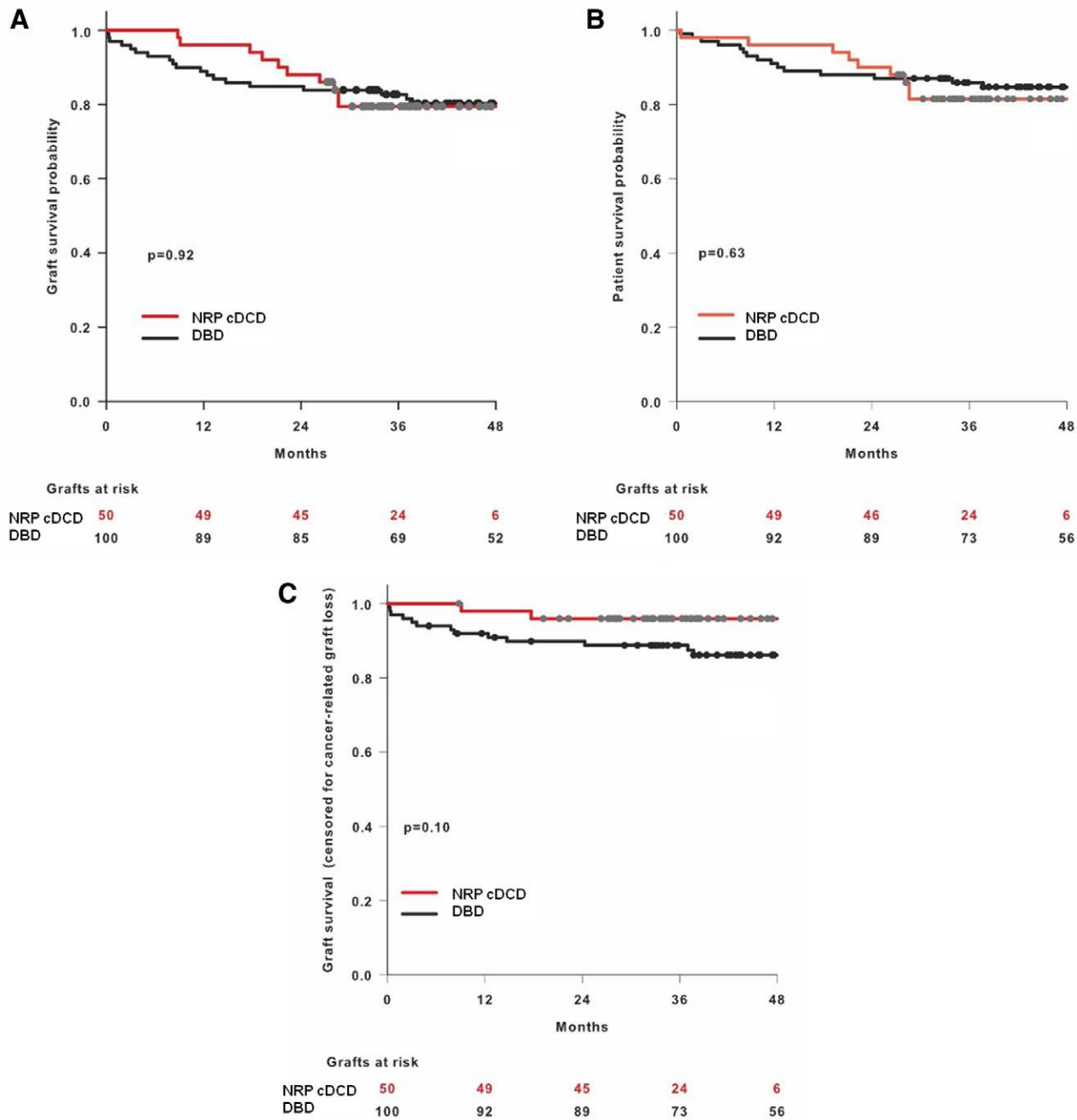

FIGURE 4. Survival outcomes after cDCD and DBD LT. A, Graft survival. B, Patient survival. C, Graft survival with cancer-related death censured. cDCD, controlled donation after circulatory death; DBD, donation after brain death; LT, liver transplantation; NRP, normothermic regional perfusion.

The ischemic-reperfusion injury issue remains a matter of debate. Several technical strategies using an ex vivo perfusion technique following organ retrieval have been developed to improve the liver graft utilization rate and decrease ischemic cholangiopathy rates. These include hypothermic perfusion after static cold storage and before reperfusion,[20] normothermic oxygenated perfusion with minimal cold storage,[21] or both.[22] The French strategy defined by ABM, that is, systematic NRP use, should be challenged by the use of machine perfusion in the future through prospective randomized trials.

It has been suggested that cDCD LT was associated with a post-LT serum transaminase increase.[3,8,23,24] Despite a higher level of transaminase before procurement in the NRP cDCD group, we observed that AST/ALT levels within the first 24 h were significantly lower in NRP cDCD group than in DBD group, which is in accordance with previous series.[6] This suggests a potential effect of NRP on postoperative ischemia-reperfusion injury. These may be because of several reasons: (1) CIT was significantly shorter in the NRP cDCD group than in the DBD group and (2) the lower transaminase levels in the first few days posttransplant may be explained by the more stringent donor selection criteria of the French protocol (ie grafts exposed to strictly < 30 min of warm ischemia, CIT <8 h, steatosis at biopsy < 20%).

The vast majority of cDCD LT were performed in patients with HCC (70% of the NRP cDCD group versus 59% in the DBD group). In reported series of LTs performed with cDCD grafts, the proportion of patients with HCC ranged from 31% to 100%.[8] In this study, we found, that compared to DBD group, NRP cDCD group had similar tumor burden (tumor size, number of nodules, and vascular invasion) but higher rate of graft loss due to tumor recurrence (12% versus 3%; $P = 0.07$; Table 3). By censoring cancer-related graft loss, graft survival tended to be higher in NRP cDCD group than in DBD group. Based on this survival result, the alpha score >2 according to the alpha-fetoprotein model[25] was considered as exclusion criteria for the French cDCD LT protocol.

Another option of premortem vessel cannulation has been proposed by a few teams.[19] One of the main limitations of our study is the inability to transpose our results in the setting of cDCD LT following premortem NRP.

In conclusion, this study provides evidence that cDCD LT following postmortem NRP can be safely and effectively performed in selected recipients with similar mid-term graft and patient survival outcomes, without increased rates of biliary complications and early graft dysfunction compared to DBD LT.

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