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Quantitative imaging for radiotherapy purposes

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ORIGINAL ARTICLE

Selected liver grafts from donation after circulatory death can be safely used for retransplantation – a multicenter retrospective study

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SUMMARY

Due to the growing number of liver transplantations (LTs), there is an increasing number of patients requiring retransplantation (reLT). Data on the use of grafts from extended criteria donors (ECD), especially donation after circulatory death (DCD), for reLT are lacking. We aimed to assess the outcome of patients undergoing reLT using a DCD graft in the Netherlands between 2001 and July 2018. Propensity score matching was used to match each DCD-reLT with three DBD-reLT cases. Primary outcomes were patient and graft survival. Secondary outcome was the incidence of biliary complications, especially nonanastomotic strictures (NAS). 21 DCD-reLT were compared with 63 matched DBD-reLTs. Donors in the DCD-reLT group had a significantly lower BMI (22.4 vs. 24.7 kg/m², *P*-value = 0.02). Comparison of recipient demographics and ischemia times yielded no significant differences. Patient and graft survival rates were comparable between the two groups. However, the occurrence of nonanastomotic strictures after DCD-reLT was significantly higher (38.1% vs. 12.7%, *P*-value = 0.02). ReLT with DCD grafts does not result in inferior patient and graft survival compared with DBD grafts in selected patients. Therefore, DCD liver grafts should not routinely be declined for patients awaiting reLT.

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Key words

deceased donors, donation after circulatory death, graft outcomes, liver retransplantation, liver transplantation, patient outcomes

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Introduction

Liver transplantation (LT) is a well-established treatment for patients suffering from end-stage liver disease. Due to the scarcity of available organs from deceased donors, the use of grafts from extended criteria donors (ECD) has increased substantially, of which grafts from donation after circulatory death (DCD) is a main parameter (1). In 2018, a DCD graft was used in 38% and 9% of all deceased donor LT in the Netherlands and United States of America, respectively (2,3). In the United Kingdom, 26% of deceased donor LT were performed with DCD grafts (4).

Liver transplantation with DCD grafts (DCD-LT) is considered to be inferior compared to LT with grafts donated after brain death (DBD-LT), due to the increased risk of complications such as early allograft dysfunction (EAD) and biliary complications (5–8). Among biliary complications, nonanastomotic strictures (NAS) are the most feared as they often require multiple interventions for biliary drainage, are largely irreversible and are known to have a negative impact on recipient and graft survival (9). The incidence of NAS, also known as ischemic cholangiopathy (IC) or ischemic-type biliary lesions (ITBL), after DCD-LT varies between 3% and 39% (6).

Since the use of grafts from marginal donors has increased, it is assumed that more recipients will develop post-transplant complications related to a suboptimal graft. Furthermore, due to improvements in surgical techniques, postoperative care and immunosuppressive regimes, the short-term survival after LT has improved significantly (10), resulting in a larger population surviving long enough to develop late graft failure. A retransplantation of the liver (reLT) is currently the only definitive treatment for allograft failure. However, it is well known that reLT is associated with inferior patient and graft survival compared with primary LT (11,12).

Despite DCD liver grafts being widely accepted, transplant physicians and surgeons tend to avoid the use of DCD grafts for reLT. However, since in some countries the availability of DBD grafts has decreased (13), the waiting time for an optimal, preferably DBD liver to become available for a reLT candidate could be too long with subsequent risk of deterioration of patient's condition, making him or her ineligible for reLT.

There is very little reported on the use of DCD grafts for patients requiring a reLT. Only one study has assessed the outcomes of ten patients undergoing reLT using DCD grafts (14). The authors concluded that the use of DCD graft should be avoided if the recipient has

a moderate to high Model for End-Stage Liver Disease (MELD) score. Unfortunately, no comparison was made with reLT using DBD grafts. Since DCD-LT is common in the Netherlands, and reLT is not an official contraindication for the use of a DCD liver, we aimed to compare the outcomes of reLT with DCD grafts in the Netherlands with that of matched DBD cases.

Patients and methods

In this multicenter retrospective study, all patients who underwent reLT using a controlled DCD liver graft (DCD-reLT) in the Netherlands from the beginning of the DCD-LT program in 2001 until July 1st 2018, were included. Pediatric LT (recipient < 18 years), reLT using a split graft, reLT in the setting of multi-organ transplantation and grafts preserved with machine perfusion were excluded. A pre-existent nationwide database on all liver retransplantations (reLT) performed between 1979 and July 2018 was used to match each DCD-reLT to three cases of reLT with DBD grafts (DBD-reLT) (15). For the matching, a propensity score matching approach with nearest-neighbor algorithm was used. The propensity scores were calculated using a logistic regression model with the following independent covariates: transplant center, number of consecutive reLT, year of reLT, donor and recipient age, last laboratory MELD score (Model for End-Stage Liver Disease) registered by Eurotransplant prior to transplantation, cold ischemia time (CIT), and interval between prior LT and ReLT. This latter matching criterion was chosen since an early reLT, is on the one hand technically less challenging than late reLT (easier hepatectomy with less adhesions), but on the other hand is performed in patients who may be sicker pre-reLT than patients undergoing a late reLT (16,17). DBD-reLT cases that met one of the previously mentioned exclusion criteria or had missing variables in one or more of the matching criteria were excluded prior to matching. Additional data on donor and organ procurement characteristics were obtained through the Eurotransplant Donor data database. Additional recipient data and data on follow-up were collected from prospective maintained databases and patients' electronic medical records. The study has been approved by the Institutional Review Board of the Erasmus MC University Medical Center Rotterdam (MEC-2019-0316).

In all DCD organ procurements in the Netherlands, withdrawal of life support takes place at the ICU or regular ward. After circulatory arrest, a mandatory no touch period of five minutes is carried out after which the donor is transported to the operating theatre. As

described in the National protocol postmortem donor organ procurement, a super-rapid retrieval technique is used in DCD donors to minimize the donor warm ischemia time (dWIT). After cannulation of aorta and inferior vena cava, cold perfusion with University of Wisconsin (UW) solution is started (18). Since pre-mortem administration of heparin is prohibited by law, heparin is added to the perfusion solution. The standard method of implantation is with a piggyback caval vein anastomosis, an end-to-end arterial and portal anastomosis, and a duct-to-duct biliary anastomosis.

The total dWIT was defined as time between withdrawal of life-supporting treatment and start of cold perfusion. The definition of asystolic dWIT was the time between circulatory arrest and cold perfusion. The CIT was defined as the period between the start of the cold perfusion in the donor and the removal of the liver from ice during the recipient procedure. The definition of recipient warm ischemia time (rWIT) used in this study is the interval between removal of the liver from ice and graft reperfusion (i.e., in the majority portal reperfusion).

The primary outcome measures of this study were patient and graft survival. Patient survival was defined as time between reLT and death, with or without functioning graft. Graft survival was calculated as time between the reLT and patient death (with or without functioning graft) or a successive retransplantation. Secondary outcomes were the incidence of three types of biliary complications: bile leakage, anastomotic strictures, and NAS. NAS was defined as any stricture of the bile duct except those localized near the biliary anastomosis and in absence of an hepatic artery thrombosis.

Continuous data were presented as median and interquartile range (IQR) and compared with the Mann–Whitney *U* test. Categorical variables were presented as number and percentages and compared with the Pearson chi-square test or the Fisher exact test where appropriate. Survival analyses was conducted using the Kaplan–Meier method, and comparisons were made with the log-rank test. All tests were two-sided with a *P*-value below 0.05 considered as significant. The propensity score matching was performed in RStudio, version 1.0.153 (RStudio Inc. Boston, MA, USA), using the MatchIt package. All other statistical analyses were performed using SPSS version 25 (IBM, Chicago, IL, USA).

Results

A total of 21 cases of DCD-reLT were included in this study. These cases were matched with 63 DBD-reLT cases. Donor and recipient demographics are given in Table 1.

Compared with DBD-reLT donors, DCD-reLT donors had a significantly lower BMI (22.4 vs. 24.7 kg/m², *P*-value = 0.02). Furthermore, there was a trend toward significance regarding the donor cause of death (*P*-value = 0.06). The majority of the DBD donors had died from a cerebrovascular accident (CVA), whereas the cause of death among DCD donors was more equally distributed between trauma, CVA, and other causes. In DCD-reLT, the median asystolic dWIT was 15.0 min (12.0–18.0 min) whereas the total dWIT was 27.5 min (22.3–30.8 min).

The majority of the recipients was male, with a median age of 51.0 years (IQR, 46.0–56.5 years) in the DCD-reLT group and 56.0 years (IQR, 46.0–62.0 years) in the DBD-reLT group (*P*-value = 0.22). The most common indication for reLT was post-transplant cholangiopathy (43% in the DCD-reLT group, 44% in the DBD-reLT group), followed by vascular complications and recurrence of the primary disease.

Table 2 shows operative data as well as data on the postoperative outcomes.

Neither the CIT nor the rWIT differed significantly between the two groups. However, the peak ALT level in the first week post-reLT was significantly higher in the DCD-reLT group (1346 IU/l vs. 833 IU/l, *P*-value = 0.04). Patients were discharged from the hospital after a median of 25 days in the DCD-reLT group and 20 days in the DBD-reLT group (*P*-value = 0.15).

Survival rates

The median follow-up of the total cohort was 5.30 years (IQR, 1.49–8.73 years). The 30 days, 1-year, 5-year, and 10-year recipient survival in the DCD-reLT group was 95%, 81%, 81%, and 81%, respectively, compared with 90%, 82%, 72%, and 59% in the DBD-reLT group (*P*-value = 0.37, Fig. 1). The causes of death of five recipients in the DCD-reLT group are listed in Table 3.

The 30 days, 1-year, 5-year, and 10-year graft survival was 95%, 81%, 81%, and 81% for the DCD-reLT group and 86%, 79%, 67%, and 53% in the DBD-reLT group (*P*-value = 0.20) (Fig. 2). Six patients needed a subsequent retransplantation: three because of an early hepatic artery thrombosis (all in the DBD-reLT group), two due to ischemic-type biliary lesions (one in each group), and one patient in the DBD-reLT group due to recurrence of primary sclerosing cholangitis.

Biliary complications

In total, 10.7% of the recipients had a bile leakage. Furthermore, five recipients in the DCD-reLT group

Table 1. Donor and recipient demographics.

	Total group N = 84	DCD-reLT N = 21	DBD-reLT N = 63	P-value
Donor				
Gender				
Male	42 (50.0)	10 (47.6)	32 (50.8)	0.80
Female	42 (50.0)	11 (52.4)	31 (49.2)	
Age (years)	40.5 (24.0–51.5)	38.0 (19.5–45.0)	42.0 (25.0–53.0)	0.11
BMI (kg/m ²)	23.5 (21.3–26.0)	22.4 (19.8–23.7)	24.7 (21.5–26.7)	0.02
Cause of death				
CVA	43 (51.2)	7 (33.3)	36 (57.1)	0.06
Trauma	26 (31.0)	7 (33.3)	19 (30.2)	
Other	15 (17.9)	7 (33.3)	8 (12.7)	
Last γ -GT (U/L)	24 (17–52)	28 (18–34)	23 (17–53)	0.96
Last ALT (U/L)	32 (21–50)	23 (15–47)	36 (21–52)	0.10
Asystolic dWIT (min)*	n/a	15.0 (12.0–18.0)	n/a	n/a
Total dWIT (min) [†]	n/a	27.5 (22.3–30.8) [‡]	n/a	n/a
Recipient				
Gender				
Male	54 (64.3)	12 (57.1)	42 (66.7)	0.43
Female	30 (35.7)	9 (42.9)	21 (33.3)	
Age (years)	54.5 (46.0–61.8)	51.0 (46.0–56.5)	56.0 (46.0–62.0)	0.22
BMI (kg/m ²)	24.3 (21.7–26.6)	22.7 (21.6–28.2)	24.3 (21.7–26.5)	0.77
Laboratory MELD score	20.0 (10.3–26.0)	19.0 (9.5–27.5)	20.0 (11.0–26.0)	0.70
Indication for reLT				
PNF	7 (8.3)	3 (14.3)	4 (6.3)	0.41
Vascular (e.g., HAT/PVT)	23 (27.4)	3 (14.3)	20 (31.7)	
Biliary (e.g., ITBL)	37 (44.0)	9 (42.9)	28 (44.4)	
Recurrent primary disease	12 (14.3)	4 (19.0)	8 (12.7)	
Other	5 (6.0)	2 (9.5)	3 (4.8)	
High urgency status	26 (31.0)	4 (19.0)	22 (34.9)	0.17
Number of reLT				
First reLT	72 (85.7)	18 (85.7)	54 (85.7)	>0.99
Second reLT or more	12 (14.3)	3 (14.3)	9 (14.3)	
Time between reLT and prior LT (days)	466 (13–2728)	1140 (166–3864)	368 (12–2685)	0.31
Graft type of prior LT				
DBD graft	61 (72.6)	15 (71.4)	46 (73.0)	0.82
DCD graft	22 (26.2)	6 (28.6)	16 (25.4)	
Living	1 (1.2)	0	1 (1.6)	

Data are shown as median (IQR) and frequency (proportion).

P-values < 0.05 were considered statistically significant which are presented in bold.

ALT, alanine transaminase; BMI, Body Mass Index; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; dWIT, donor Warm Ischemia Time; γ -GT, Gamma-glutamyltransferase; LT, liver transplantation; MELD, model for end-stage liver disease; reLT, liver retransplantation.

*Asystolic dWIT is defined as the time between circulatory arrest and start of cold perfusion.

[†]Total dWIT is defined as time between withdrawal of life-supporting treatment and cold perfusion.

[‡]Proportion of missing data for this variable is 23.8%.

(23.8%) and eight in the DBD-reLT group (12.7%) developed an anastomotic stricture (P -value = 0.30). The proportion of recipients developing NAS was significantly higher in the DCD-reLT group (38.1% vs.

12.7%, P -value = 0.02). The majority of the NAS after DCD-reLT were of the focal type. The median time interval between reLT and diagnosis of NAS was 170 days (IQR 102–282 days).

Table 2. Surgical and postoperative demographics.

	Total group N = 84	DCD-reLT N = 21	DBD-reLT N = 63	P-value
Operation				
rWIT (minutes)	40 (32.8–46.3)	44.0 (35.0–48.0)	39.0 (31.5–43.0)*	0.07
CIT (minutes)	444 (377–524)	440 (355–518)	448 (389–527)	0.69
Blood loss (ml) [†]	3600 (2000–5900)	4819 (2675–8175) [†]	3200 (1767–5450) [‡]	0.09
Postoperative outcomes				
ICU stay (days)	2.0 (1.3–5.0)	2.0 (2.0–4.0)	2.0 (1.0–5.0)	0.90
Hospital stay (days)	21.0 (14.0–30.0)	25.0 (14.0–34.5)	19.5 (13.0–25.8) [§]	0.15
Peak ALT within 1st week	1011 (540–1626)	1346 (526–2518)	833 (526–1305)	0.04
Hepatic artery thrombosis	9 (10.7)	2 (9.5)	7 (11.1)	>0.99
Bile leak	9 (10.7)	2 (9.5)	7 (11.1)	>0.99
Anastomotic strictures	13 (15.5)	5 (23.8)	8 (12.7)	0.30
Nonanastomotic strictures	16 (19.0)	8 (38.1)	8 (12.7)	0.02
Death	24 (28.6)	5 (23.8)	19 (30.2)	0.58
Retransplantation	6 (7.1)	1 (4.8)	5 (7.9)	>0.99

Data are shown as median (IQR) and frequency (proportion).

P-values < 0.05 were considered statistically significant which are presented in bold.

ALT, alanine transaminase; BAR, balance of risk; CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after circulatory death; ICU, Intensive Care Unit; LT, liver transplantation; MELD, model for end-stage liver disease; reLT, liver retransplantation; rWIT, recipient Warm Ischemia Time.

*Proportion of missing data for this variable is 3.2%.

[†]Proportion of missing data for this variable is 4.8%.

[‡]Proportion of missing data for this variable is 15.9%.

[§]Proportion of missing data for this variable is 1.6%.

Discussion

The relative shortage of available liver grafts has led to a more widespread use of DCD grafts. However, the outcomes after reLT with a DCD graft have rarely been reported in literature. This is the first study to analyze the outcomes after DCD-reLT and compare these with outcomes after matched DBD-reLT. Our results suggest that reLT with a DCD graft in selected patients does not result in inferior outcome when compared to matched DBD-reLTs.

The survival rates after DCD-reLT in this study are substantially higher than presented in the previous study on DCD-reLT performed by Perry et al. in 2011 (14). This could be due to the substantially lower MELD score in our population (median of 20.0 vs. a median of 27.0 reported by Perry et al.). Unfortunately, it is unclear whether in the study by Perry et al. the MELD score included (non) standard exception points. Since our median laboratory MELD score is that much lower, we are unable to refute or endorse the conclusion from Perry et al. that the use of DCD grafts should be avoided in high MELD recipients awaiting reLT. However, a recent published study by Taylor et al. concluded

that accepting a DCD graft has a survival advantage over waiting for a DBD liver, especially in recipients with a high MELD score (19). As this study only included first-transplant recipients, it is doubtful whether the conclusions made by Taylor and colleagues can be extrapolated to the field of reLT. Based on our results, it is indicated that at least in recipients with low-to-moderate laboratory MELD score the use of a DCD graft is justifiable for reLT.

The significantly lower donor BMI in the DCD-reLT group is probably the result of strict selection by transplant physicians and surgeons. Since there seems to be some association between BMI and degree of steatosis, a known risk factor for poor outcome after LT (20,21), transplant professionals may be reluctant to accept the liver from an overweight DCD donor for reLT. We believe that it is unlikely that the lower donor BMI of the DCD-group alone has resulted in the relatively high survival rates of this group, because median donor BMI of both groups was within the healthy weight category according to the WHO definition (22).

When compared with DBD grafts, LT with DCD grafts is generally at higher risk of developing biliary complications post-transplantation, especially NAS. A

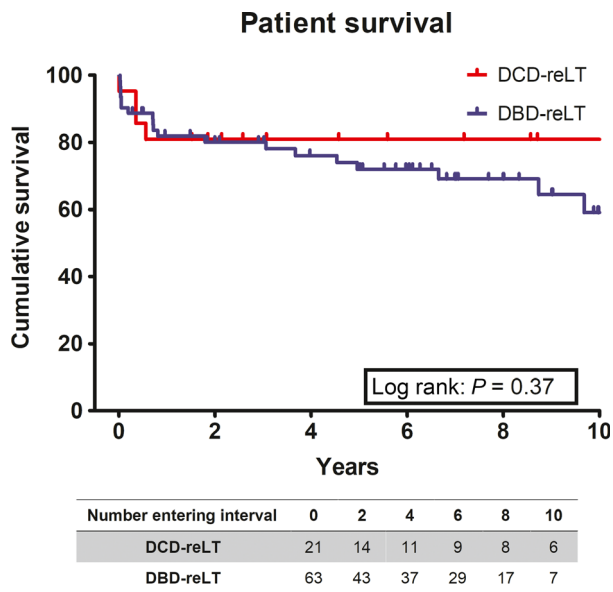


Figure 1 Kaplan–Meier curve of patient survival after DCD-reLT and DBD-reLT. Patient survival is defined as death (with or without functioning graft). DBD-reLT: liver retransplantation with graft from donation after brain death. DCD-reLT: liver retransplantation with graft from donation after circulatory death.

similar trend can be seen in the current study. Although the development of NAS post-transplantation can have a substantial influence on the survival rates, we believe it should not discourage transplant professionals in using DCD grafts for the indication of reLT. Firstly, because the majority of the NAS cases reported after DCD-reLT in our study were of the focal type and could be treated conservatively by endoscopic therapy. Only two recipients required a new transplant because

Table 3. Causes of death after DCD-reLT.

Patient	Graft type	Interval between reLT and death (days)	Cause of death
1.	DCD-reLT	1	Myocardial infarction in septic patient
2.	DCD-reLT	129	Multiple organ failure
3.	DCD-reLT	129	Recurrent giant cell hepatitis
4.	DCD-reLT	205	Pseudomonas infection in patient with recurrent hepatitis C infection
5.	DCD-reLT	4941	Recurrent decompensated liver cirrhosis

of this complication. Furthermore, the field of machine perfusion is evolving rapidly. Research has shown that with the use of machine perfusion, the incidence of biliary complications post-transplant can be reduced (23–26). Currently, several international trials regarding machine perfusion are ongoing.

Surprisingly, the incidence of NAS after especially DBD-reLT in the current study is higher than expected. There could be several explanations for this. First, the high NAS incidence in the DBD-cohort could be the result of the matching. Furthermore, until recently, the donor hepatectomy time (i.e., the time between the start of cold perfusion in the donor and the liver being stored on ice) was relatively long in the Netherlands. Research has shown that a prolonged hepatectomy time is a risk factor for the development of NAS (27,28). Finally, the high incidences of NAS in this reLT cohort could also imply that a reLT, independent of graft type, has a higher risk of developing postoperative NAS. Unfortunately, literature on this topic is lacking.

With the renewed interest in the use of DCD grafts, we believe that the results of our study are very relevant for further practice in these centers. With careful selection, recipient and graft survival after DCD-reLT appear similar to the survival in DBD-reLT. Therefore, grafts for reLT should not be rejected based on the DCD status alone but a careful assessment of additional donor factors is needed for a case-by-case decision to use these grafts. Furthermore, making use of DCD donors for reLT may facilitate the current ethical debate regarding reLT. That is, if transplant surgeons and physicians will accept DCD grafts for retransplantation, more DBD grafts will remain available for recipients on the waiting list awaiting their first-transplant. At the same time, expansion of the donor pool with DCD donors will result in more expedited reLT for those in need. Finally, with the emerging technologies in the field of machine perfusion, it can be anticipated that the quality of DCD grafts can be improved, resulting in among other a decreased incidence of post-transplant cholangiopathy (23,29,30).

One strength of this study is the comparison of outcome after DCD-reLT with a matched control group of DBD-reLT cases. This has made a proper comparison of the two groups possible, from which it can be concluded that survival after DCD-reLT is under certain circumstances similar to that after DBD-reLT. This study also has several limitations. Firstly, we had to define dWIT as time between withdrawal of life support and cold perfusion. We were unable to calculate the

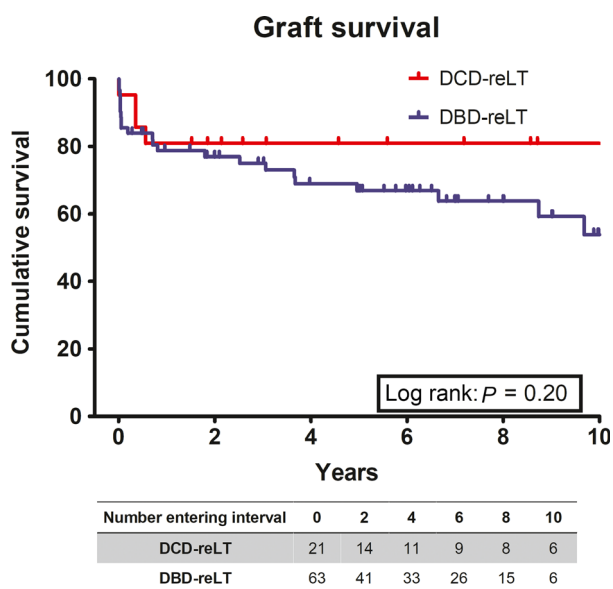


Figure 2 Kaplan–Meier curve of graft survival after DCD-reLT and DBD-reLT. Graft survival is defined as death (with or without functioning graft) or consecutive retransplantation. DBD-reLT: liver retransplantation with graft from donation after brain death. DCD-reLT: liver retransplantation with graft from donation after circulatory death.

more important functional warm ischemia time in the donor since data on hemodynamic status during the agonal phase are lacking or improperly recorded. Furthermore, the study had a retrospective design, which is prone to bias and confounding. Finally, the sample size of this study is relatively small, which made detailed statistical analysis such as multivariate analysis impossible.

In conclusion, reLT with a DCD graft can yield similar patient and graft survival rates as reLT with donation after brain death. Therefore, DCD itself should not preclude the use of such donors in patients awaiting retransplantation. However, careful selection of the offered DCD livers probably remains mandatory, especially to minimize the chance of developing NAS post-retransplantation. Larger studies are needed to confirm our results.

Authorship

MR, OL, WP, and RP: designed the study. MR, OL, and DH: collected the data. MR and OL: performed the analyses and wrote the manuscript. All co-authors reviewed the manuscript.

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Conflict of interest

The authors have declared no conflicts of interest.

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