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# Liver transplant with controlled donors after circulatory death with normothermic regional perfusion and brain dead donors: A multicenter cohort study of transfusion, one-year graft survival and mortality

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ABSTRACT

*Background:* Controlled donation after circulatory death (cDCD) has expanded the donor pool for liver transplantation (LT). However, transfusion requirements and perioperative outcomes should be elucidated. The aim of this multicenter study was to assess red blood cell (RBC) transfusions, one-year graft and patient survival after LT after cDCD with normothermic regional perfusion (NRP) compared with donors after brain death (DBD).

*Methods:* 591 LT carried out in ten centers during 2019 were reviewed. Thromboelastometry was used to manage coagulation and blood product transfusion in all centers. Normothermic regional perfusion was the standard technique for organ recovery.

*Results:* 447 patients received DBD and 144 cDCD with NRP. Baseline MCF Extem was lower in the cDCD group There were no differences in the percentage of patients (63% vs. 61% $p = 0.69$), nor in the number of RBC units transfused (4.7 (0.2) vs 5.5 (0.4) in DBD vs cDCD, $p = 0.11$. Twenty-six patients (6%) died during admission for LT in the DBD group compared with 3 patients (2%) in the cDCD group ($p = 0.15$). To overcome the bias due to a worse coagulation profile in cDCD recipients, matched samples were compared. No differences in baseline laboratory data, or in intraoperative use of RBC or one-year outcome data were observed between DBD and cDCD recipients.

*Conclusions:* cDCD with NRP is not associated with increased RBC transfusion. No differences in graft and patient survival between cDCD and DBD were found. Donors after controlled circulatory death with NRP can increasingly be utilized with safety, improving the imbalance between organ donors and the ever-growing demand.

## 1. Introduction

The availability of donors for liver transplantation (LT) is inferior to

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**Abbreviations**

| | |
|---|---|
| cDCD | controlled donation after circulatory death |
| DBD | donor after brain dead |
| LT | liver transplant |
| MT | Massive transfusion |
| PRS | post reperfusion syndrome |

the ever-growing demand. Graft availability is essential to avoid death or drop out in waiting lists due to deterioration and to ensure that patients are in the best physical condition possible prior to the procedure. To expand the donor organ pool, in addition to donors after brain death (DBD), livers donated after circulatory death (DCD) are increasingly used [1]. While DBD continues to form the basis for the majority of organ transplant activity globally, DCD now represents 30–50% in some European countries [2]. Between 2012 and 2019, more than 800 LT using grafts from DCD donors were performed in Spain. Therefore, DCD is an accepted strategy to expand the potential donor pool for LT [3].

In a previous series comparing uncontrolled DCD vs. DBD recipients, all coagulation parameters and Rotem values were worse in DCD at reperfusion of the graft. Also, significant differences with respect to RBC, fresh frozen plasma, platelets and cryoprecipitate administration were found [4]. Procurement of uncontrolled liver grafts may produce extensive endothelial damage, which could explain the deterioration in coagulation, post reperfusion syndrome (PRS) and poorer outcomes.

Currently, controlled donation after circulatory death (cDCD) using postmortem normothermic regional perfusion (NRP) has become standard in Spain, and guidelines have been issued by the Spanish Liver Transplantation Society [5]. Outcomes from cDCD donors are related to the graft quality, which requires a short ischemia time [6,7]. Even so, there remains an increased risk of operative morbidity, mainly due to ischemia reperfusion injury [1]. However, most studies examine the outcome, ignoring the intraoperative period; data on the anesthetic management of coagulation and the transfusion requirements of cDCD with NRP with normothermic regional perfusion (NRP) vs DBD are lacking.

The amount of hemoderivatives transfused is a known independent risk factor for patient and graft survival in LT [8]. Initial studies showed that cDCD recipients had higher rates of short-term post-LT renal dysfunction and massive transfusion (MT) compared with DBD [9]. However, in a more recent retrospective single-center study of adult LT, the propensity matching score showed that cDCD LT is not associated with higher transfusion requirements [10].

Thromboelastometry-guided transfusion protocols have changed transfusion policy in LT. Overall blood product transfusion is significantly reduced in most studies using thromboelastometry, and currently it is accepted as a standard in the management of coagulation in LT [11,12]. However, few studies have assessed the need for RBC transfusion based on the type of donors (DBD vs. cDCD), including intraoperative rotational thromboelastometry (Rotem) data. The aim of this study was to compare RBC transfusions and one-year graft and patient survival between cDCD with NRP and DBD recipients in a large consecutive series of patients from ten Spanish high volume LT centers.

## 2. Methods

Data from consecutive LT performed between January and December 2019 in ten centers were retrospectively registered. Pediatric recipients were excluded. Rotem-guided management was part of the standard intraoperative protocol. DBD and cDCD donors were included. cDCD organ recovery was performed in all centers using postmortem normothermic regional perfusion and the acceptance criteria strictly followed the consensus of the Spanish Liver Transplantation Society related to cDCD. A description of the organ retrieval technique is provided [5]. In brief, a bolus of heparin is administered and cannulation to establish the NRP is performed before withdrawal of ventilatory support after consent was obtained. Unilateral femoral vessels are cannulated, the contralateral femoral artery is cannulated with a deflated aortic occlusion balloon catheter, advanced into the supraceliac aorta under radiographic control. With cannulation complete, the endotracheal tube from the ventilator is disconnected, marking the start of total warm ischemia. Death is declared after 5 min of no spontaneous circulation and respiration. The aortic occlusion balloon is then inflated and the NRP circuit initiated. Proper positioning of the balloon, excluding the aortic arch vessels, is confirmed by chest radiograph and the absence of flow measured in the left radial arterial catheter. NRP is run for a minimum of one and a maximum of 4 h. Donor blood is then warmed and oxygenated using an extracorporeal membrane oxygenator circuit before return to the donor, followed by in situ cold perfusion with preservation fluid. All organs are subject to static cold storage after recovery.

Transfusion policy and coagulation management by thromboelastometry was a standardized approach at all centers. The Ethics Research Committee approved the study (HCB/2019/1160), ClinicalTrials.gov identification NCT04945135. The work has been reported in line with the STROCSS criteria [13].

Demographic data, donor type, hemodynamic monitoring, surgical technique, and hemoglobin level were recorded. Tranexamic acid administration, post reperfusion syndrome (PRS) according to Aggarwal criteria [14], other major hemodynamic complications (defined as arrhythmia with hemodynamic instability, acute myocardial ischemia, acute pulmonary embolism, massive air embolism and cardiac arrest), and intraoperative RBC transfusion were recorded. One-year graft survival and mortality were recorded.

To determinate equality in hemostasis and coagulation between groups, at baseline the maximum clotting firmness (MCF) of thromboelastometry (ROTEM sigma, TEM international, Munich, Germany) immediately before surgery was collected. MCF correlates well with the blood platelet count and plasmatic fibrinogen concentrations [15].

The potential observation of no differences between cDCD and DBD does not provide sufficient evidence for rejection of the null hypothesis and does not necessarily suggest the equivalence of both types of donors. Therefore, we designed a non-inferiority study. The main variables used to demonstrate non-inferiority between cDCD and DBD were the percentage of patients who received RBC, the numbers of units of RBC transfused, the percentage of patients receiving $\geq$6 RBC (massive transfusion [MT]), the development of PRS, and graft and patient survival at a one-year. RBC transfusions were compared as were the confidence intervals (CI) of the differences observed in the mean RBC transfused in each group, which allows a degree of uncertainty associated with the observed value. The margin ($\Delta$), the maximum acceptable extent of clinical non-inferiority for the percentage of RBC transfused patients, was established at 10% on the basis of a previous random study in LT and transfusion [16], which showed that 10% differences in patients transfused were not significant. The margin ($\Delta$) for PRS was established as 5% and the margin ($\Delta$) for mortality was established as 2% on the basis of a previous random study in LT [16].

As we included all consecutive patients in whom LT was performed during the study period (year 2019) in all centers, non-inferiority was demonstrated using all LT patients. Inferential testing for the main variables and the odds ratio and 95% confidence intervals (CI) were calculated using log-binomial regression models, and a p value was calculated using a likelihood ratio test. Other variables were analyzed using Fisher's exact test to compare categorical variables and the Mann-Whitney test for ordinal and continuous data. The Kaplan-Meier estimator was used to estimate survival for graft and patients. Multivariate analysis was performed by including variables that reached significance in the univariate analysis, together with variables considered clinically relevant for the endpoint.

Data were expressed as median and interquartile range (IQR), means and standard error or 95% CI as required. All analyses were performed using SPSS version 25 and the level of significance was established as 5% for a two-sided comparison.

## 3. Results

During 2019, 591 adult LT were performed in the ten centers, and all patients were included in the analysis: 447 patients received a DBD graft and 144 patients a cDCD with NRP graft. The percentage of patients included per center ranges from 5 to 15% of the total. Piggyback was the standard surgical technique.

The main demographic, baseline and intraoperative data are summarized in Table 1. No differences according to age, sex or previous hemoglobin levels were found. No differences were found in donor data. The underlying liver disease in patients with cirrhosis was hepatitis C virus 35%, alcoholism 35%, hepatocellular carcinoma 30%, homogeneously distributes in both groups, whereas the rest were a miscellany of etiologies: biliary, acute-subacute liver failure, Andrade disease, polycystic disease, Budd-Chiari and primary non-function.

The Model for End-Stage Liver Disease (MELD) score was significantly higher in the DBD group, while cirrhosis was predominant in the cDCD group (Table 1). Baseline MCF Extem was lower in the cDCD group. Baseline fibrinolysis was present in 3% of patients with a baseline thromboelastogram. Tranexamic acid was administered during surgery in 235 patients (40%) with no between-group significant differences.

**Table 1**
Demographic, baseline and outcome data in all patients.

| | DBD, n = 447 | cDCD, n = 144 | p |
|---|---|---|---|
| Age years | 59(53–64) | 59(53–64) | 0.38 |
| Sex, male (%) | 313(70) | 108 (75) | 0.14 |
| MELD | 15(10–20) | 13(10–18) | 0.038 |
| Cirrhosis/others (%) | 36/64 | 53/47 | 0.002 |
| Comorbidity (%) | | | 0.428 |
| Cardiovascular[a] | 18 | 16 | |
| HPS-POPH | 10 | 12 | |
| COPD | 5 | 7 | |
| Previous abdominal surgery (%) | 12 | 15 | 0.176 |
| Portal vein thrombosis (%) | 14 | 12 | 0.138 |
| Donor data | | | |
| Age | 57(47–70) | 60(51–72) | 0.345 |
| Sex, male (%) | 236(53) | 79(55) | 0.425 |
| BMI | 26(24–28) | 23(23–29) | 0.625 |
| Cause of death (%) | | | 0.531 |
| Anoxia | 16 | 18 | |
| CT | 14 | 12 | |
| CVA | 62 | 70 | |
| Perfusion time, min | – | 95(73–127) | |
| Hemoglobin g/L | 11.2 (9.5–13.4) | 11.3 (9.5–13.5) | 0.444 |
| Baseline MCF Extem, mm[b] | n = 369<br>55(46–61) | n = 132<br>51(44–59) | 0.005 |
| Cold Ischemia time, (minutes) | 345(285–407) | 330(275–383) | 0.091 |
| RBC %, 95% CI | 63 (59–67) | 61(53–69) | 0.693 |
| RBC, units [c] | 4.7 (0.2) | 5.5 (0.4) | 0.112 |
| MT %, 95% CI | 17(14–20) | 25(18–32) | 0.038 |
| PRS %, 95% CI | 27 (23–31) | 33 (26–40) | 0.170 |
| Tranexamic %, 95% CI | 39(35–43) | 42(34–50) | 0.494 |
| 1-year patient survival %, 95% CI | 91(88–93) | 92(88–96) | 0.734 |
| 1-year graft survival %, 95% CI | 89(86–93) | 90(85–95) | 1.000 |

BMI: body mass index; DBD: donor after brain death, CVA: cardiovascular accident. cDCD: donor after circulatory death; CT: cranial trauma; HPS: hepatopulmonary syndrome; POPH: portopulmonary hypertension; RBC: red blood cells; MELD: Model for End-Stage Liver Disease score. Data are expressed as median and range or median and IQ (25–75%). MT: massive transfusion.

[a] Cardiovascular: arterial hypertension, coronary disease, diabetes mellitus, obesity.

[b] In 90 patients (88 in the DBD group and 10 in the cDCD group), baseline MCF Extem was not available.

[c] In transfused patients.

Ischemia time was non-significantly longer in DBD grafts. RBC transfusion was 2% lower in the cDCD group. Similarly, there were no between-group differences in the number of RBC units administered. PRS occurred in 122 patients (27%) in the DBD group and 48 patients (33%) in the cDCD group.

Transfusion episodes are shown in Table 2. The mean of RBC units transfused was similar in the two groups, but MT was more common in cDCD recipients. Outliers (>10 RBC units) were similar in the two groups.

Major hemodynamic complications were observed in 52 patients (9%, 95% CI 7–11) and were similar between DBD and cDCD recipients: 8.5% and 9.7%, respectively (p = 0.61). The rate of major hemodynamic complications was 6% (95% CI 3–9) in non-transfused patients, 8% (95% CI 5–11) in patients transfused but not massively, and 18% (95% CI 16–20) in patients with MT (p = 0.004). Twenty-six patients (6%, 95% CI 4–8) died during admission for LT in the DBD group compared with 3 patients (2%. 95% CI 0–4), in the cDCD group (odds ratio 0.41 (95% CI 0.14–1.21).

When actuarial survival was plotted, there were no between-group differences in: one-year patient survival, DBD 91% (95%CI, 88–93) vs cDCD 92% (95%CI, 88–96), p = 0.734; and one-year graft survival, DBD 89% (95%CI, 86–93) vs cDCD 90% (95%CI, 85–95) (p = 1.00). (Fig. 1).

More cDCD recipients required MT than DBD recipients. MT was required in 76 patients (17%) in the DBD group and 36 patients (25%) in the cDCD group (p = 0.03) ((Supplemental Table 1)). cDCD patients had 10% more PRS. The requirement for tranexamic acid was 50% higher in cDCD recipients. Of the 76 patients requiring MT in the DBD group, major hemodynamic complications occurred in 18% (95% CI 14–21) vs 17% (95% CI 11–18) for the 36 patients with MT in the cDCD group. One-year patient survival was lower in DBD than cDCD massively transfused: 72% (95% CI 62–82) vs 89 (95% CI 79–99) p = 0.03 (Supplemental Table 1).

To overcome the bias due to a worse coagulation profile in cDCD recipients as reflected by the lower MCF, we created a matched sample of the two groups. Data from the resulting 231 patients (169 DBD and 62 cDCD) are shown in Table 3. No differences in baseline laboratory data, intraoperative use of red blood cells or one-year outcome data were observed between DBD and cDCD recipients.

To verify the non-inferiority of cDCD, a multivariate analysis was made in recipients of DBD and cDCD matched by the MCF. After including the most relevant variables, only RBC transfusion (> 6 RBC units) and major hemodynamic complications reached significance for one year patient survival (p = 0.000, OR 0.05 (0.01-0.25) and (p<0.000, OR 0.15(0.05-0.42)), respectively. Haemoglobin at baseline and recipient age reached significance for RBC transfusion (p<0.000, OR 0.55 (0.49-0.62) 0.55(0.49-0.62) and p = 0.02, OR 1.05 (1.00-1.10), respectively. (Table 4).

## 4. Discussion

The results of this large, multicenter series show that there were no

**Table 2**
Transfusion episodes DBD and cDCD liver transplant recipients.

| RBC (Unit) | DBD n = 447 | cDCD n = 144 | p |
|---|---|---|---|
| 0 | 165 (37%) | 56 (39%) | 0.693 |
| 1 | 29 (6.5%) | 3 (2%) | |
| 2 | 68 (15%) | 16 (11%) | |
| 3 | 33 (7%) | 12 (8%) | |
| 4 | 50 (11%) | 14 (10%) | |
| 5 | 26 (6%) | 7 (5%) | |
| (≥6 | 76 (17%%) | 36 (25%) | 0.038 |
| >10 | 18 (4%) | 11 (7.6%) | 0.11 |
| Mean and SE | 2.9 (0.19) | 3.3(0.33) | 0.29 |

DBD: donor after brain death, cDCD: controlled donor after circulatory death; RBC: red blood cells.

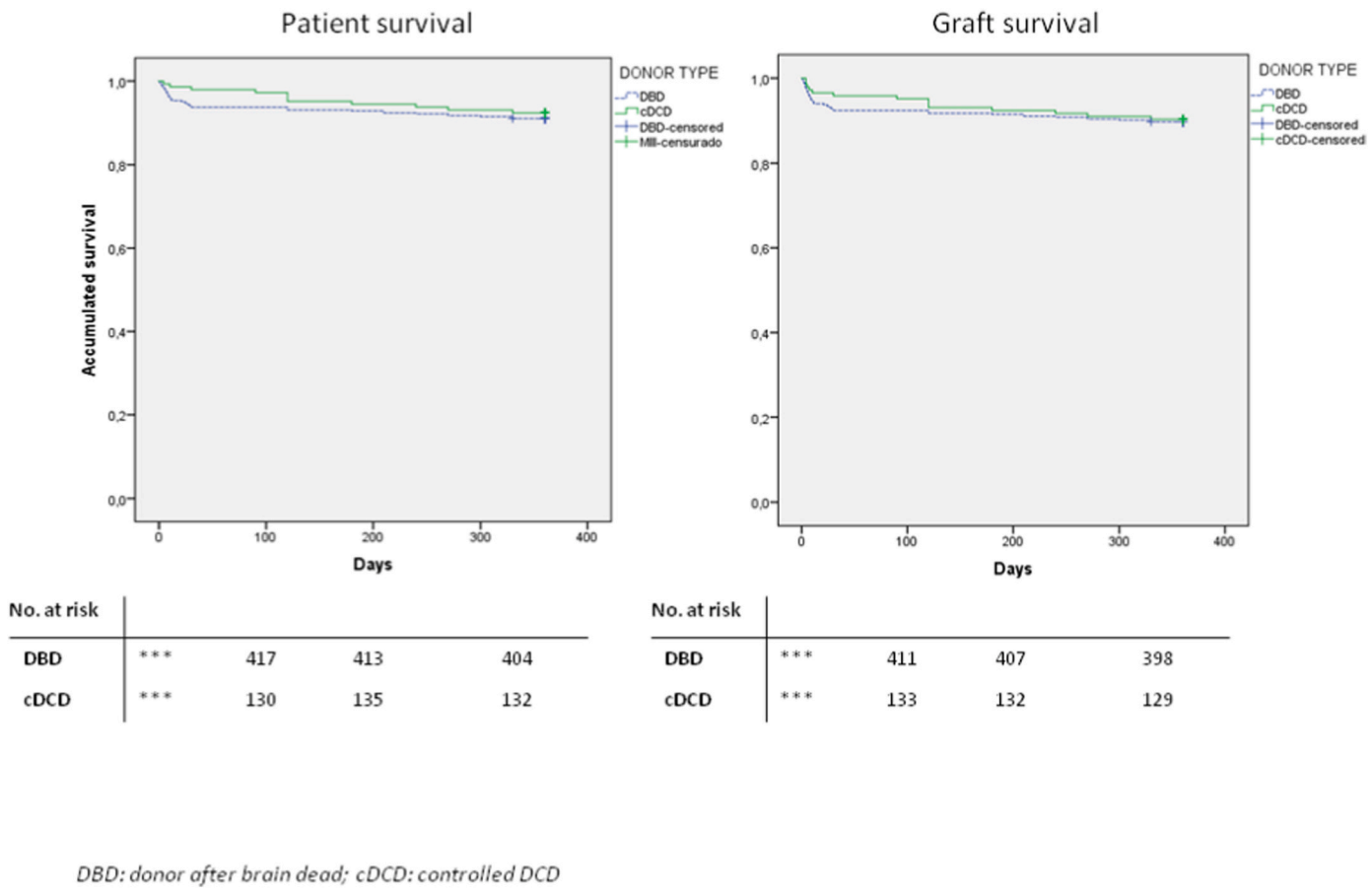


**Fig. 1.** Patient and graft survival according to donor type.

significant differences in the percentage of patients who received RBC, according to the type of donation (cDCD with NRP vs. DBD). We found that 39% of cDCD recipients received no RBC, and there were no differences with DBD recipients. One-year graft and patient survival were non-significantly higher in cDCD recipients. The greater frequency of MT in cDCD recipients disappeared after matching by the baseline coagulation profile. Therefore, our results suggest the non-inferiority of cDCD with NRP in comparison with DBD.

Our data confirm the results reported by Karangwa et al. [10] who found no differences between cDCD and DBD in RBC transfusion or fibrinolysis after reperfusion, suggesting that cDCD with NRP is a suitable alternative to DBD in the era of graft scarcity.

Differences in cDCD organ recovery between centers may have been limited due to a 2018 consensus of the Spanish Liver Transplantation Society that addressed issues related to cDCD liver evaluation, acceptance criteria, recovery, and recipient selection [5]. In addition, there were no differences in graft ischemia between groups, or between centers (data non shown). All centers use a thromboelastometry-based algorithm, which could compensate for variations in management between centers. The mean number of cases per center was >25, and no one center influenced the results (data not shown).

There were no differences in the transfusion rate of recipients of cDCD livers recovered with NRP compared with standard DBD liver recipients. This may be attributed to NRP, which restores near-physiological conditions and reduces histological changes associated with ischemia-reperfusion injury and endothelial inflammation, decreasing the release of tissue factor, as a coagulation cascade trigger [17].

Pre-operative anemia has been associated with higher rates of intra-operative blood transfusions [18], whereas the type of donor has not. We found no significant differences in the hemoglobin level between cDCD and DBD. Postoperative and one-year survival were similar in cDCD with NRP and DBD. There was a difference in the MELD score, which was higher in DBD recipients, but did not influence outcomes, since MELD has discriminative ability for the prediction of 90-day waitlist mortality, but only predicts postoperative mortality for values > 40 [19]; on the other hand, postoperative mortality in LT is related to preoperative immune dysfunction and sepsis, age, and cardiac risk.

In our series, MT influenced mortality, mostly in DBD recipients. A study found that transfusion of >11 RBC units was associated with heart failure and mortality [20]. In our series, transfusion of >10 RBC units occurred in a very small percentage of patients so its influence on mortality could not be assessed.

A cohort study of simultaneous kidney and liver transplantation from cDCD donors found liver-kidney graft and patient one-year survival rates were similar to DBD donors, although a higher incidence of biliary complications was observed in cDCD recipients [21]. In a cohort of cDCD and DBD recipients, after adjustments for preoperative and pre-reperfusion risks via propensity matching, cDCD grafts remained a risk factor for post-reperfusion hyperkalemia and PRS [22]. In a large series comparing cDCD with DBD recipients, the incidence of PRS, arrhythmia requiring cardiopulmonary resuscitation, and treatments for hyperkalemia were similar, but a significant increase in total intra-operative and post-reperfusion blood products was reported [23]. The same authors studied the influence of moderate steatosis of the liver after circulatory death donation, and concluded that higher rates of PRS, cardiac arrest, and RBC and fresh frozen plasma transfusions were related to steatosis [23].

The main difference with these studies is that we used NRP. In our series, all cDCD grafts were obtained after normothermic perfusion and major hemodynamic disturbances were observed in only 9% of patients, with similar results in the two cohorts, suggesting that NRP cDCD livers

**Table 3**
Demographic, baseline and outcome data of patients matched by MCF Extem.

| | DBD, n = 169 | cDCD, n = 62 | p |
|---|---|---|---|
| Age years | 60(54–64) | 56(52–63) | 0.313 |
| Sex, male (%) | 112(66) | 47(76) | 0.200 |
| MELD | 15(10–19) | 12(10–15) | 0.051 |
| Cirrhosis/others (%) | 64/35 | 69/31 | 0.534 |
| Hemoglobin g/L | 11.6 (9.5–13.5) | 11.3 (9.5–13.5) | 0.286 |
| Comorbidity (%) | | | 0.594 |
| Cardiovascular[a] | 12 | 10 | |
| HPS-POPH | 6 | 8 | |
| COPD | 4 | 3 | |
| Previous abdominal surgery (%) | 15 | 12 | 0.810 |
| Portal vein thrombosis (%) | 15 | 10 | 0.687 |
| Donor data | | | |
| Age | 55(47–69) | 61(51–73) | 0.413 |
| Sex, male (%) | 91(54) | 37(60) | 0.825 |
| BMI | 26(23–27) | 26(24–31) | 0.305 |
| Cause of death (%) | | | 0.115 |
| Anoxia | 18 | 20 | |
| CT | 17 | 12 | |
| CVA | 65 | 68 | |
| Perfusion time, min | – | 94(65–130) | |
| Baseline MCF Extem, mm[a] | n = 169 | n = 62 | 0.154 |
| | 54(52–58) | 54(49–57) | |
| Cold ischemia time, (minutes) | 322(280–392) | 326(279–367) | 0.408 |
| RBC %, 95% CI | 60 (53–67) | 53(41–65) | 0.452 |
| RBC, units [b] | 4.4 (0.5) | 5.2 (0.6) | 0.692 |
| MT %, 95% CI | 12(7–17) | 19(10–28) | 0.196 |
| PRS %, 95% CI | 31 (24–38) | 34 (23–45) | 0.750 |
| Tranexamic %, 95% CI | 40(33–47) | 42(30–54) | 0.880 |
| 1-year patient survival %, 95% CI | 92(88–96) | 90(83–97) | 0.600 |
| 1-year graft survival %,95% CI | 90(86–94) | 90(83–97) | 1.000 |

BMI: body mass index; DBD: donor after brain death, CVA: cardiovascular accident. cDCD: donor after circulatory death; CT: cranial trauma; HPS: hepatopulmonary syndrome; POPH: portopulmonary hypertension; RBC: red blood cells; MELD: Model for End-Stage Liver Disease score. Data are expressed as median and range or median and IQ (25–75%). MT: massive transfusion.
**In 90 patients (88 in the DBD group and 10 in the cDCD group), baseline MCF Extem was not available.
[a] Cardiovascular: arterial hypertension, coronary disease, diabetes mellitus, obesity.
[b] In transfused patients.

**Table 4**
Multivariate analysis to identify variables associated with one-year patient survival and RBC transfusion.

| One year patient survival | | | |
|---|---|---|---|
| Variables | Odds Ratio | 95% CI | P value |
| MELD | 0.92 | 0.83–1.02 | 0.114 |
| Age (years) | 0.94 | 0.83–1.07 | 0.369 |
| Sex | 0.41 | 0.70–2.49 | 0.339 |
| Type of donor | 1.62 | 0.18–14 | 0.660 |
| CIT (min) | 0.99 | 0.98–1.00 | 0.144 |
| Major hemodynamic complications | 0.98 | 0.04–23 | 0.994 |
| RBC transfusion (>6 RBC units) | 0.04 | 0.01–0.35 | 0.003 |
| RBC transfusion | | | |
| Variables | Odds Ratio | 95% CI | P value |
| MELD | 1.06 | 0.99–1.14 | 0.077 |
| Age | 1.05 | 1.00–1.10 | 0.028 |
| Sex | 2.48 | 0.98–6.24 | 0.053 |
| Type of donor | 1.33 | 0.54–3.28 | 0.525 |
| CIT (min) | 1.00 | 0.99–1.00 | 0.156 |
| Major hemodynamic complications | 12.56 | 0.93–168 | 0.060 |
| Hemoglobin baseline (g/L) | 0.64 | 0.52–0.78 | 0.000 |

CIT:Cold ischemia time. RBC: Red blood cell transfusion.

may behave more like DBD livers in terms of reperfusion [24].

The main limitation of the study is the retrospective nature of the data. For this reason, only non-confounding data were collected, such as RBC transfusion and outcomes. Homogeneity was assured because only centers with a thromboelastometry-based algorithm were included in the analysis and all centers used normothermic perfusion to obtain the graft.

## 5. Conclusion

In summary, in a recent, large series of consecutive LT in 10 centers, non-inferiority of cDCD with NRP grafts to DBD grafts was demonstrated with respect to RBC transfusion, post reperfusion syndrome and post-operative one-year patient and graft survival. Therefore, not specific intraoperative management seems to be required in them. This study suggests that cDCD with NRP is safe and improves the imbalance between organ donors and the ever-growing demand.

## Provenance and peer review

Not commissioned, externally peer reviewed.

## Ethic approval

The Ethics Research Committee of the Hospital Clinic of Barcelona approved the study (HCB/2019/1160).

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None.

## Authorship

- A. Sabaté, A. Blasi and L Viguera: Concept and design, data collection, data analysis and interpretation, manuscript writing and final approval of the manuscript.
- E. Reverter: data analysis and interpretation. Final approval of the manuscript.
- B. Arjona, M. Caballero, I. Chocron, C. García-Palenciano, R. Gutierrez, MJ. Martin, J. Pérez-Peña, J. Pitera, and I. Zarragoikoetxea: Data collection and interpretation. Final approval of the manuscript.

## Trial registry number

1. Name of the registry: ClinicalTrials.gov
2. Unique Identifying number or registration ID: NCT04945135
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/ct2/show/NCT04945135?id=NCT04945135&draw=2&rank=1

## Guarantor

Annabel Blasi.
Antoni Sabté.

## Data statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## CRediT authorship contribution statement

Laura Viguera: Formal analysis, Writing – original draft, designed the study, analyzsed the data, wrote the paper and drew up the final manuscript. Annabel Blasi: Formal analysis, Writing – original draft, designed the study, analyzsed the data, wrote the paper and drew up the final manuscript. Enric Reverter: Formal analysis, performed specific

data analysis. Begoña Arjona: Conceptualization, Funding acquisition, Formal analysis, Writing – original draft, contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published. Marta Caballero: Conceptualization, Funding acquisition, Formal analysis, Writing – original draft, contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published. 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## Declaration of competing interest

None.

## Appendix A. Supplementary data

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