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Original Article

Outcomes of lung and liver transplantation after simultaneous recovery using abdominal normothermic regional perfusion in donors after the circulatory determination of death versus donors after brain death

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ABSTRACT

Normothermic regional perfusion (NRP) in controlled donation after the circulatory determination of death (cDCD) is a growing preservation technique for abdominal organs that coexists with the rapid recovery of lungs. We aimed to describe the outcomes of lung

Abbreviations: cDCD, controlled donation after circulatory death; DBD, donation after brain death; ECMO, extracorporeal membrane oxygenation; FWIT, functional warm ischemic time; IQR, interquartile range; ISHLT, International Heart and Lung Transplantation Society; NRP, normothermic regional perfusion; LuTx, lung transplantation; LiTx, liver transplantation; PGD, primary graft dysfunction; PNF, primary nonfunction; RR, rapid recovery.

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donation after circulatory death
normothermic regional perfusion
donation after brain death
rapid recovery

transplantation (LuTx) and liver transplantation (LiTx) when both grafts are simultaneously recovered from cDCD donors using NRP and compare them with grafts recovered from donation after brain death (DBD) donors. All LuTx and LiTx meeting these criteria during January 2015 to December 2020 in Spain were included in the study. Simultaneous recovery of lungs and livers was undertaken in 227 (17%) donors after cDCD with NRP and 1879 (21%) DBD donors ($P < .001$). Primary graft dysfunction grade-3 within the first 72 hours was similar in both LuTx groups (14.7% cDCD vs. 10.5% DBD; $P = .139$). LuTx survival at 1 and 3 years was 79.9% and 66.4% in cDCD vs. 81.9% and 69.7% in DBD ($P = .403$). The incidence of primary nonfunction and ischemic cholangiopathy was similar in both LiTx groups. Graft survival at 1 and 3 years was 89.7% and 80.8% in cDCD vs. 88.2% and 82.1% in DBD LiTx ($P = .669$). In conclusion, the simultaneous rapid recovery of lungs and preservation of abdominal organs with NRP in cDCD donors is feasible and offers similar outcomes in both LuTx and LiTx recipients to transplants using DBD grafts.

1. Introduction

Donors after the neurological determination of death, also known as donation after brain death (DBD) donors, are the most frequent type of deceased organ donors and currently represent the gold standard for comparison. However, controlled donation after the circulatory determination of death (cDCD) has become an established strategy for increasing the donor pool in an important number of countries.[1,2] In the cDCD scenario, the rapid recovery (RR) of lungs and abdominal grafts is the conventional approach. Outcomes of lung transplantation (LuTx) using grafts from cDCD donors have been reported to not differ substantially from those obtained with grafts from DBD donors.[3,4] In contrast, the RR of cDCD liver transplantation (LiTx) has been associated with acceptable outcomes, though with an increased risk of graft loss, primary graft dysfunction (PGD), and biliary complications compared with DBD livers.[5-10] In recent years, normothermic regional perfusion (NRP) of abdominal organs has emerged as an in situ preservation strategy capable of improving the results of cDCD LiTx.[11-16]

In Spain, NRP has become a generalized technique for the in situ preservation and recovery of abdominal organs in cDCD.[17] In parallel, the transplantation of lungs obtained from cDCD donors has increased 13-fold from 2015 to 2019.[18] The RR of lungs when abdominal NRP is applied is a challenging and complex procedure. Although the benefits of NRP on the outcomes of abdominal organs are well established, there is limited information on its impact on the quality of cDCD donor lungs.[19,20] It is also questionable whether lung recovery may negatively affect the outcomes of livers obtained from cDCD donors subject to NRP.

The aim of this study is to describe the outcomes of LuTx and LiTx when both lungs and liver are simultaneously recovered from cDCD donors and NRP is used and compare them with the gold standard, DBD donors.

2. Patients and Methods

2.1. Study design

This is multicenter, nationwide, retrospective, observational cohort study. All cDCD donors managed with the NRP technique and all DBD donors in whom both lungs and liver grafts were recovered during January 2015 to December 2020 in Spain were included in the analysis. Information on donor characteristics, utilization of organs, baseline recipient features and posttransplant outcomes were obtained from the Spanish National Registry on Donation and Transplantation and the Spanish National Lung and Liver Transplant Registries.

2.2. Selection criteria of lungs and livers from cDCD donors

Selection criteria for cDCD and DBD donor lungs are essentially the same. Lungs are considered suitable for transplantation if there is no evidence of parenchyma consolidation, recurrent purulent secretions, macroscopic signs of emphysema or large bullae, presence of suspicious nodules (which would require frozen histologic confirmation), or if the partial pressure of oxygen in arterial blood/fraction of inspired oxygen is below 300 mmHg with a positive end expiratory pressure value of 5 cmH_2O.

Selection criteria for cDCD livers are similar to those applicable to DBD and are based on macroscopic appearance and absence of irregular perfusion/ischemic areas, fibrosis, or steatosis >30% in pathology. As an exception, an upper age limit of 70 to 75 years is applied to cDCD but not to DBD livers.

2.3. Description of the organ recovery technique in cDCD with abdominal NRP

The preparation, management and operative approach in cDCD when abdominal NRP is used has been described

elsewhere.[21-23] Briefly, peripheral femoral cannulation is performed percutaneously or surgically after heparin administration (500-600 units/kg). Through the contralateral femoral artery, an occlusive balloon is placed in the descending aorta that is inflated once death is declared and before the initiation of NRP, aiming to prevent cerebral perfusion during NRP. To ensure the thoracic aorta is properly blocked, 2 arterial lines (one from the femoral arterial cannula and the other from the left radial artery) are monitored during the procedure, as previously published.[21-23]

The withdrawal of life-sustaining therapies usually takes place in the operating theater or in a hospital ward close to the operating room. Death is declared respecting a no-touch period of at least 5 minutes. NRP is initiated after the determination of death. The donor is reintubated and ventilated with 50% oxygen at tidal volume of 7 mL/kg ideal body weight and a positive end expiratory pressure value of 5 cmH_20. A median sternotomy is performed simultaneously. In order to avoid low blood flow in the pump due to the absence of venous return from the thorax and cranium, the cDCD donor receives 1 to 1.5 L of serum saline immediately before the vena cava ligation. For lung perfusion, the preservation solution (50-60 mL/kg) is infused through the pulmonary artery, and the left atrial appendage is opened for drainage. Both pleurae are opened, and the lung grafts are checked for macroscopic evaluation. Lung graft recovery is then carried out after heart removal in a standard fashion. Special care has to be taken with hemostasis in order to prevent any unnecessary blood loss. The azygos vein is ligated for the same reason.

During NRP, the pump flow is maintained at 2 to 2.4 L/min. Target parameters are: continuous pressure of 60 to 65 mmHg in the femoral artery cannula, body temperature 37°C, pH 7.35 to 7.45, and hematocrit >25%. Blood units are transfused if required. NRP is maintained for 90 to 120 minutes.

In order to assess liver ischemic injury, blood samples from the extracorporeal membrane oxygenation (ECMO) device are immediately taken after starting NRP and at least every 30 minutes. Biochemistry, serum lactate levels, and hematocrit are analyzed. If alanine transaminase or aspartate transaminase values are over 4 times their upper normal limits during NRP, the liver is discarded for clinical use, even with a normal macroscopic appearance. The liver recovery technique does not differ from that in the DBD setting.

2.4. Postoperative course

For LuTx recipients, the immunosuppression regimen is standardized in all centers and is based on the combination of one anticalcineurin drug (ideally tacrolimus, cyclosporine as second choice), one antimetabolite (mofetil mycophenolate), and steroids. As induction therapy, the most common drug is basiliximab (first dose at day 1, and second dose at day 4).

The immunosuppression protocol used in LiTx is also based on the combination of an anticalcineurin drug (tacrolimus), steroids, and one antimetabolite (mofetil mycophenolate) on patients with postoperative renal dysfunction. Patients with renal impairment before liver transplantation receive induction therapy with basiliximab (1 or 2 doses).

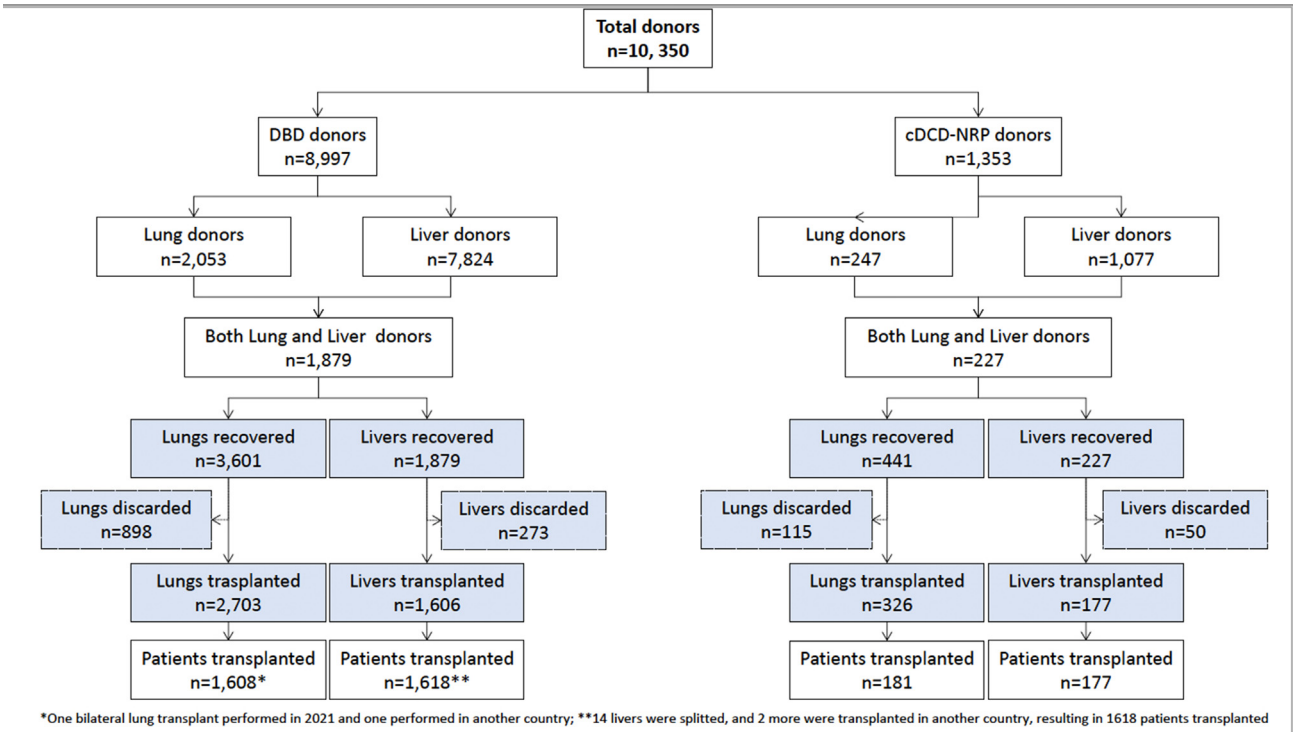


Figure 1. Study flowchart. cDCD-NRP, controlled donation after the circulatory determination of death, subject to normothermic regional perfusion; DBD, donation after brain death.

2.5. Definition of variables

PGD in LuTx is defined according to the 2005 International Heart and Lung Transplantation Society (ISHLT) consensus statement[24] for LuTx performed from 2015 to 2017. The definition of PGD applied to procedures performed from 2018 to 2020 is based on the ISHLT consensus statement released in 2017.[25]

Primary nonfunction (PNF) in LiTx is defined as an immediate graft failure resulting in either emergent retransplantation or death. The diagnosis of ischemic-type biliary lesions in the posttransplant period is based on the presence of non-anastomotic biliary strictures, with or without the need for prestenotic dilatations, in the presence of a patent hepatic artery.

Functional warm ischemic time (FWIT) in cDCD donors is defined as the time between systolic blood pressure below 60 mmHg and the initiation of target organ perfusion. In the case of lung grafts, this last time point is set when the preservation solution is infused through the pulmonary artery, and the accepted time limit for declining the organ is 90 minutes. With regards to the liver, the FWIT finishes when NRP is commenced. The upper limit for FWIT in livers is set at 30 minutes.

We define utilization rate as the proportion of grafts transplanted from the total of organs recovered.

2.6. Statistical analysis

Qualitative variables are represented as frequencies and percentages, and quantitative variables by the mean and standard deviation or the median and interquartile range (IQR), depending on the dispersion of the sample. Group comparisons were made using the Mann-Whitney U test or the median test for quantitative variables, as appropriate, and by the chi-squared test for qualitative variables.

Kaplan-Meier curves were used for 1- and 3-year patient survival (lung) and noncensored for death graft survival (liver), with log-rank tests for comparisons.

Table 1
Demographic characteristics of donors from whom lungs and liver were simultaneously recovered, by donor type (n = 2106).

		DBD donors (n = 1879)		cDCD-NRP donors (n = 227)		*P*
Donor characteristics						
Sex (male), n (%)		927	(49.3%)	133	(58.6%)	.008
Age (y), mean (SD)		52.8	(15.2)	54.4	(12.7)	.317
Age >60 y, n (%)		627	(33.4%)	75	(33.0%)	.921
Age >70 y, n (%)		175	(9.3%)	14	(6.2%)	.117
Smoking history, n (%)		702	(39.2%)	78	(37.1%)	.564
Arterial hypertension, n (%)		687	(38.0%)	84	(40.2%)	.537
Diabetes mellitus, n (%)		181	(10.6%)	34	(17.4%)	.004
Cause of death, n (%)						
Brain hemorrhage		1350	(71.8%)	125	(55.1%)	<.001
Anoxic brain injury		125	(6.7%)	63	(27.8%)	
Traumatic brain injury		329	(17.5%)	19	(8.4%)	
Other		75	(4.0%)	20	(8.8%)	
Mechanical ventilation (d), median (IQR)		1.8	(1.5-3.5)	7.4	(3.7-11.9)	<.001
Last PaO_2/FiO_2, median (IQR)		441	(385-500)	429	(366-492)	.318
Times in cDCD						
WLST-CA (min), median (IQR)				12	(8-17)	
Liver	Total WIT (min), median (IQR)			19	(14-25)	
	Functional WIT (min), median (IQR)			12	(9-18)	
Lungs	Total WIT (min), median (IQR)			33	(25-45)	
	Functional WIT (min), median (IQR)			27	(20-38)	
NRP duration (min), median (IQR)				77	(50-112)	

CA, cardiac arrest; DBD, donors after brain death; cDCD-NRP, controlled donors after the circulatory determination of death, subject to normothermic regional perfusion; IQR, interquartile range; PaO_2/FiO_2, partial pressure of oxygen in arterial blood/fraction of inspired oxygen; WIT, warm ischemic time; WLST, withdraw of life-sustaining therapies.
Missing values (DBD/cDCD-NRP): Smoking history (88/17); arterial hypertension (71/18); diabetes mellitus (168/32); mechanical ventilation (158/30); last PaO_2/FiO_2 (82/22); total and functional WIT for cDCD livers (2); total and functional WIT for cDCD lungs (44); NRP duration (14).

2.7. Ethical statement

The project was approved by the Institutional Review Board of the Hospital Universitario Puerta de Hierro-Majadahonda and conducted in compliance with the principles of the Declaration of Helsinki.

3. Results

From January 2015 to December 2020, at least one organ was recovered for transplantation from 8997 DBD donors and 1353 cDCD donors subject to abdominal NRP. The simultaneous recovery of lungs and livers was undertaken in 1879

Table 2
Liver and lung grafts offered, recovered and transplanted, by donor type.

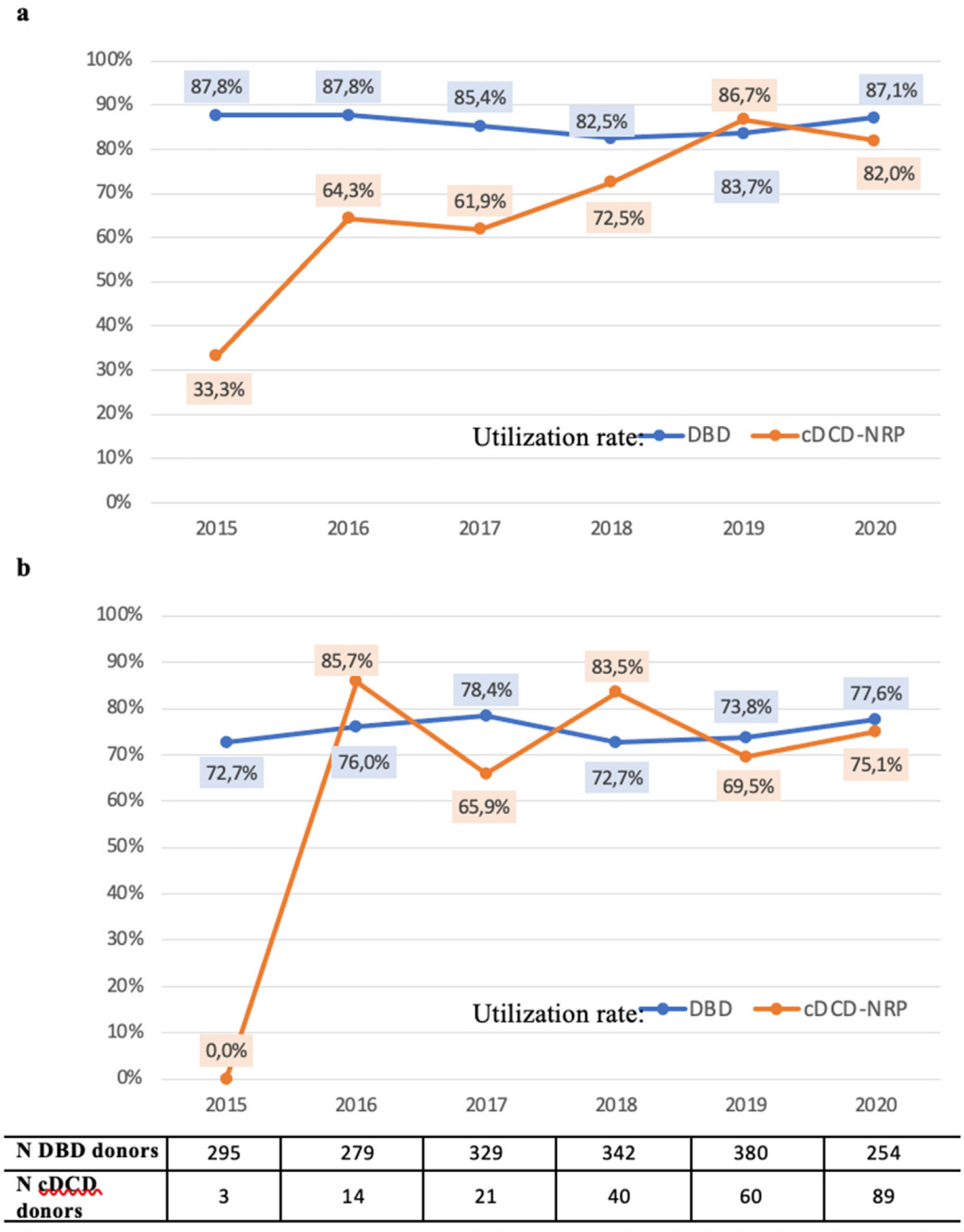
	DBD donors (N = 1879)		cDCD-NRP donors (N = 227)		*P*
Utilized liver donors	1606	(85.5%)	177	(78.0%)	.003
Liver grafts recovered	**1879**		**227**		
Liver grafts transplanted	1606	(85.5%)	177	(78.0%)	.003
Liver grafts discarded	**N = 273**		**N = 50**		
Steatosis	86	(31.5%)	7	(14.0%)	
Macroscopic appearance	50	(18.3%)	10	(20.0%)	
Irregular perfusion/ischemia	25	(9.2%)	14	(28.0%)	
Tumor in other organs	28	(10.3%)	4	(8.0%)	
Cirrhosis	22	(8.1%)	2	(4.0%)	
Pathologic tissue (biopsy)	18	(6.6%)	2	(4.0%)	
Ateromathosis	13	(4.8%)	1	(2.0%)	
Surgical problems	10	(3.7%)	4	(8.0%)	
Fibrosis	6	(2.2%)	2	(4.0%)	
Tumor in the graft	7	(2.6%)	0	(0.0%)	
Other	8	(2.9%)	4	(8.0%)	
Utilized lung donors	**1456**	**(77.5%)**	**172**	**(75.8%)**	**.560**
Lung grafts recovered	**3601**		**441**		
Lung grafts transplanted	2703	(75.1%)	326	(73.9%)	.602
Lung grafts discarded	**N = 898**		**N = 115**		
Macroscopic appearance	332	(37.0%)	56	(48.7%)	
P/F ratio < 300 mmHg	147	(16.4%)	14	(12.2%)	
Pathologic tissue (biopsy)	116	(12.9%)	5	(4.3%)	
Medical history	65	(7.2%)	11	(9.6%)	
Other	59	(6.6%)	12	(10.4%)	
Contusion	30	(3.3%)	2	(1.7%)	
Tumor in other organs	38	(4.2%)	3	(2.6%)	
Tumor in the graft	31	(3.5%)	3	(2.6%)	
Recipient surgical or logistic problems	31	(3.5%)	0	-	
Irregular perfusion/ischemia	15	(1.7%)	7	(6.1%)	
Recovery surgical problems	19	(2.1%)	2	(1.7%)	
Long ischemia time	6	(0.7%)	0	-	
Anatomical problems	5	(0.6%)	0	-	
Logistic problems	4	(0.4%)	0	-	

cDCD-NRP, controlled donation after the circulatory determination of death subject to normothermic regional perfusion; DBD, donation after brain death; P/F, partial pressure of oxygen in arterial blood/fraction of inspired oxygen.

(21%) DBD donors and in 227 (17%) cDCD donors subject to abdominal NRP ($P < .001$). A flow chart is displayed in Figure 1.

Demographic and clinical characteristics of donors in whom a simultaneous recovery of lungs and livers was undertaken are displayed in Table 1. Compared with DBD donors, cDCD donors were more frequently male (58.6% vs. 49.3%; $P = .008$) and diabetic (17.4% vs. 10.6%; $P = .004$) and had more frequently passed away as a result of an anoxic brain injury (27.8% vs. 6.7%; $P < .001$). The median duration of mechanical ventilation was also significantly longer in cDCD donors (7.4 [IQR, 3.7-11.9] vs. 1.8 [IQR, 1.5-3.5] days; $P < .001$).

Statistically significant differences were found in the percentage of livers recovered that were used for transplantation between cDCD and DBD donors (78% vs. 85.5%; $P = .003$). However, the percentage of lung grafts recovered that were transplanted was similar between the 2 groups (73.9% vs 75.1%; $P = .602$). In the cDCD cohort, 172 lungs out of the 227 donors (75.8%) were transplanted when the liver was also recovered. Table 2 summarizes the reasons for discarding



N DBD donors	295	279	329	342	380	254
N cDCD donors	3	14	21	40	60	89

Figure 2. Evolution of the utilization rate for liver (a) and lung (b) grafts from 2015 to 2020. cDCD-NRP, controlled donation after the circulatory determination of death, subject to normothermic regional perfusion; DBD, donation after brain death.

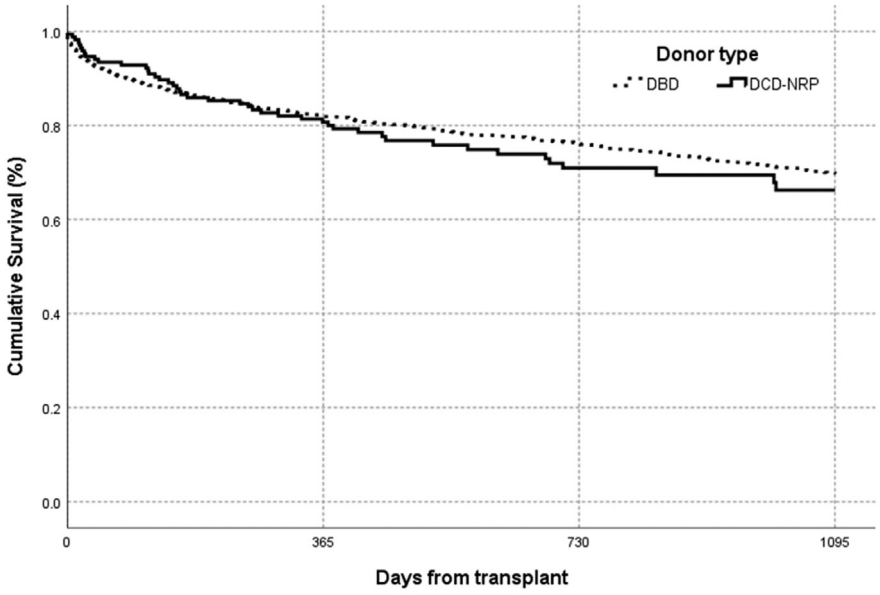
livers and lungs recovered. Notably, there was no documented technical problem in lung procurement that affected liver recovery and vice versa. Utilization rates of livers and lungs over the years are displayed in Figure 2.

In total, 181 LuTx were performed with organs obtained from cDCD donors subject to NRP and 1606 LuTx with organs obtained from DBD donors. Demographic and clinical features of LuTx recipients are represented in Table 3, with no differences between the groups, apart from a more frequent use of statins (28.1% vs 16.4%; $P = .017$) and bilateral transplants (80.1% vs. 67.2%; $P = .001$) in recipients of cDCD lungs. Five cases in the cDCD-NRP cohort were evaluated using ex vivo lung perfusion and further transplanted. In terms of development of PGD grade 3 during the first 72 hours, there was no statistically significant difference between the groups (14.7% in cDCD vs. 10.5% in DBD; $P = .139$). Mortality at 30 days did not show significant differences either (5.6% in cDCD vs. 6.3% in DBD; $P = .502$). Patient survival at 1 and 3 years was 79.9% and 66.4% in the cDCD group, compared with 82.0% and 69.7% in the DBD group, respectively ($P = .403$) (Fig. 3). When the early (2017) vs. the latest (2020) experience was analyzed, we found no significant differences in 1-month and

Table 3
Characteristics of lung transplant recipients and variables related to the procedure, by donor type.

	Global (N = 1787)		DBD donors (N = 1606)		cDCD-NRP donors (N = 181)		*P*
Sex (male), n (%)	1135	(63.5%)	1009	(62.8%)	126	(69.6%)	.072
Age (y), mean (SD)	53.4	(13.0)	53.4	(13.0)	54.3	(12.4)	.368
Age >60 years, n (%)	738	(41.3%)	656	(40.8%)	82	(45.3%)	.248
BMI, mean (SD)	24.8	(4.5)	24.8	(4.5)	24.9	(4.3)	.549
Cause of transplant, n (%)							
Emphysema/COPD/AATD	622	(34.8%)	553	(34.4%)	69	(38.1%)	.921
Diffuse interstitial pulmonary disease	690	(38.6%)	625	(38.9%)	65	(35.9%)	
Cystic fibrosis/bronchiectasis	201	(11.2%)	180	(11.2%)	21	(11.6%)	
Primary pulmonary arterial	96	(5.4%)	88	(5.5%)	8	(4.4%)	
hypertension+ venoocclusive disease							
Retransplant	55	(3.1%)	49	(3.1%)	6	(3.3%)	
Other	123	(6.9%)	111	(6.9%)	12	(6.6%)	
Pulmonary arterial hypertension, n (%)	102	(5.7%)	94	(5.9%)	8	(4.4%)	.431
Smoking history, n (%)	627	(68.8%)	547	(68.0%)	80	(75.5%)	.101
Alcohol history, n (%)	58	(8.6%)	48	(8.1%)	10	(13.0%)	.147
Arterial hypertension, n (%)	156	(17.4%)	141	(17.3%)	15	(19.0%)	.702
Diabetes mellitus, n (%)	77	(8.7%)	66	(8.2%)	11	(14.1%)	.078
Use of statins, n (%)	133	(17.3%)	115	(16.4%)	18	(28.1%)	.017
Transplant type, n (%)							
Unilateral	549	(30.7%)	513	(31.9%)	36	(19.9%)	
Bilateral	1224	(68.5%)	1079	(67.2%)	145	(80.1%)	.001
Heart-Lung	14	(0.9%)	14	(0.9%)	-		
Urgent transplant, n (%)	197	(11.0%)	179	(11.1%)	18	(9.9%)	.625
Cold ischemic time >6 h, n (%)	557	(41.1%)	487	(40.2%)	70	(48.3%)	.063
Hospital stay (d), mean (IQR)	32	(23-49)	32	(23-50)	33	(23-45)	.793
Hospital stay >30 d, n (%)	785	(52.4%)	699	(52.2%)	86	(54.4%)	.596
Follow-up (d), median (IQR)	796	(375-1477)	863	(384-1493)	467	(276-1011)	<.001

AATD, alpha-1 antitrypsin deficiency; BMI, body mass index; cDCD-NRP, controlled donation after the circulatory determination of death subject to normothermic regional perfusion; COPD, chronic obstructive pulmonary disease; DBD, donation after brain death; IQR, interquartile range; PAH, pulmonary arterial hypertension; SD, standard deviation.
Missing values (DBD/cDCD-NRP): BMI (785/86); smoking history (801/75); alcohol history (1010/104); arterial hypertension (790/102); diabetes mellitus (802/103); use of statins (903/117); cold ischemic time (396/36); hospital stay (266/14).



	Survival probability (number at risk)		
	1 month	1 year	3 years
DBD (N=1579)	93.7 (N=1458)	82.0 (N=1222)	69.7 (N=696)
DCD-NRP (N=170)	94.4 (N=165)	79.9 (N=124)	66.4 (N=37)

Figure 3. Overall survival for LuTx with lungs from DBD and cDCD-NRP donors. DBD, donation after brain death; cDCD-NRP, controlled donation after the circulatory determination of death, subject to normothermic regional perfusion; LuTx, lung transplantation.

1-year survival between the 2 cohorts (Supplementary Material S1).

The number of LiTx performed was 177 from cDCD donors subject to NRP and 1618 from DBD donors. Demographic and clinical characteristics of LiTx recipients are displayed in Table 4. Incidence of early complications after LiTx did not show any statistically significant difference between recipients of cDCD vs. DBD organs in terms of PNF, ischemic-type biliary lesions, arterial thrombosis, or acute rejection (Table 5). No statistically significant difference was found in survival at 30 days (94.7% in cDCD vs. 94.2% in DBD; $P = .620$). Graft survival at 1 and 3 years was 89.7% and 80.8% in cDCD vs. 88.2% and 82.1% in DBD, respectively, with no statistically significant differences between the groups ($P = .669$) (Fig. 4). In the same line as for LuTx outcomes, the early and late experience did not show statistically significant differences in terms of overall survival (Supplementary Material S1).

We also analyzed the outcomes of LiTx recipients of grafts obtained from 240 cDCD donors subject to abdominal NRP during the study period, attending to whether lungs were simultaneously recovered or not (in 177 out of the 240 cDCD donors subject to NRP with simultaneous offer of the 2 types of organs, the lungs were recovered). No statistically significant differences were found between these 2 groups, neither in terms of post-transplant complications nor in survival at 1 and 3 years (Supplementary Material S2 and S3).

4. Discussion

One of the most important challenges in cDCD is to maximize organ utilization while ensuring appropriate outcomes after transplantation. LuTx using cDCD donor grafts leads to post-transplant results that are comparable to DBD and so do LiTx obtained from cDCD donors when NRP is used.[14-16] However, the simultaneous recovery of both grafts from cDCD donors when abdominal NRP is applied is hampered by its technical complexity. In addition, it can be argued that abdominal NRP may have a deleterious effect upon the quality of lungs and that lung recovery may negatively impact upon LiTx outcomes. Since the combination of the RR of lung grafts and abdominal NRP may become a more generalized technique in cDCD, we considered it highly pertinent to analyze the most relevant outcomes of both LuTx and LiTx when both types of grafts are obtained in this setting and compare them with the current gold standard, DBD. To the best of our knowledge, this study is the largest published to date that deepens these aspects. Though some preliminary experiences have shown the feasibility of this approach, the present multicenter, nationwide study reveals that this complex combined recover procedure can be normalized and become the standard, not just in highly selected centers.

The success of this particular recovery procedure relies on several crucial elements that concern a range of professionals, such as donor coordinators, staff managing the donor in the

Table 4
Characteristics of liver transplant recipients and variables related to the procedure, by donor type.

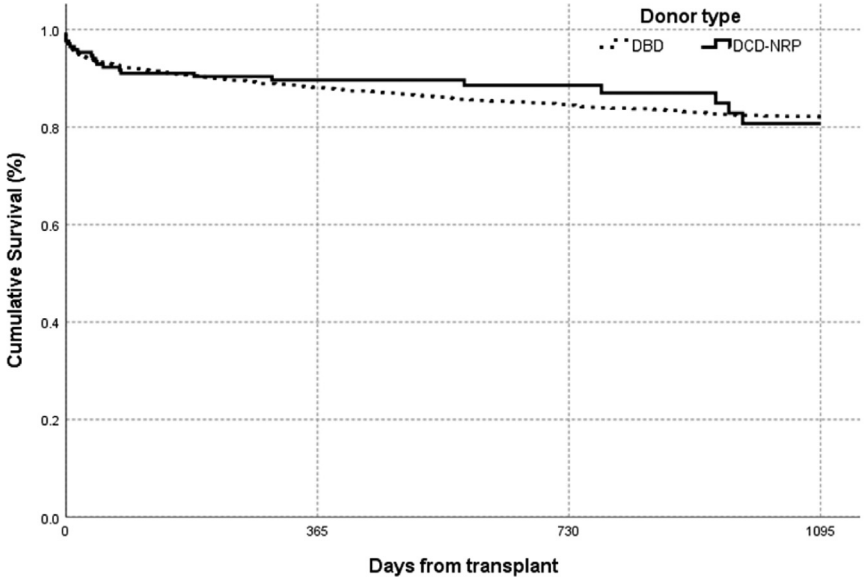
	GLOBAL (N = 1795)		DBD (N = 1618)		cDCD-NRP (N = 177)		*P*
Sex (male), n (%)	1263	(70.4%)	1132	(70.0%)	131	(74.0%)	.263
Age (y), mean (SD)	53.3	(14.2)	53.0	(14.6)	56.9	(10.0)	.002
Age >60 y, n (%)	690	(38.4%)	614	(37.9%)	76	(42.9%)	.195
Cause of transplant, n (%)							
Hepatocelular carcinoma	495	(27.6%)	432	(26.7%)	63	(35.6%)	<.001
Hepatocelular carcinoma + cirrhosis	462	(25.7%)	400	(24.7%)	62	(35.0%)	
Viral/alcoholic cirrhosis without carcinoma	616	(34.3%)	541	(33.4%)	75	(42.4%)	
Cirrhosis of other etiology	103	(5.7%)	89	(5.5%)	14	(7.9%)	
Other	285	(15.9%)	271	(16.7%)	14	(7.9%)	
Acute/subacute liver failure	106	(5.9%)	103	(6.4%)	3	(1.7%)	
Retransplant	190	(10.6%)	182	(11.2%)	8	(4.5%)	
HCV cirrhosis, n (%)	370	(20.6%)	325	(20.1%)	45	(25.4%)	.096
Alcohol cirrhosis, n (%)	646	(36.0%)	562	(34.7%)	84	(47.5%)	.001
Smoking history, n (%)	418	(56.6%)	343	(56.0%)	75	(60.0%)	.405
Alcohol history, n (%)	385	(51.1%)	307	(48.8%)	78	(62.4%)	.005
Hypertension, n (%)	201	(26.7%)	168	(26.7%)	33	(26.8%)	.970
Diabetes mellitus, n (%)	227	(28.4%)	199	(29.4%)	28	(22.8%)	.133
Transplant type, n (%)							
Whole liver	1643	(91.5%)	1477	(91.3%)	166	(93.8%)	
Split	30	(1.7%)	30	(1.9%)	0		.175
Combined	122	(6.8%)	111	(6.9%)	11	(6.2%)	
MELD score							
Mean (SD)	16.6	(7.8)	16.8	(7.9)	14.7	(7.2)	<.001
Median (IQR)	16	(10-21)	16	(10-21)	13	(9-19)	.005
MELD score ≥15, n (%)	781	(57.5%)	708	(59.1%)	73	(45.1%)	.001
Urgent transplant, n (%)	192	(10.7%)	185	(11.5%)	7	(4.0%)	.002
Cold ischemic time >6 h, n (%)	727	(43.9%)	668	(45.2%)	59	(33.3%)	.003
Follow-up (d), median (IQR)	920	(418-1556)	1003	(464-1612)	575	(230-935)	<.001

cDCD-NRP, controlled donation after the circulatory determination of death subject to normothermic regional perfusion; DBD, donation after brain death; HCV, hepatitis C virus; MELD, model for end-stage liver disease; IQR, interquartile range; SD, standard deviation.
Missing values (DBD/cDCD-NRP): smoking history (1005/52); alcohol history (989/52); hypertension (988/54); diabetes mellitus (941/54); MELD score (421/15); urgent transplant (7/0); cold ischemic time (139/0).

intensive care unit and the ECMO device during NRP, perfusionists, and surgeons responsible for the recovery of thoracic and abdominal organs. This combined organ procurement technique must be managed by experienced donor coordinators or intensivists and surgical teams, whose cooperation is critical. Indeed, such cooperation has resulted in an increased number of grafts available for transplantation in multiorgan DBD,[21] cDCD,[22,23,26] and even pediatric cDCD processes in Spain.[27,28] In the case of thoracic surgeons, a scrupulous technique has to be performed during all of the recovery process, and fluent communication with other professionals in the theater must be ensured. One of the main challenges is the hemodynamic instability during NRP resulting from blood loss that may happen in the thoracic cavity after recovering the lung. For this reason, it is extremely important to be meticulous with the hemostasis, cauterizing all small vessels after the removal. Another important gesture is ligating the azigos vein. The staff managing the ECMO must be alerted when the inferior vena cava is going to be clamped, since 1.5 to 2 L must be administered before the clamping in order to keep hemodynamic stability. These technical details have been published by British and Spanish groups.[22,23,26,29,30]

Table 5
Incidence of liver graft complications, by donor type.

	Global (N = 1307)		DBD (N = 1162)		DCD-NRP (N = 145)		*P*
Primary nonfunction, n (%)	30	(2.3%)	24	(2.1%)	6	(4.1%)	.134
Ischemic cholangiopathy, n (%)	8	(0.6%)	7	(0.6%)	1	(0.6%)	1.000
Arterial thrombosis, n (%)	57	(4.4%)	52	(4.5%)	5	(3.4%)	.568
Acute rejection, n (%)	49	(3.7%)	42	(3.7%)	6	(4.1%)	.794
Other biliary complications, n (%)	110	(8.4%)	98	(8.4%)	12	(8.3%)	.949



	Survival probability (number at risk)		
	1 month	1 year	3 years
DBD (N=1578)	94.2 (N=1481)	88.2 (N=1252)	82.1 (N=729)
DCD-NRP (N=171)	94.1 (N=157)	89.7 (N=114)	80.8 (N=33)

LuTx: Lung transplantation
LiTx: Liver transplantation

Figure 4. Overall survival for LiTx with grafts from DBD and cDCD-NRP donors. DBD, donation after brain death; cDCD-NRP, controlled donation after the circulatory determination of death, subject to normothermic regional perfusion; LiTx: liver transplantation; LuTx, lung transplantation.

4.1. Outcomes of LuTx of cDCD donors subject to abdominal NRP

Some initial experiences on the combined recovery of lungs when using abdominal NRP in cDCD have been published, with promising results.[20,22,26] However, these were single-center studies with a reduced number of cases and limited follow-up. Tanaka et al[26] observed similar outcomes in 28 consecutive cDCD LuTx when comparing the RR of lungs and abdominal organs vs. the RR of lungs combined with abdominal NRP. Miñambres et al[22] analyzed the outcomes of LuTx and LiTx using grafts recovered from the same 19 cDCD donors subject to NRP vs. those obtained from 34 DBD donors. In total, 21 LuTx recipients of cDCD organs were compared with 41 LuTx recipients

of DBD donors. The authors did not find any significant difference in early posttransplant outcomes (PGD, days of mechanical ventilation, or length-of-stay in the intensive care unit) and mid-term survival (90%, 84%, and 84% at 3 months, 1 year, and 2 years in the cDCD group vs. 90%, 90% ,and 90% in the DBD group; $P = .577$). In a larger series from the same group,[20] the authors found that the rates of PGD grade 3 at 72 hours was higher in recipients of cDCD lungs (10% vs. 3.4%; $P < .001$), but without an impact on early mortality or mid-term survival. Notably, in the present multicenter study, we did not find any statistically significant difference in terms of either the incidence of PGD or early mortality between the groups.

Several other studies have been published deepening the comparison between LuTx from DBD and cDCD donors but using the RR of abdominal organs instead of NRP.[28-30] All have reported comparable outcomes between the 2 cohorts. Barbero et al[31] showed an incidence of PGD grade >2 of 26.1% and 17.4% at 24 and 72 hours, respectively, in the cDCD group, which is similar to the rate of PGD observed in our study. The same observation has been made by others.[32,33] Our experience, which solely includes LuTx from cDCD donors subject to abdominal NRP, shows similar rates of PGD grade 3 than the abovementioned studies, which used the RR technique. This suggests that LuTx from cDCD donors, in the more complex scenario of organ recovery that is posed by abdominal NRP, presents outcomes comparable to those obtained when the RR technique is used for abdominal organs.

The excellent early postoperative outcomes achieved in our series of cDCD LuTx were obtained despite the longer duration of mechanical ventilation in cDCD donors compared with DBD donors, which increases the possibility of lung damage or infection. Notably, both our DBD and cDCD donors received protocolized comprehensive treatment involving careful bedside management,[21] with identical partial pressure of oxygen in arterial blood/fraction of inspired oxygen values in both groups before lung recovery. In addition, no specific selection criteria were applied to cDCD lungs. For example, although donor age is one of the most important determinants of recipient outcomes, donor selection in cDCD did not take age into account. In fact, the median age of cDCD donors was 55 years, higher than the one described in most studies analyzing the outcomes of cDCD LuTx,[4] suggesting that this combined recovery approach is also safe in marginal lung grafts. Actually, 33% of our lung donors were greater than 60 years of age, which may explain the nearly 80% of first year overall survival in the cDCD cohort. We did not make any special selection of LuTx recipients in the cDCD group in terms of age either, with recipient age being similar to that of recipients of DBD lungs. Finally, our study collected the experience of all LuTx groups and multiple donor centers across the country, with all initial learning curves having been captured. Therefore, this was not only the description of outcomes from highly qualified LuTx or donor centers, but a real-life picture of this challenging procedure, where grafts obtained from different centers around the country were allocated in all LuTx programs with excellent results.

4.2. Outcomes of LiTx of controlled DCD donors subject to NRP and simultaneous lung recovery

With regards to the LiTx results, Miñambres et al[22] observed no statistically significant differences between cDCD donors subject to NRP compared with DBD donors when lungs were simultaneously recovered, in terms of complications in the short term, such as early graft dysfunction (18.8% vs. 17.2%; $P = .6$), PNF (12.2% vs. 0% ; $P = .121$) and arterial thrombosis (6.3% vs. 3.4%; $P = .590$). Furthermore, mid-term survival of LiTx was not significantly different between the 2 groups (87.5%, 87.5%, and 87.5% at 1 month, 1 year, and 2 years in the cDCD group vs. 96%, 96%, and 84.5% in the DBD group, respectively; $P = .496$). Our study confirmed these outcomes in a larger series, reassuring that the RR of lungs in cDCD does not have a negative impact on LiTx outcomes.

Another important aspect analyzed in the present study is the comparison of the evolution of cDCD LiTx when NRP is used, attending to whether the lungs were effectively recovered. There were no statistically significant differences in either the main early post LiTx outcomes or mid-term survival. These results suggest that the recovery of the lung itself does not have a clinically nor a statistically significant impact on results of LiTx, when a scrupulous technique in terms of rapidity and hemostasis is carried out. We believe this is a crucial message to both abdominal and thoracic transplant groups who are reluctant to use an a priori very challenging procedure.

4.3. Utilization of lungs and livers from cDCD donors

We also analyzed the liver and lung grafts that were discarded during the recovery process, which were attributed to different reasons. The first LuTx from a cDCD donor was performed in 2015. Since then, the rate of lungs discarded has been steady and comparable to DBD. With regards to the liver, the most frequent reason for discarding the organ was an ischemic appearance or bad perfusion. The percentage of discarded livers was higher in the cDCD group than in the DBD group as has been observed in most international studies and can be explained by the poor tolerance of livers to ischemic injury.[5,6] In addition, this rate of discarded livers can be justified by the advanced age of cDCD donors, many in their sixties. However, the rate of discarded livers remained similar in the 2 donor cohorts since 2018.

4.4. Limitations

Our study has the limitations inherent to a registry study. However, the commitment of all transplant groups for including all transplant patients over the years and the high quality of the database, which is periodically audited, must be highlighted. Furthermore, the nature of this nationwide registry-based study may even strengthen its value because the experience reflects the donation activity across the entire country, including not only high volume centers but also medium or small size

hospitals where these complex procedures have been successfully carried out. Finally, we acknowledge that it is not possible to know if NRP can adversely impact the utilization of cDCD lungs. However, the NRP did not seem to affect the percentage of accepted and transplanted lungs or the early function of the cDCD grafts.

4.5. Conclusion

In conclusion, this is the largest and unique multicenter study to date on the use of abdominal NRP combined with the RR of lungs in cDCD. The simultaneous RR of lungs and the in situ preservation of abdominal organs with NRP in cDCD donors is feasible and offers outcomes in both LuTx and LiTx similar to the current gold standard. Moreover, whether lungs are finally recovered or not does not seem to have a significant impact on LiTx outcomes in the immediate postoperative period or in the mid-term. Our results may contribute to increase the utilization of organs obtained from cDCD donors as the use of abdominal NRP expands and hence may help to improve the access of patients to life-saving transplant procedures.

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Data availability

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

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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Appendix A. Supplementary data

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