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Lung transplantation from uncontrolled and controlled donation after circulatory death: similar outcomes to brain death donors

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SUMMARY

Controlled donation after circulatory death donors (cDCD) are becoming a frequent source of lungs grafts worldwide. Conversely, lung transplantations (LTx) from uncontrolled donors (uDCD) are sporadically reported. We aimed to review our institutional experience using both uDCD and cDCD and compare to LTx from brain death donors (DBD). This is a retrospective analysis of all LTx performed between January 2013 and December 2019 in our institution. Donor and recipient characteristics were collected and univariate, multivariate and survival analyses were carried out comparing the three cohorts of donors. A total of 239 (84.7%) LTx were performed from DBD, 29 (10.3%) from cDCD and 14 (5%) from uDCD. There were no statistically significant differences in primary graft dysfunction grade 3 at 72 h, 30- and 90-day mortality, need for extracorporeal membrane oxygenation after procedure, ICU and hospital length of stay, airway complications, CLAD incidence or survival at 1 and 3 years after transplant (DBD: 87.1% and 78.1%; cDCD: 89.7% and 89.7%; uDCD: 85.7% and 85.7% respectively; $P = 0.42$). Short- and mid-term outcomes are comparable between the three types of donors. These findings may encourage and reinforce all types of donation after circulatory death programmes as a valid and growing source of suitable organs for transplantation.

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Key words
brain death donors, controlled donors after circulatory death, early mortality, lung transplantation, overall survival, uncontrolled donors after circulatory death

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Introduction

Lung transplantation (LTx) represents a proven treatment for a selected cohort of patients suffering end-stage lung disease. Despite the increasing numbers of LTx performed worldwide, there is still a global shortage of donors. Along with primary graft dysfunction (PGD) and chronic graft failure (CLAD), these three factors remain the major challenging limitations.

Several strategies have been advocated to palliate the scarcity of available organs such as *ex vivo* lung perfusion (EVLP) [1], optimizing donor management in intensive care units (ICU) [2], living donations [3], lobar transplantation [4] and donation after circulatory death (DCD) [5–14].

Among them, one of the most widely implemented strategies has been the use of lungs from DCD. In a recent publication from the International Society of Heart and Lung Transplantation (ISHLT) an increasing percentage of DCD use from 2003 to 2016 is reported [15]. Furthermore, a significant number of countries and LTx programmes have communicated similar data: in the USA, an increase of 24% was reported from 2006 to 2008 [16]; in the UK and Australia, 14% and 28% of the LTx procedures were from DCD respectively [17,18]; in Spain, 18% of all transplanted lungs are from DCD donors and the number of DCD LTx has increased 13-fold from 2012 to 2019 [19]. However, the vast majority of these studies are based on Maastricht category III (controlled) DCD donors (cDCD) [20]. Only a few centres worldwide have reported their LTx outcomes from Maastricht category I and II (uncontrolled) DCD donors (uDCD) [8,10,21,22].

This manuscript aims to analyse the entire experience of our institution in LTx from both uDCD and cDCD programmes and to compare the primary outcomes with LTx from DBD.

Materials and methods

Study design

This is a single institution retrospective review including all lung transplants performed between January 2013 and December 2019. The study was approved by our Institutional Ethical Board (Project ID: PI_146-20).

Redo lung transplantations were excluded. All variables were collected from electronic patient records.

The following donor demographic characteristics were collected: donor type, age, sex, duration of mechanical ventilation, smoking history, partial oxygen pressure over fractional inspired oxygen concentration (PaO_2/FiO_2) and cold ischaemia time (CIT). For cDCD donors, the following variables related to warm ischaemia time were collected: withdrawal of life support therapies (WLST) to cardiac arrest (CA) time, CA-cold perfusion time, WLST-cold perfusion time and systolic blood pressure (sBP) <60 mmHg to cold perfusion time. For uDCD donors, additional timing variables were included: witness cardiac arrest to advanced resuscitation manoeuvres time, time to topical cooling, time to pulmonary artery (PA) flushing and total ischaemia time.

Recipient and procedure data were collected: age, sex, diagnosis, lung allocation score (LAS), secondary pulmonary hypertension, smoking history, body mass index (BMI), 6 minute walking test (6MWT), pretransplant medical condition and cardiopulmonary support during the surgery (ECMO/cardiopulmonary bypass). Main postoperative outcomes were also collected: PGD, intubation time, postoperative ECMO, ICU and hospital length of stay (LOS), acute cellular rejection, airway complication, early mortality (30- and 90-day mortality), overall survival and CLAD incidence.

cDCD protocol

Our cDCD programme started in 2013 [23]. The protocol can be summarized as follows: after family agreement to WLST, the patient is evaluated as a potential donor applying the same criteria for DBD. It is our current institutional policy to perform normothermic perfusion for abdominal organs [14]. Therefore, a veno-arterial extracorporeal membrane (VA-ECMO) is placed in the ICU after an unfractioned heparin bolus of 1000 IU/kg. When the placement of the VA-ECMO for abdominal preservation is not feasible or the family does not give their consent, rapid surgery is carried out for lungs, liver or kidney recovery.

After WLST, asystole must occur within the next 2 h; otherwise, the patient is transferred back to ICU for comfort measures. If asystole did occur, a 5-min hands-off period is followed and ICU staff certify death and proceed to perform orotracheal intubation. Median sternotomy is performed, the PA is flushed and a macroscopic assessment is carried out. Mechanical ventilation is restored 5 min after the declaration of death (10 min after asystole) with volume-control ventilation, 5 cmH_2O of PEEP, 6–7 ml/kg of tidal volume and FiO_2 50%.

If any concerns arise during the procurement, such as donor instability or prolonged agonal phase, EVLP is considered for further assessment.

uDCD protocol

Our uncontrolled DCD protocol (Maastricht category I and II) is described elsewhere [9]. Briefly, after a witnessed cardiac arrest, advanced resuscitation manoeuvres must be started within the first 15 min. These manoeuvres are continued during transportation to Hospital Universitario Clínico San Carlos, where the ICU staff certify death. The legal permission of two separate judges is required; the first is to perform organ preservation manoeuvres, including femoral VA-ECMO and placement of an inflated Fogarty catheter in the thoracic descending aorta. Additionally, a 24-Fr chest tube is inserted in each pleural cavity, ventilation halted and cold low potassium dextran base solution (4 °C) instilled into the cavity for topical cooling. Meanwhile, oesophageal temperature is monitored aiming for a pleural cavity below 21 °C. We tolerate 150 min maximum from witnessed cardiac arrest to the topical cooling manoeuvre. In this situation, next of kin and the second judge's permission for organ retrieval are requested before *in situ* organ evaluation.

Hence, for lung evaluation, chest cavities are drained and ventilation restored. While through a median sternotomy, PA is flushed with 30–50 ml/kg, 300 ml of donor's blood mixed with Perfadex is further infused and a blood sample taken from the left atrium and each of the four pulmonary veins. Furthermore, a temperature corrected blood gas analysis is performed.

Our thresholds at this point are a maximum topical cooling to PA rinsing time no longer than 240 min and a PaO_2/FiO_2 ratio above 400. Only excellently preserved organs are immediately transplanted. Contrarily, if any concerns exist about the organ's quality or the procurement, EVLP is indicated.

Definition of variables

The PGD grade was based on the ISHLT Working Group document on Primary Dysfunction Report [24].

In the cDCD cohort, the withdrawal time or 'agonal phase' was defined as the time between WLST and CA. The functional warm ischaemia time (FWIT) was defined as the duration between sBP <60 mmHg and PA flushing. No-circulatory time was defined as the duration from CA to PA flush. While for uDCD, we defined preservation time as the period between topical cooling and PA flush.

Cold ischaemia time was defined as the duration between aortic cross-clamp in DBD or time of flushing through PA in uDCD or cDCD and the reperfusion in the recipient. Airway complication was defined as bronchoscopy findings that required any interventions such as debridement, balloon dilatation or stenting.

The time of perfusion during the *ex vivo* was not considered in the cold ischaemia time.

Statistical analysis

Descriptive analysis has been performed by means of absolute and relative frequencies for categorical variables and mean (standard deviation), or median (percentiles 25 and 75), minimum and maximum values for numerical variables. Univariate analysis was performed using the chi-square or Fisher's exact tests for categorical variables and Kruskal–Wallis with *post hoc* Mann–Whitney tests for numerical variables. Bonferroni correction was applied for multiple testing.

Analyses for 30-, 90- and 365-day mortality were performed using three sets of univariate logistic regressions, showing the odds ratios (OR) along with the corresponding 95% confidence intervals. From the significant associated variables, we developed a multivariate logistic regression model for mortality at 90 and 365 days.

Overall survival was defined as time from transplant to death from any cause, considering those patients alive at the last time of follow-up (30 June 2020) as censored. Survival curves were obtained using the Kaplan–Meier method and comparison thereof using the log-rank test.

All estimated coefficients are shown together with their respective confidence intervals. The significance level is set at 0.05. The statistical software used was STATA/IC v.16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX, USA: StataCorp LLC.).

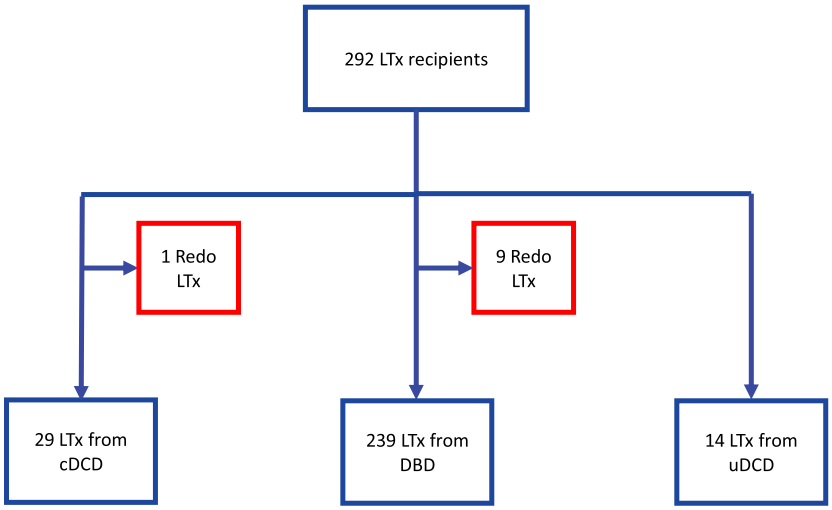

Figure 1 Flow chart of patients included in the study. cDCD, controlled donor after circulatory death; LTx, lung transplantation; uDCD, uncontrolled donor after circulatory death.

Results

From January 2013 to December 2019, 292 LTx were performed in our institution. Redo LTx were excluded from the analysis (n = 10; Fig. 1). In the final analysis, 239 recipients received DBD lungs (84.7%). The majority of the LTx from DCD was from controlled donors (Maastricht category III), n = 29 (10.3%), with

Table 1. Donor demographic characteristics.

Variables	DBD (n = 239)	cDCD (n = 29)	uDCD (n = 14)	P-value
Median age (IQR)	56 (46–64)	59 (46–68)	50 (42–53)	0.029
Gender				
Male (%)	108 (45.2)	15 (51.7)	13 (92.9)	0.002
Female (%)	131 (54.8)	14 (48.3)	1 (7.1)	
BMI, median (IQR)	25.4 (23.4–27.8)	26.2 (23.7–27.8)	27.8 (27.8–29.2)	0.763
Cause of brain injury				
CVA (%)	171 (71.5)	21 (72.4)	0	<0.001
Anoxia (%)	17 (7.1)	7 (24.1)	0	
Trauma (%)	43 (18)	1 (3.5)	0	
Other (%)	8 (3.6)	0	0	
Unexpected cardiac arrest (%)			14 (100)	
Days on MV, median (IQR)	1.8 (1.2–3.6)	7.6 (5–12.2)	0	<0.001
Smoking history (%)	106 (45.3)	6 (21.43)	6 (54.4)	0.162
PaO_2/FiO_2, median (IQR)	446 (391–498)	405 (358–495)	461 (440–666)	0.081
Withdrawal time				
WLST-CA (min), median (IQR)		15 (13–21)		
No circulatory time				
CA-PA flush (min), median (IQR)		15 (12–20)		
WLST-PA flush (min), median (IQR)		32 (29–38)		
Functional warm ischemia time				
sBP<60-PA flush (min), median (IQR)		22 (20–30)		
CA-topical cooling time, median (IQR)			122.5 (83–150)	
Preservation time				
Topical cooling-PA flush time, median (IQR)			160 (110–235)	
Use of EVLP (%)	8 (3.4)	3 (10.3)	4 (28.6)	0.02

BMI, body mass index; CA, cardiac arrest; cDCD, controlled donors after circulatory death; CVA, cerebrovascular accident; DBD, death brain donors; EVLP, *ex vivo* lung perfusion; PA, pulmonary artery; PaO_2/FiO_2, partial oxygen pressure over fractional inspired oxygen concentration; uDCD, uncontrolled donors after circulatory death; WLST, withdrawal of life sustaining therapy. Data are presented as n, median (interquartile range) or n (%).

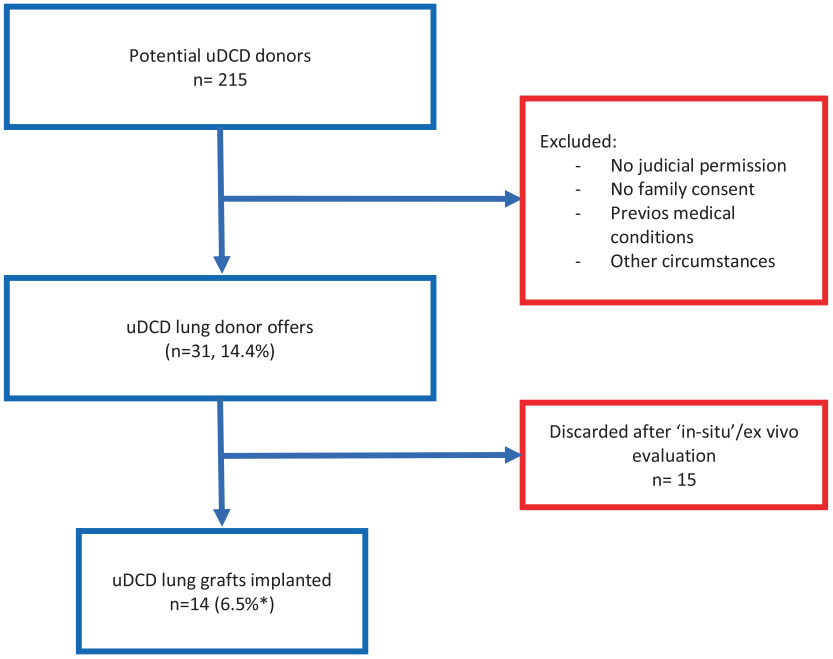

Figure 2 Utilization rate of uDCD lung donors. *Final utilization rate out of the total potential uDCD donors (n = 215). uDCD, uncontrolled donor after circulatory death.

uncontrolled donors (Maastricht category I and II) being less frequent, n = 14 (5%).

Donor demographic characteristics

Descriptive demographics for donors are summarized in Table 1. Donors from the uDCD cohort were significantly younger than donors from either DBD or cDCD (P = 0.029). Also, the proportion of males was significantly higher in uDCD (92.1% vs. 45.2% in DBD and 51.7% in cDCD respectively; P = 0.002). All uDCD donors suffered an unexpected cardiac arrest, which led to immediate brain injury.

The cDCD cohort showed a significantly higher number of days on mechanical ventilation (MV) before donation (7.6 days in the cDCD cohort vs. 1.8 days in DBD and 0 days in uDCD; $P < 0.001$).

Ex vivo lung perfusion was used in a significantly different proportion depending on the cohort (28.6% of uDCD, 11.5% in cDCD and 3.4% in DBD; P = 0.02).

Regarding the cDCD cohort, the median 'agonal phase' was 15 min, the median FWIT was 22 min and the systolic warm time was 15 min. Regarding uDCD, the median time between cardiac arrest and topical cooling was 122.5 min and the median preservation time was 160 min.

With regard to the uDCD cohort of donors, 215 patients were transferred by emergency transportation services as potential uDCD donors during the study period. Of which, 31 (14.4%) uDCD donors were identified to be potential lung donors. Sixteen grafts were retrieved and 14 LTx were finally performed out of the total potential uDCD donors. The remaining two lung grafts were rejected after *ex vivo* evaluation. Thus, the utilization rate was 6.5% (Fig. 2).

Recipient characteristics

Recipient variables are displayed in Table 2. No statistically significant differences were found between the three types of donors regarding age, gender, diagnosis, BMI, LAS, smoking history, 6MWT, pretransplant mean pulmonary artery pressure (mPAP), pretransplant status or bridge to transplant.

Transplant-related characteristics and short- to mid-term outcomes

Table 3 summarizes the transplant-related characteristics. Most of the procedures were bilateral LTx regardless of the type of donor (82.4% in DBD, 96.6% in cDCD and 85.7% in uDCD; P = 0.144).

Meanwhile, median CITs for the first and second graft were significantly higher in the uDCD group (609 and 780 min in uDCD vs. 318 and 420 in DBD, vs. 320 and 460 in cDCD respectively; $P < 0.001$).

Regarding intraoperative support, cardiopulmonary bypass (CPB) was substituted for extracorporeal

Table 2. Recipient demographic characteristics.

Variables	DBD (*n* = 239)	cDCD (*n* = 29)	uDCD (*n* = 14)	*P*-value
Median age (IQR)	58 (52–62)	59 (51–63)	55 (52–59)	0.297
Gender (%)				
Male	152 (63.6)	18 (62.1)	13 (92.9)	0.079
Female	87 (36.4)	11 (37.9)	1 (7.1)	
Diagnosis (%)				
COPD	87 (36.4)	13 (44.8)	7 (50)	0.742
A1-AT deficit	9 (3.8)	0	1 (7.1)	
IPF	47 (19.7)	3 (10.3)	3 (21.4)	
Other ILD	40 (16.7)	7 (24.1)	1 (7.1)	
Fibro-emphysema	8 (3.6)	1 (3.46)	0	
CF	19 (8)	4 (13.8)	2 (14.3)	
Bronchiectasis	8 (3.6)	1 (3.45)	0	
Miscellanea	21 (8.8)	0	0	
BMI, median (IQR)	24.9 (22–27)	24 (22–27)	26.4 (22–28)	0.549
LAS, median (IQR)	34.5 (32.6–39)	35 (33–39)	33 (31.9–39)	0.701
6MWT, median (IQR)	340 (256–416)	375 (300–432)	329 (300–394)	0.55
Pretransplant SHP, median (IQR)	22 (17–27)	22 (17–26)	23.5 (22–26)	0.524
Bridge to transplant (%)				
No bridge	217 (91.2)	26 (89.7)	14 (100)	0.577
ECLS	3 (1.3)*	1 (3.4)†	0	
IMV	11 (4.6)*	2 (6.9)†	0	
NIMV	10 (2.9)	1 (3.4)	0	

6MWT, 6 minute walking test; A1-AT, deficit alpha-1 antitrypsin; BMI, body mass index; cDCD, controlled donors after circulatory death; CF, cystic fibrosis; CMV, cytomegalovirus; OPD, chronic obstructive pulmonary disease; DBD, death brain donors; D-pTLC, donor predicted total lung capacity; ECLS, extracorporeal life support; ILD, interstitial lung disease; IMV, invasive mechanical ventilation; IPF, idiopathic pulmonary fibrosis; LAS, lung allocation score; NIMV, noninvasive mechanical ventilation; R-pTLC, recipient predicted total lung capacity; SPH, secondary pulmonary hypertension; uDCD, uncontrolled donors after circulatory death.

Data are presented as *n*, median (IQR) or *n* (%).

*Two patients were bridged with ECLS were also under IMV.

†This patient was bridged with both ECLS and IMV.

membrane oxygenation (ECMO) between 2015 and 2016 at our centre, with the latter being our current standard if intraoperative assistance is needed. No statistically significant differences were found in the proportion of patients who needed intraoperative assistance or the need for prolonged ECMO after LTx.

Early outcomes are shown in Table 4. There were no statistically significant differences in the grade of PGD at any time point between groups, including PGD grade 3 at 72 h (15.1% in DBD, 24.1% in cDCD and 21.3% in uDCD, $P = 0.173$; Fig. 3). The need of postoperative ECMO due to severe PGD was in a similar proportion (13.4% in DBD cohort, 21.4% in cDCD and 21.4% in uDCD, $P = 0.402$).

Reintervention due to haemothorax, median intubation time, rate of tracheostomy, ICU and hospital LOS were also comparable between the three cohorts of donors.

There was no statistically significant difference between groups as regards to incidence of airway complication (7.9%, 6.8% and 7.1% in DBD, cDCD and uDCD respectively; $P = 0.258$).

Early mortality was not significantly different between groups: 30- and 90-day mortality rate was, respectively, 4.6% and 7.5% for DBD, 3.44% and 3.44% for cDCD, 7.1% and 7.1% for uDCD. Univariate logistic regression did not show excess of risk in 30-day mortality (cDCD OR 0.91, CI 95%: 0.11–7.47; uDCD OR 1.96, CI 95%: 0.23–16.71) or 90-day mortality (cDCD OR 0.46, CI 95%: 0.59–3.64; uDCD OR 1.004, CI 95%: 0.12–8.14) when cDCD or uDCD were compared to DBD.

A multivariate model was built in order to evaluate the variables associated with 90-day and 1-year mortality, showing that the use of CPB as intraoperative support and the presence of PGD grade 3 at 72 h had an increased risk of mortality (Tables 5 and 6).

Table 3. Transplant-related characteristics.

Variables	DBD (n = 239)	cDCD (n = 29)	uDCD (n = 14)	P-value
Type of LTx (%)				
Single	42 (17.6)	1 (3.4)	2 (14.3)	0.144
Double	197 (82.4)	28 (96.6)	12 (85.7)	
1st graft cold IT (min), median (IQR)	318 (280–360)	320 (300–375)	609 (585–720)	<0.001
2nd graft cold IT (min), median (IQR)	420 (380–480)	460 (420–495)	780 (720–810)	<0.001
Intraoperative support (%)				
No support	135 (56.5)	14 (48.3)	10 (71.4)	0.405
CPB	35 (14.6)	5 (17.2)	3 (21.4)	
ECMO	69 (28.9)	10 (34.5)	1 (7.2)	
Prolonged ECMO after LTx (%)				
No	206 (87.7)	24 (82.8)	13 (92.9)	0.765
VA-ECMO	7 (3)	0	0	
VV-ECMO	17 (7.2)	4 (13.8)	1 (7.1)	

cDCD, controlled donors after circulatory death; CPB, cardiopulmonary bypass; DBD, death brain donors; ECMO, extracorporeal membrane oxygenation; IT, ischemia time; LTx, lung transplantation; uDCD, uncontrolled donors after circulatory death; VA, veno-arterial; VV, veno-venous.

Data are presented as n, median (range) or n (%).

Survival and follow-up

The Kaplan–Meier survival curve comparison is shown in Fig. 4. No significant differences were found in 1- and 3-year survival (DBD group: 87.1% and 78.1%, cDCD group: 89.7% and 89.7%, uDCD group: 85.7% and 85.7% respectively; $P = 0.42$). The number of patients in each group who developed CLAD over the study period was not significantly different (17.8%, 14.3% and 7.7% in DBD, cDCD and uDCD respectively; $P = 0.592$). CLAD-free survival was not included due to limited follow-up time.

The mean best postoperative FEV1 was similar among groups (2.5, 2.9 and 2.8 L in DBD, cDCD and uDCD respectively; $P = 0.258$).

Discussion

This study represents our most recent clinical experience (2013–2019), including all LTx performed from donors after brain death (DBD) and two types of donors after circulatory death. We currently have active protocols for both Maastricht III (cDCD) and Maastricht I–II categories (uDCD), which allows for a unique and fair comparison between the three cohorts of donors. To our knowledge, this is the first analysis showing comparable early and mid-term outcomes between LTx using DBD, cDCD and uDCD donors in a single institution.

To date, there have been multiple publications reporting single institution experiences, showing comparable early and mid-term outcomes between controlled DCD and DBD. In 2012, Levvey *et al.* [18] published exceptional outcomes using cDCD donors, reporting similar perioperative outcomes and survival at 1 and 5 years of 97% and 90% respectively. Machuca *et al.* [25] from the Toronto group showed comparable results between cDCD and DBD in their cohort. More recently, Ruttens *et al.* compared short- and long-term outcomes from 59 cDCD vs. 331 DBD, reporting no significant differences in early postoperative results. Furthermore, the authors found comparable survival rates at 1, 3 and 5 years (90.9%, 83.2% and 78% in the DBD group vs. 87.3%, 75.7% and 70.9% in the cDCD group) [26]. In 2019, Barbero *et al.* [11] showed no differences in perioperative outcomes (duration of mechanical ventilation, use of cardio-respiratory support after the transplant, early graft function or mortality at 90 days). Thus, there were comparable survival rates at 1 and 5 years: 82% and 61% for DBD vs. 75% and 51% for cDCD. In addition, the ISHLT registry reported comparable post-transplant survival rates at 30 days, 1 and 5 years (97%, 88% and 61% in the DBD cohort vs. 96%, 89% and 63% in the cDCD group) [15]. Finally, a systematic review and a meta-analysis published in 2020 [27] revealed that 1-year survival and PGD grade 2 and 3 were similar between DBD and cDCD. In contrast, airway complications and long-term survival were compromised against cDCD. However, the authors stated that the latter findings should be interpreted cautiously.

Table 4. Postoperative outcomes.

Variables	DBD (*n* = 239)	cDCD (*n* = 29)	uDCD (*n* = 14)	*P*-value
PGD grade				
24 h (%)				
0	89 (38.5)	9 (31)	3 (21.4)	0.258
1	57 (24.7)	4 (13.8)	1 (7.1)	
2	39 (16.9)	3 (10.3)	3 (21.4)	
3	46 (19.9)	11 (37.9)	7 (50)	
48 h (%)				
0	99 (43)	8 (27.6)	4 (28.6)	0.459
1	52 (22.6)	9 (31.3)	2 (14.2)	
2	38 (16.5)	5 (17.2)	4 (28.6)	
3	41 (17.8)	7 (24.1)	4 (28.6)	
72 h (%)				
0	110 (47.6)	7 (24.1)	4 (28.6)	0.173
1	46 (19.9)	10 (34.5)	3 (21.3)	
2	40 (17.3)	5 (17.2)	4 (28.6)	
3	35 (15.1)	7 (24.1)	3 (21.3)	
Reintervention (%)	25 (10.5)	5 (17.2)	3 (21.2)	0.15
Postoperative ECMO (%)	31 (13.4)	6 (21.4)	3 (21.4)	0.402
Intubation time, median (IQR)	2 (1–14)	2 (2–5)	3 (1–15)	0.556
Tracheostomy (%)	67 (28.6)	7 (24.1)	6 (42.9)	0.437
ICU LOS, median (IQR)	9 (5–21)	7 (5–26)	9.5 (7–30)	0.774
Hospital LOS, median (IQR)	43 (34–61)	41 (32–61)	45 (37–58)	0.704
30-day mortality (%)	11 (4.6)	1 (3.44)	1 (7.1)	0.841
90-day mortality (%)	18 (7.5)	1 (3.44)	1 (7.1)	0.719
In-hospital mortality (%)	22 (9.21)	2 (6.9)	2 (14.3)	0.735
Airway complications (%)	19 (7.9)	2 (6)	1 (7.1)	0.852
Best post-Op FEV1, ml, median (IQR)	2.5 (1.9–3.1)	2.9 (2.2–3.2)	2.8 (2.2–3.8)	0.258
CLAD (%)	39 (17.8)	4 (14.3)	1 (7.1)	0.592

cDCD, controlled donors after circulatory death; CLAD, chronic lung allograft dysfunction; DBD, death brain donors; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in one second; ICU, intensive care unit; LOS, length of stay; PGD, primary graft dysfunction; post-Op, postoperative; uDCD, uncontrolled donors after circulatory death.

Data are presented as *n*, median (IQR) or *n* (%).

Our experience with cDCD does not differ from internationally reported outcomes in the perioperative period or in the mid-term. Even though the incidence of PGD grade 3 at 72 h is higher in cDCD than in the DBD cohort, these differences are not statistically significant and are comparable to other recent published series [11,12]. More importantly, early mortality at 30 and 90 days is also similar between cDCD and DBD (also in comparison to uDCD). Moreover, mid-term survival appears to be similar and it is comparable to other cDCD series reported to date. Also, as we previously reported [14], the outcomes are invariably excellent regardless of the protocol for procurement, rapid surgery or normothermic preservation for abdominal organs using previously placed VA-ECMO.

Several recently published uDCD clinical series have shown excellent outcomes [8,10]. The Toronto group reported five cases with no PGD grade 3 at any time and no mortality at 30 days [10]. Their protocol consists of simple but effective preservation manoeuvres, CPAP of 20 cmH_2O and prone position of the donors, followed by EVLP evaluation. Suverbiola *et al.* [8] reported eight cases with 87.5% of 5-year survival rate. Their preservation method is essentially the same as that which our group has maintained since the uDCD programme was started in 2002: resuscitation manoeuvres until topical cooling are placed (ensuring a pleural cavity temperature below 21 °C), followed by antegrade flush and lung function testing using 300 ml of the donor's blood. Only excellent preserved grafts with PaO_2/FiO_2 ratio above 400 and without any macroscopic negative findings go direct to transplantation, reserving EVLP assessment for uncertain grafts or further validation of lung function. We believe that ensuring strict compliance with the criteria that have been set in the protocol, with EVLP support if required, is critical to obtain suitable grafts.

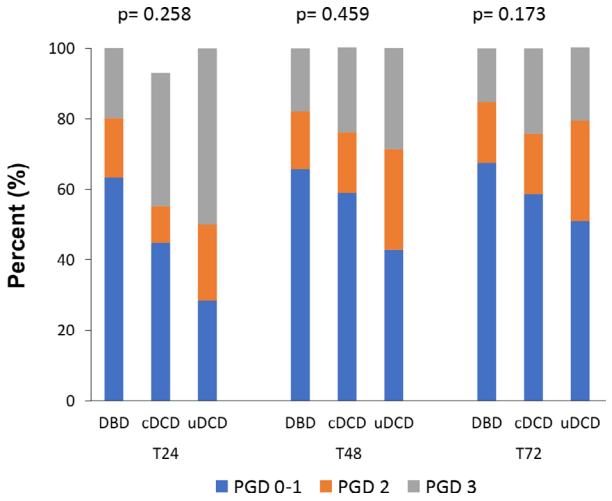

Figure 3 Prevalence and severity of PGD at 24, 48 and 72 h after LTx.

We have previously reported a survival rate of 81.6% 90 days after LTx from uDCD donors (study period between 2002 and 2012) [21]. In the present study, we currently show a 90-day survival of 92.9% and a mortality of 7.1% (one patient). Moreover, mid-term survival has improved substantially in the first and third year after transplant from 71.1% and 60.3% to 85.7% at both time points in the present study. Several factors could be linked to this improvement, such as the temporal effect following the surgical technique, more experience in donor and recipient selection or unique medical treatments. However, we believe that the development of an efficient ECMO program has been the main change in our practice over the last decade, allowing us to treat more patients in the early postoperative period. Moreover, also in a prior report [21], our incidence of PGD grade 3 was 34.2% in DBD and 24% uDCD. Currently, the incidence in uDCD remains similar, while that in DBD has decreased. This might be because most uDCD were performed using CPB as our standard practice up until 2016 when we changed to ECMO. Even though this manuscript does not cover a specific analysis of the impact of intraoperative ECMO in the perioperative course after LTx, the multivariate analysis showed that CPB acts as a risk factor for mortality, while ECMO has a protective effect. Therefore, as other groups have previously reported [28,29], we believe that the change in policy to ECMO as intraoperative support may have played an essential role in the improvement of PGD in DBD and early mortality globally.

Some advantages may be associated with the comparable outcomes of LTx from uDCD with LTx from DBD. uDCD donors are significantly younger than the rest of donor cohorts and they were not exposed to the potential harm secondary to prolonged mechanical ventilation. Furthermore, the absence of exposure to the 'cytokine storm' described after the institution of brain death could be beneficial in the uDCD setting. Also, interestingly, although the total ischaemia time is

Table 5. Multivariable analysis for analysing mortality at 90 days after LTx.

Variables	OR	Standard error	95% CI	*P*-value
Intraoperative support				
CPB	5.13	4.02	1.10–23.89	0.037
ECMO	2.61	1.98	0.59–11.56	0.205
PGD grade 3 at 72 h	13.78	8.64	4.02–47.15	<0.001

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; PGD, primary graft dysfunction.

Table 6. Multivariable analysis for analysing mortality at 1 year after LTx.

Variables	OR	Standard error	95% CI	*P*-value
Donor age	1.01	0.18	0.98–1.05	0.317
LAS	0.99	0.01	0.966.52–1.03	0.983
Intraoperative support				
CBP	3.35	1.94	1.07–10.43	0.036
ECMO	2.33	1.22	0.83–6.52	0.107
PGD grade 3 at 72 h	4.36	2	1.76–10.75	0.001

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; LAS, lung allocation score; OR, odds ratio; PGD, primary graft dysfunction.

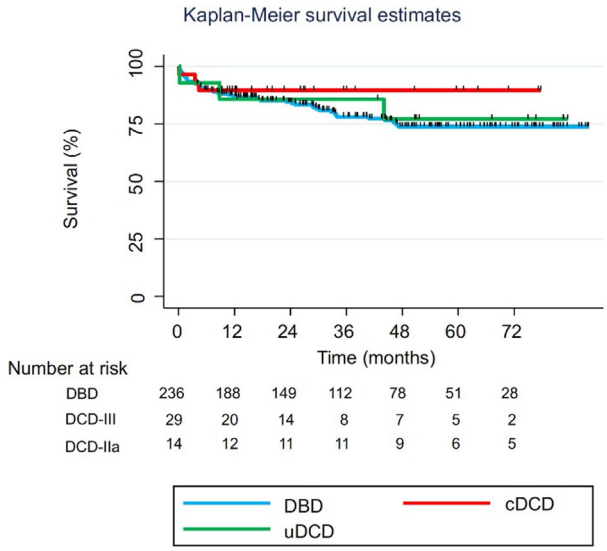

Figure 4 Kaplan–Meier survival curves comparison between lung transplantation from DBD, cDCD and uDCD.

significantly longer in the uDCD scenario, it seems not to have an impact on early mortality rate.

Ex vivo lung perfusion has been advocated as a useful, not to say essential, tool to evaluate and distinguish whether grafts from uDCD are suitable for transplantation [10]. In our cohort, only four cases out of 14 (28.6%) underwent *ex vivo* perfusion. In two cases a portable *ex vivo* platform (Organ Care System, Transmedics™) was used only for transportation. In the remaining two cases, an *ex vivo* evaluation was necessary to reassess the lung grafts (the last of them using Vivoline®LS1; XVIVO Ltd., Göteborg, Sweden). During the transition time to one platform to another, all LTx from uDCD were performed strictly according to our protocol, without *ex vivo* perfusion. In fact, our current policy indicates EVLP assessment when any concern arises about the suitability for direct LTx. Although these recent data endorse our protocol so far, we acknowledge that having an EVLP platform available is essential to develop and maintain a complex programme of donation such as uDCD. Furthermore, the authors strongly believe that it is crucial to have the possibility of an EVLP evaluation for those transplant programmes that also use cDCD and extended criteria DBD donors.

With regard to airway complications, the figures showed no evidence of a higher rate of complications requiring endobronchial intervention (debridement, stenting or balloon dilatation) in cDCD or uDCD groups compared to DBD. Nevertheless, an in-depth analysis of the supposed bronchial healing impairment of DCD lungs may be necessary to investigate this aspect further.

As this is a single-centre review, it has limitations. However, we believe that this fact is also a strength, as we were able to compare three different cohorts of donors in the same environment, showing comparable outcomes. Because our aim was to conduct a fair comparison, we included LTx from 2013 when we started the cDCD programme, which resulted in a reduced number of uDCD. Nevertheless, we think that these 14 uDCD cases represent a significant source of data, given the scarce number of case series reported internationally. Moreover, although the utilization rate is low (6.5%), uDCD donors represent a unique cohort that could expand the donor pool and help palliate the scarcity of lung grafts by increasing the opportunities available to recipients on waiting lists.

In conclusion, the analysis of our LTx cohort using DBD, cDCD or uDCD lungs, showed comparable outcomes in the early postoperative period, including early mortality and mid-term survival. We strongly believe that the outcomes described in this manuscript reinforce the idea of widening our donor pool using all types of available donors.

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Conflicts of interest

The authors have no conflict of interest to disclose.

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