ASTS
Leadership Development Program
October 18–21, 2020

The Premier Executive Management Course Designed Exclusively for the Field of Transplantation

In a field of increasing regulation and complexity, you need an edge to succeed.

The ASTS Leadership Development Program will introduce you to expert coaches to improve your transplant center's performance and accelerate your career success.

Learn. Lead. Succeed.

Learn more at ASTS.org/LDP.

ASTS
American Society of Transplant Surgeons®

Kellogg School of Management
Northwestern

Northwestern University Kellogg School of Management James L. Allen Center, Evanston, IL

Received: 1 July 2018 | Revised: 29 November 2018 | Accepted: 10 December 2018

DOI: 10.1111/ajt.15243

AJT

ORIGINAL ARTICLE

Uncontrolled donation after circulatory death: A cohort study of data from a long-standing deceased-donor kidney transplantation program

Ana I. Sánchez-Fructuoso[1] | Isabel Pérez-Flores[1] | Francisco Del Río[2] | Jesús Blázquez[3] | Natividad Calvo[1] | Maria Á. Moreno de la Higuera[1] | Angel Gómez[3] | Santiago Alonso-Lera[4] | Ana Soria[2] | Manuel González[2] | Ervigio Corral[5] | Alonso Mateos[6] | Jesús Moreno-Sierra[2] | Cristina Fernández Pérez[7]

[1]Nephrology Department, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain

[2]Transplantation Coordination Unit, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain

[3]Urology Department, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain

[4]Surgery Department, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain

[5]SAMUR, Madrid, Spain

[6]SUMMA112, School of Medicine, Francisco de Vitoria University, Madrid, Spain

[7]Preventive Medicine, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain

Correspondence
Ana I. Sánchez Fructuoso
Email: sanchezfructuoso@gmail.com

Despite good long-term outcomes of kidney transplants from controlled donation after circulatory death (DCD) donors, there are few uncontrolled DCD (uDCD) programs. This longitudinal study compares outcomes for all uDCD (N = 774) and all donation after brain death (DBD) (N = 613) kidney transplants performed from 1996 to 2015 at our center. DBD transplants were divided into those from standard-criteria (SCD) (N = 366) and expanded-criteria (N = 247) brain-dead donors (ECD). One-, 5-, and 10-year graft survival rates were 91.7%, 85.7%, and 80.6% for SCD; 86.0%, 75.8%, and 61.4% for ECD; and 85.1%, 78.1%, and 72.2% for uDCD, respectively. Graft survival was worse in recipients of uDCD kidneys than of SCD (P = .004) but better than in transplants from ECD (P = .021). The main cause of graft loss in the uDCD transplants was primary nonfunction. Through logistic regression, donor death due to pulmonary embolism (OR 4.31, 95% CI 1.65-11.23), extrahospital CPR time ≥75 minutes (OR1.94, 95%CI 1.18-3.22), and in-hospital CPR time ≥50 minutes (OR 1.79, 95% CI 1.09-2.93) emerged as predictive factors of primary nonunction. According to the outcomes of our long-standing kidney transplantation program, uDCD could help expand the kidney donor pool.

KEYWORDS

clinical research/practice, donors and donation: donation after brain death (DBD), donors and donation: donation after circulatory death (DCD), donors and donation: extended criteria, kidney transplantation/nephrology, organ procurement, organ procurement and allocation

1 | INTRODUCTION

Waiting lists for kidney transplantation worldwide are set to become longer as demands continue to outstrip supplies.[1,2] In Spain, the number of waitlisted patients remains around 4000, which exceeds the annual number of kidney transplantations performed.[2] Although there is room to expand the use of donation after brain death (DBD) kidneys, additional sources also need to be considered such as donation after circulatory death (DCD).

In the early 1990s, interest in DCD donors emerged as a viable alternative to circumvent the shortage of organs. In 1995, the Maastricht classification system categorized DCD donors according

Abbreviations: cDCD, controlled donation after circulatory death; CPR, cardiopulmonary resuscitation; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; ECD, expanded-criteria brain-dead donors; PNF, primary nonfunction; SCD, standard-criteria brain-dead donors; uDCD, uncontrolled donation after circulatory death.

to whether circulatory arrest was uncontrolled (categories I and II) or controlled (categories III and IV).[3] This classification scheme was subsequently redefined.[4,5]

Today, most DCD donors are category III, such that the majority of studies addressing the use of DCD donors have focused on controlled donors (cDCD).[6-22] In contrast, there are scarce data available on outcomes such as long-term renal function and graft survival in recipients of uncontrolled DCD (uDCD) kidneys.[4,23-27] France, The Netherlands, and Spain have some experience with this category of donor, and our center has probably the world's longest standing experience with uDCD.[4,27]

The factors that affect outcome after transplantation using kidneys from controlled DCD have been well-established, whereas for uDCD donors these are largely unknown. In this article, we compare outcomes of uDCD and DBD transplants in our cohort of kidney transplant recipients and identify factors affecting graft survival in uDCD transplants.

2 | METHODS

2.1 | Donor program

In 1989 our hospital started a program to obtain organs from cDCD. In 1996, this program was extended to include organs procured from uDCD, ie, persons who die suddenly on the street of irreversible cardiac arrest. A formal agreement was established with the ambulance services of our city whereby, following unsuccessful cardiopulmonary resuscitation (CPR), patients are transferred to our hospital. This protocol in no case affects any CPR maneuver. First, all measures and times specified in the established CPR procedures are undertaken, and only when cardiac arrest is considered irreversible (when an effective heartbeat cannot be recovered after a stipulated period of usually 30 minutes, or when the lesions provoking the cardiac arrest are incompatible with life) is the patient evaluated as a potential donor. When an individual has been classified as a candidate for donation, the emergency team continues with cardiac massage, mechanical ventilation, and intravenous fluid perfusion to maintain adequate hemodynamic conditions during transport to the hospital. Upon arrival, the transplant coordination team checks the conventional prerequisites for donation and then transfers the deceased donor to the operating room where the femoral vein and artery are cannulated via an incision in the right side of the groin and connected to a cardiopulmonary bypass machine with external oxygenation. In 96.5% of uDCD donors, hypothermic regional perfusion was used and in the remaining 3.5% normothermic regional perfusion (when the liver was also procured). This procedure has been described in detail in a preliminary study.[27] From 1996 to 2001, our uDCD donor criteria were age 6 to 55 years, cardiac arrest time ≤15 minutes, CPR time ≤ 120 minutes, extracorporeal bypass time ≤4 hours, and warm ischemia time (defined as the time from cardiac arrest to the onset of organ perfusion) ≤150 minutes. From 2002, the age limit for donation was raised to 60 years, CPR time to 150 minutes and warm ischemia time to 180 minutes. Remaining criteria are the standard criteria established for DBD. After kidney extraction, a biopsy specimen of the graft is obtained for histological viability testing. The preservation solution used is Celsior® (Genzyme Polyclonals, Catalent Limoges S.A.S., France). If cold ischemia time (from the start of cold storage to the onset of graft perfusion) is longer than 24 hours the donor is rejected.

Since November 2005, provided there were consumables available, uDCD grafts were maintained on a perfusion machine until the time of transplant (65.8% of cases).

Recipient characteristics were the same for receiving a kidney from a uDCD or a brain-dead donor.

2.2 | Study population

The study design was a retrospective analysis of data from a prospective multipurpose cohort. The cohort was composed of all consecutive kidney transplants performed at our hospital from January 1996 to December 2015. Over this period, 1473 kidneys were recovered from uDCD donors (Figure 1). Of these, 930 (63.1%) proved suitable for transplant: 804 were transplanted at our center and the remaining 126 were sent to other centers as we had no recipients with compatible blood groups. The remaining 543 (36.9%) grafts were rejected for transplant mainly because of poor perfusion, inadequate renal histology findings, and severe arteriosclerosis in the donor. Remaining causes are detailed in Figure 1.

Over the study period, 1534 deceased-donor transplants were conducted at our hospital: 807 were from DCD donors (789 from uDCD donors and 18 from cDCD donors) and 727 from DBD donors (Figure 2). Patients were excluded if they had undergone a dual kidney transplant (N = 114 from DBD donors and 15 from uDCD donors) or were cDCD transplant recipients (N = 18). This left a study population of 1387 adult kidney transplant recipients, 774 from uDCD donors and 613 from DBD donors. The DBD recipients were divided according to UNOS criteria[28] into those receiving a kidney from a standard-criteria brain-dead donor (SCD) (N = 366) or from an expanded-criteria brain-dead donor (ECD) (N = 247). Analysis included follow-up data collected until May 2018. Ten recipient patients were lost to follow-up at a median time post-transplant of 5 years (minimum 2 years; maximum 12 years).

In Figure 3, we provide the total number of kidney transplants from deceased donors conducted at our hospital.

2.3 | Treatment and outcome measures

Over the study period, the immunosuppression treatment given to kidney transplant recipients varied. From January 1996 to July 1996, patients mainly received quadruple sequential therapy (antithymocyte globulin 7 days, azathioprine, prednisone from the time of transplant and cyclosporine from day 5). From this time onwards, the immunosuppression regimen was cyclosporine or tacrolimus plus prednisone and mycophenolate. From March 2001, anti-IL2 receptor antibodies were added to the tacrolimus (starting dose 0.1 mg/kg/day to achieve trough levels around 5 ng/mL) plus prednisone and mycophenolate regimen in DCD and ECD recipients. After August 2008, most uDCD recipients were treated with antithymocyte globulin 5-7 days, mycophenolate, prednisone from the time of

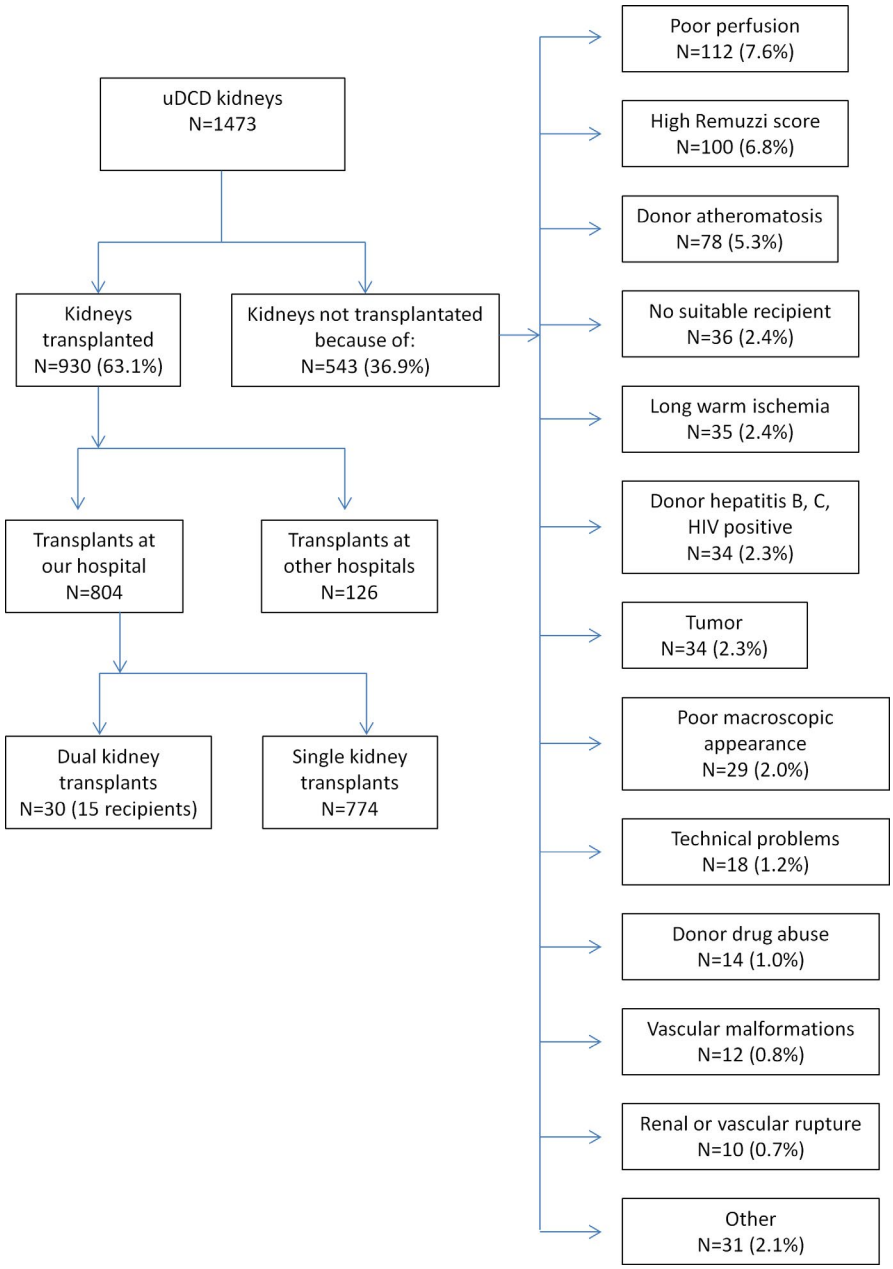


FIGURE 1 Use of kidneys from uncontrolled donation after circulatory death (uDCD) donors at our center (Hospital Clínico San Carlos, Madrid, Spain) over the period January 1996 to December 2015 [Color figure can be viewed at wileyonlinelibrary.com]

transplant and tacrolimus introduced from day 5. This regimen was used in some DBD recipients. Subsequent ambulatory patient management did not vary according to donor type.

Primary nonfunction (PNF) was defined as a never functioning graft following transplant. All nephrectomy specimens were exhaustively reviewed to establish the cause of PNF.

Delayed graft function (DGF) was defined as a need for dialysis in the first week posttransplant. When managing patients with DGF, a graft biopsy is obtained every 7-9 days to check for subclinical acute rejection.

Graft survival (noncensored for death) was calculated from the date of transplantation to the date of irreversible graft failure signified by return to long-term dialysis (or retransplantation) or the date of the last follow-up during the period when the transplant was still functioning or to the date of death.

Graft survival censored for death was calculated from the date of transplantation to the date of irreversible graft failure signified by return to long-term dialysis (or retransplantation) or the date of last follow-up during the period when the transplant was still functioning. In the event of death with a functioning graft, the follow-up period was censored at the date of death.

Estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease equation.[29]

The study protocol received institutional review board approval according to Spanish legislation.

2.4 | Statistical analysis

Continuous variables, expressed as means and standard deviation (SD), were compared by analysis of variance. The chi-square test or

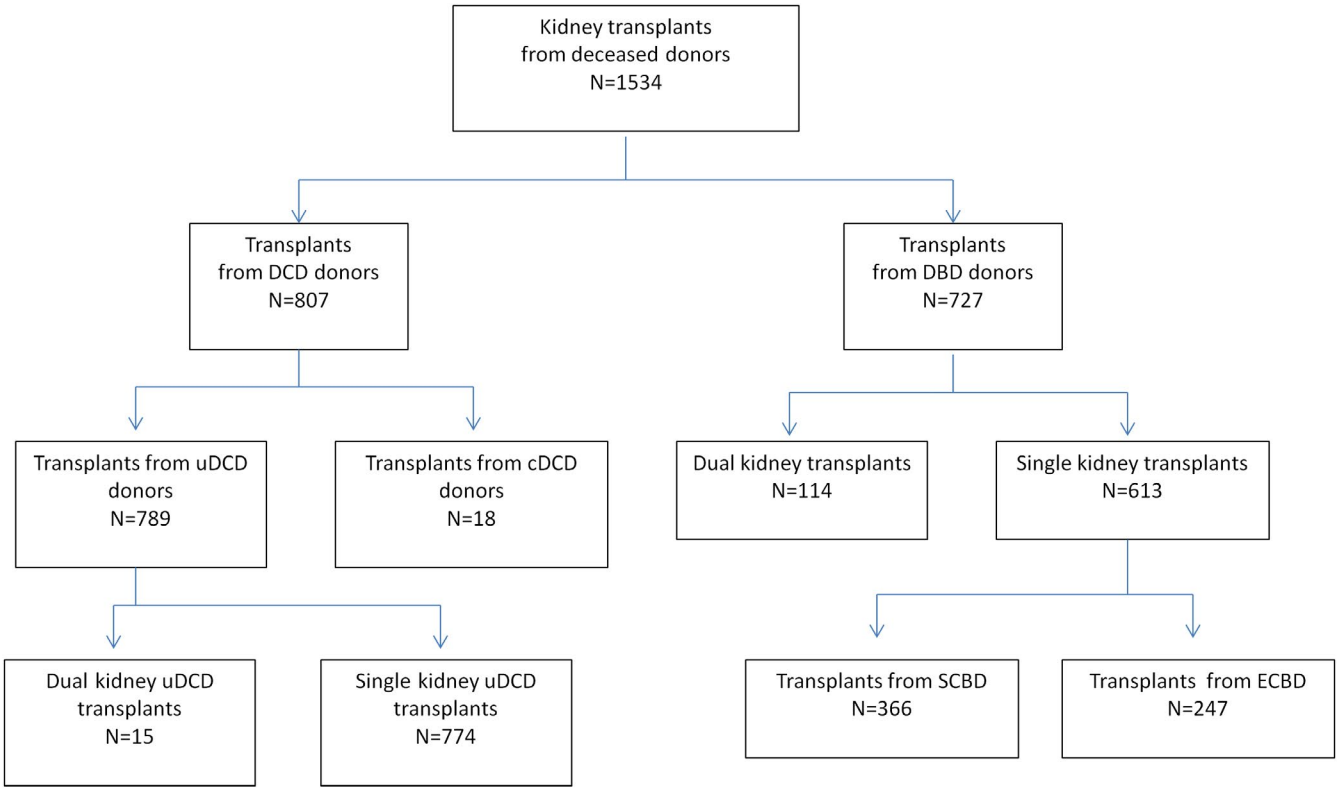


FIGURE 2 Deceased-donor kidney transplants performed at our center (Hospital Clínico San Carlos, Madrid, Spain) over the period January 1996 to December 2015. DCD, donation after circulatory death; uDCD, uncontrolled donation after circulatory death; cDCD, controlled donation after circulatory death; DBD, donation after brain death; SCD, standard-criteria brain-dead donors; ECD, expanded-criteria brain-dead donors [Color figure can be viewed at wileyonlinelibrary.com]

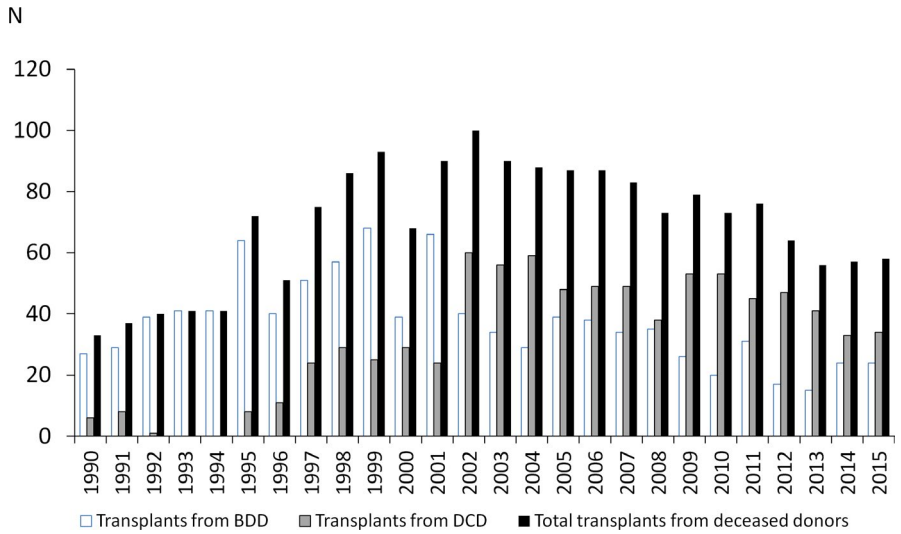


FIGURE 3 Total number of kidney transplants performed by year from deceased donors at our center (Hospital Clínico San Carlos, Madrid, Spain) over the period January 1996 to December 2015. White bars = DBD transplants, gray bars = DCD transplants, black bars = total transplants from deceased donors [Color figure can be viewed at wileyonlinelibrary.com]

Fisher's test were used to compare categorical variables. Asymmetric variables, provided as the median and first and third quartiles (IQR: p25-p75), were compared by the median test.

The annual transplantation rate was calculated as the number of patients transplanted in the year *100/(prevalent patients on January 1 plus new patients added in the year). Odds ratios and their 95% confidence intervals (CI) were calculated as the relative effect of rates of a given variable for 2015 referred to corresponding rates for 1996.

Kaplan-Meier curves were used to examine graft survival. Associated *P* values were derived from the log-rank test.

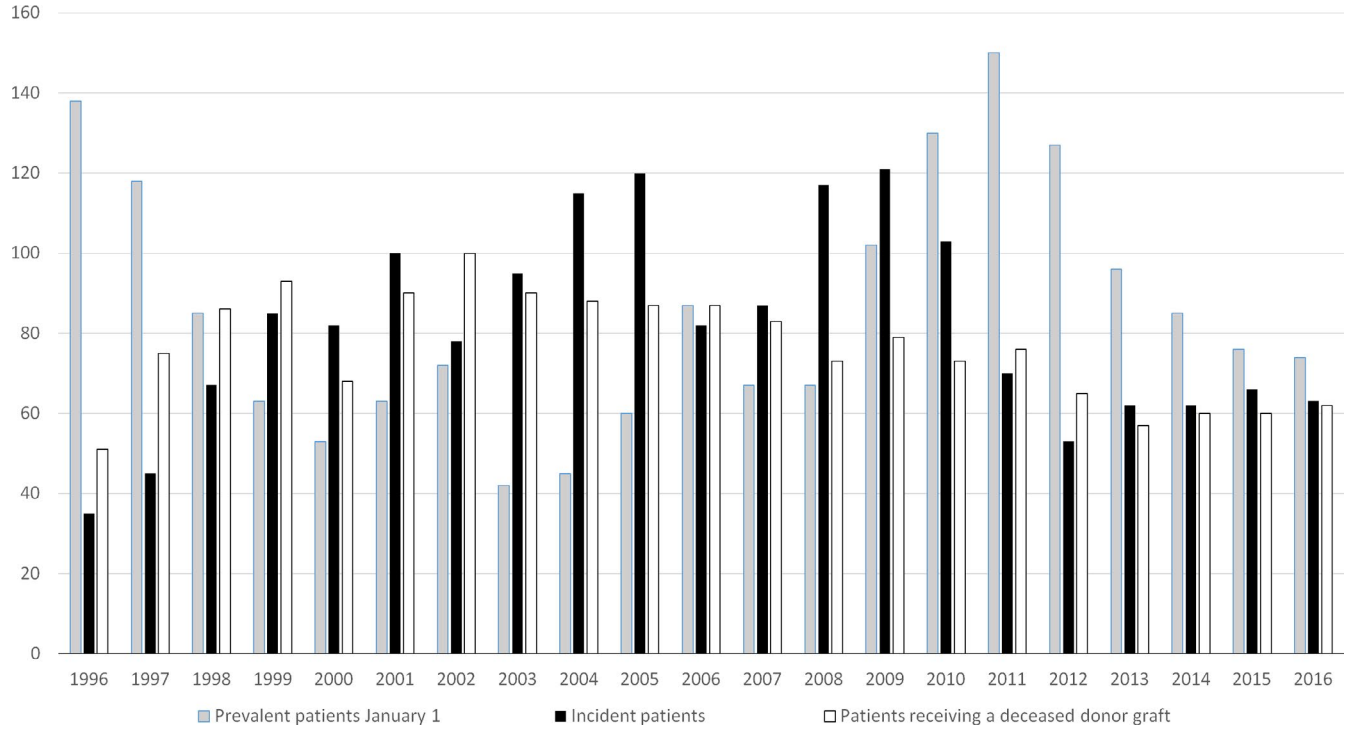


FIGURE 4 Numbers of prevalent patients on the waiting list on January 1 (gray bars), incident patients (black bars), and transplants (white bars) by year [Color figure can be viewed at wileyonlinelibrary.com]

To identify donor factors possibly associated with graft loss due to PNF, we conducted a univariate analysis including the variables: donor sex, age, and cause of death; warm and cold ischemia times; regional perfusion (hypothermic or normothermic); machine preservation; recipient sex, age, and cause of end-stage renal disease; prior transplantation; preformed anti-HLA antibodies; HLA mismatch; calcineurin inhibitor treatment pretransplant; and era. Cutoffs for cardiac arrest and CPR times were based on the 75th percentile of the sample. A logistic regression model was constructed adjusted by backward stepwise regression based on maximum likelihood estimators including variables showing a $P < .15$ in the univariate analysis. Odds ratios and their significance were calculated for each variable according to criteria for entry ($P = .05$) and removal ($P = .10$). Possible interactions were assessed by introducing multiplicative terms (cause of death*cardiac arrest time, cause of death*CPR time, cause of death*donor age, cause of death*cold ischemia time, perfusion machine* cardiac arrest time, perfusion machine* CPR time). The discriminative ability of the logistic models was determined through the area under the receiver operating characteristic curve (AUROC) and 95% CI. Models were calibrated by comparing predicted versus observed probabilities after calculating these from the adjusted model coefficients; probabilities were divided into intervals on the basis of their deciles. The Hosmer-Lemeshow test was used to assess goodness of fit. Model selection was based on that showing the highest discriminative power, good calibration, viable capacity, and fulfilling the principle of parsimony (explaining the maximum variability outcome variable with the smallest number of variables included). Data were available for all transplants.

All statistical tests were performed using the packages SPSS 20.0 and STATA 12.0. Significance was set at $P < .05$.

3 | RESULTS

3.1 | Impacts on the waiting list

In Figure 4 we provide the numbers of prevalent patients on the kidney transplantation waiting list on January 1 of each year, as well

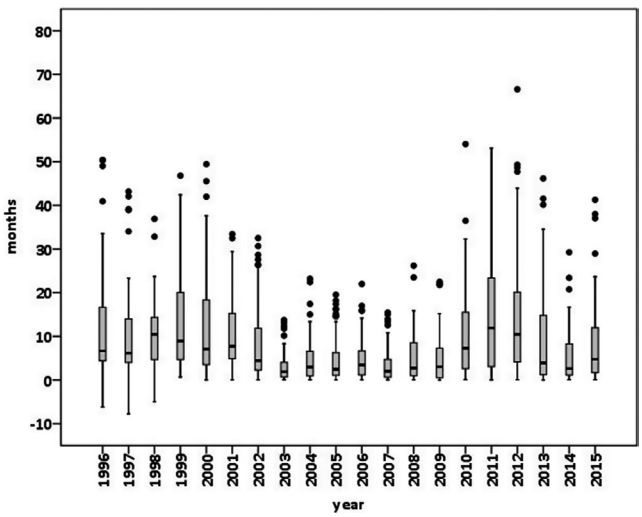


FIGURE 5 Median times to transplant from addition to our waiting list by year. Box plots represent the median and interquartile range. Outliers indicated with small dots

as the number of incident patients on our list and transplants conducted each year. Because of the increased number of transplants performed at the program outset, individuals listed at other centers were transferred to our hospital, introducing wide variability in incident patients.

Figure 5 shows the median time until transplantation from when the patient is waitlisted at our center.

The median time from dialysis onset to transplantation was 27.8 months over the period 1990-1995 (IQR 14.1-54.7) and 19.6 months for the era 1996-2015 (IQR 8.9-36.2) ($P < .001$). Annual deceased-donor transplant rate increased from 29% in 1996 to 42.3% in 2015 (OR 1.75; IQR 1.07-2.87, $P = .0241$) and exceeded 65% in some years such as 2002 and 2003. Over the study period, 101 patients received a deceased-donor transplant in a predialysis situation.

3.2 | Outcomes

Median follow-up was 10.8 years (IQR 6.6-15.3).

Table 1 lists the general characteristics of the uDCD and DBD transplants. As expected, the groups were not comparable in terms of donor age, sex, cause of death, or recipient immunosuppression. Uncontrolled DCD were predominantly male and the most common cause of death was heart disease. In uDCD recipients, cold ischemia time was shorter at the expense of slightly worse HLA-DR compatibility. Uncontrolled donor time variables in minutes were cardiac arrest median 10 (IQR 5-13), extrahospital CPR mean 62.8 (SD 20.6), in-hospital CPR mean 45.5 (SD 14.8), and total warm ischemia mean 116.8 (SD 20.2).

Transplantation outcomes are provided in Table 2. Higher rates of both PNF and DGF were detected in the uDCD graft recipients. Acute rejection was similar across the 3 groups. Kidney function was better in recipients of grafts from SCD at all follow-up times. At 5 and 10 years, kidney function was better in uDCD than ECD recipients ($P < .001$ and $P = .021$, respectively). Graft survival in uDCD recipients was worse than in SCD recipients ($P = .004$) but better than in ECD transplants ($P = .021$) (Figure 6). After the third month, graft survival times were practically parallel for transplants from uDCD donors and standard-criteria donors. When grafts lost to PNF were excluded from the graft survival analysis, no differences were observed between uDCD and SCD recipients ($P = .997$).

As recipients of grafts from ECD were older than recipients of uDCD grafts, a subanalysis of graft survival in patients older than 60 years was conducted. Mean recipient ages were comparable [65.8, 65.8, and 66.1 years for recipients of uDCD, SCD, and ECD, respectively ($P = .369$)]. Graft survival (death censored) (Figure 7) was worse in recipients of ECD ($P = .032$ vs uDCD and $P = .042$ vs SCD). Death not-censored graft survival was better in recipients of uDCD compared to ECD ($P = .047$).

Figure 8 shows graft survival (death censored) after stratifying recipients according to the presence or absence of DGF. Patients with PNF were excluded. In patients with DGF, graft survival was better in uDCD vs SCD transplant recipients ($P = .014$) and similar when DGF was present ($P = .585$). Kidney transplantation from ECD showed worse graft survival regardless of DGF. In SCD and ECD graft recipients with DGF, graft survival was significantly lower than in those without DGF ($P < .001$ and $P = .012$, respectively). However, in uDCD recipients, the presence of DGF was not related to a worse prognosis ($P = .324$).

Table S1 provides our 1-year death-censored graft survival rates by era and Table S2 lists PNF causes in recipients of uDCD grafts also by era.

3.3 | Primary nonfunction

The causes of PNF are summarized in Table 2. The most frequent cause was glomerular, arteriolar, and arterial thrombosis with fibrinoid necrosis in arteriole and arterial walls in both kidneys of the same donor (Figure 9). In these transplants, the presence of antibody-mediated rejection or cellular-mediated rejection was ruled out according to revised Banff 2017 classification criteria.[30] These kidney grafts showed poor perfusion after declamping and were explanted during the transplant surgery itself or within 24 hours of surgery. Other causes of PNF were renal artery or vein thrombosis, associated with surgical problems or secondary to perigraft fluid collection and torsion or kinking of the renal vessels; in none of these grafts was fibrinoid necrosis detected.

To identify factors associated with graft loss due to PNF, we compared through logistic regression uDCD transplant recipients with PNF (N = 96) and without PNF (N = 678) (Table 3).

According to logistic regression, the donor factors emerging as predictive of PNF were death by pulmonary embolism, extrahospital CPR time ≥75 minutes, in-hospital CPR time ≥ 50 minutes, and era. The area under the multivariate analysis curve was 0.68 (95%CI 0.62-0.74) and the Hosmer-Lemeshow test $P = .930$. The predicted and observed incidences of this model are depicted in Figure S1.

We also compared the data included in the multivariate analysis by different time intervals (Table S3). This comparison revealed significant differences mainly in uDCD characteristics. Comparing the era 2006-2010 with 1996-2000, donors and recipients were older, CPR and bypass times were longer, cold ischemia time was shorter, and a perfusion machine was used in a greater percentage of cases (Table 3).

Pretransplant graft biopsy findings revealed no data that could indicate compromised subsequent graft viability (data not shown). When pulmonary embolism and trauma were excluded from the analysis, the risk of PNF decreased from OR 3.31 (95% CI 1.89-5.80) to 2.22 (95% CI 1.15-4.27) in uDCD recipients compared to SCD recipients.

4 | DISCUSSION

The use of uDCD has enabled our center to notably increase the number of kidney transplantations and thus also considerably

TABLE 1 Donor and recipient characteristics in uDCD, standard-criteria, and expanded-criteria kidney transplants

	uDCD (N = 774)	SCD (N = 366)	ECD (N = 247)	*P* value
Donor age (y), mean (SD)	40.4 (10.9)	34.6 (12.2)	62.7 (7.7)	<.001
Male donors, %	85.9	61.7	56.9	<.001
Cause of donor death, %				<.001
Cerebrovascular stroke	1.7	40.2	81.8	
Trauma	12.1	43.4	11.3	
Cardiopathy	78.6	2.5	1.2	
Anoxic encephalopathy	2.5	9.3	3.2	
Pulmonary embolism	2.7	0.5	0	
Other	2.5	4.1	2.4	
Recipient age (y), mean (SD)	50.4 (13,3)	47.3 (13.1)	56.1 (12.3)	<.001
Male recipients, %	65.0	62.6	63.6	.716
Time on dialysis (mo.), median (IQR)	15.2 (6.6-30.4)	19.9 (7.9-36.4)	20.0 (8.9-39.4)	.006
Body mass index (kg/m2), mean (SD)	26.0 (4.4)	25.6 (4.3)	25.9 (4.2)	.463
Cold ischemia time, mean (SD)	17.4 (3.3)	19.5 (4.4)	20.3 (4.9)	<.001
Diabetic recipients, %	11	7.1	18.2	<.001
HLA mismatch, mean (SD)				
DR	1.25 (0.66)	1.14 (0.69)	1.18 (0.66)	.022
B	1.53 (0.58)	1.52 (0.59)	1.51 (0.53)	.864
A	1.41 (0.63)	1.37 (0.54)	1.32 (0.65)	.100
HLA-DR mismatch, %				.075
0	12.0	17.5	14.3	
1	50.5	50.6	53.1	
2	37.5	31.7	32.7	
HLA A and B mismatch, %				.576
0	0	0	0	
1-2	28.9	31.1	32.0	
3-4	71.1	68.9	68.0	
Regraft, %	14.6	17.5	16.2	.431
Preformed anti-HLA antibodies, %				.099
0%	85.3	80.6	78.9	
1%-19%	8.0	9.6	8.9	
20%-49%	3.1	4.6	4.5	
≥50%	3.6	5.2	7.7	
Initial immunosuppression treatment, %				
Polyclonal antibodies	41.7	18.0	29.1	<.001
Anti-IL2 receptor antibodies	43.9	12.6	21.5	<.001
Cyclosporine	13.0	35.5	40.1	<.001
Tacrolimus	84.2	63.9	59.9	<.001
Azathioprine	3.4	14.5	13.8	<.001
Mycophenolate	96.6	84.4	83.0	<.001
mTOR inhibitors	3.5	1.9	5.7	.044
Other	0.5	0.3	0.4	.840

uDCD, uncontrolled donation after circulatory death; SCD, standard-criteria brain-dead donors; ECD, expanded-criteria brain-dead donors.

shorten the waiting list. This uDCD program has had an important effect in increasing the annual deceased-donor transplant rate compared with previous eras; for example, it was 1.75 times higher in 2015 than in 1996 (42% vs 29%, respectively). Our experience could be of interest to other countries. For example, according to the Organ Procurement and Transplantation

TABLE 2 Outcomes recorded in the uDCD, SCD, and ECD transplant recipients

	uDCD (N = 774)	SCD (N = 366)	ECD (N = 247)	*P* value
Primary nonfunction, N (%)	96 (12.3)	15 (4.1)	20 (8.1)	<.001
Acute rejection	6 (0.8)	6 (1.6)	5 (2.0)	
Surgical complication	30 (3.9)	7 (1.9)	7 (2.8)	
Transplant renal vein thrombosis	6 (0.8)	1 (0.3)	3 (1.2)	
Transplant renal artery thrombosis	8 (1.0)	3 (0.8)	3 (1.2)	
Hemorrhage	6 (0.7)	2 (0.5)	1 (0.4)	
Arteriovenous fistula	2 (0.3)	0 (0)	0 (0)	
Urological complications	5 (0.6)	1 (0.3)	0 (0)	
Torsion of transplant vessels	2 (0.3)	0 (0)	0 (0)	
Iliac artery thrombosis	1 (0.1)	0 (0)	0 (0)	
TMA	51 (6.6)	0 (0)	3 (1.2)	
Other	9 (1.2)	2 (0.5)	5 (2.0)	
Need for dialysis in immediate posttransplant period, N (%)[a]	445 (65.1)	63 (17.7)	58 (25.1)	<.001
Acute rejection, N (%)	223 (30.1)	125 (34.2)	69 (27.9)	.217
Biopsy-proven	219 (28.2)	96 (26.2)	55 (22.3)	.171
Clinically suspected	14 (1.8)	29 (7.9)	14 (5.7)	<.001
Estimated filtration rate 1 year posttransplant, mL/min, mean (SD)	46.2 (15.7)	56.9(16.9)	44.8 (16.5)	<.001
Estimated filtration rate 5 years posttransplant, mL/min, mean (SD)	46.0(16.2)	54.1 (16.5)	39.6 (14.6)[b]	<.001
Estimated filtration rate 10 years posttransplant, mL/min, mean (SD)	48.6 (17.6)	57.6 (20.0)	40.0 (15.4)[c]	<.001
Proteinuria 1 years posttransplant, mg (day, median (IQR)	223 (126-457)	179 (104-351)	243 (130-513)	.005
Proteinuria 5 years posttransplant, mg (day, median (IQR)	208 (128-456)	172 (108-328)	221 (133-524)	.063
Proteinuria 10 years posttransplant, mg (day, median (IQR)	234 (126-434)	160 (101-319)	230 (158-456)	<.001
Graft survival (death censored), % (SE) {number at risk}				<.001[d]
1 year	85.1 (1.3) {639}	91.7 (1.4) {331}	86.0 (2.2) {199}	
5 years	78.1 (1.5) {485}	85.7 (1.9) {282}	75.8 (2.9) {133}	
10 years	72.2 (1.8) {277}	80.6 (2.2) {197}	61.4 (3.7) {68}	
Graft survival (death not censored), % (SE) {number at risk}				<.001[e]
1 year	82.7 (1.4) {639}	90.4 (1.5) {331}	81.0 (2.5) {199}	
5 years	71.1 (1.7) {485}	80.7 (2.1) {282}	64.4 (3.1) {133}	
10 years	60.1 (2.0) {277}	68.2 (2.5) {197}	43.7 (3.6) {68}	
Graft survival (death censored) excluding grafts lost to PNF, % (SE) {number at risk}				<.001[f]
1 year	97.2 (0.6) {639}	95.7 (1.1) {331}	93.6 (1.6) {199}	
5 years	90.9 (1.2) {485}	89.9 (1.6) {282}	83.1 (2.7) {133}	
10 years	84.6 (1.6) {277}	85.0 (2.0) {197}	67.9 (3.8) {68}	
Causes of graft loss, N (%)				<.001
Acute rejection	29 (3.7)	20 (5.5)	11 (4.5)	
IFTA	63 (8.1)	40 (10.9)	41 (16.6)	
Surgical complications	33 (4.3)	9 (2.5)	7 (2.8)	
Glomerular, arteriolar, and arterial thrombosis with fibrinoid necrosis	51 (6.6)	0 (0)	3 (1.2)	
Other	32 (4.1)	18 (4.9)	23 (9.3)	
Patient survival up to 10 years, % (SE) {number at risk}				<.001

(Continues)

TABLE 2 (Continued)

	uDCD (N = 774)	SCD (N = 366)	ECD (N = 247)	*P* value
1 year	96.2 (0.7) {639}	98.3 (0.7) {331}	92.8 (1.7) {199}	
5 years	89.6 (1.2) {485}	93.9 (1.3) {282}	83.7 (2.6) {133}	
10 years	82.2 (1.7) {277}	84.8 (2.1) {197}	69.7 (3.9) {68}	

uDCD, uncontrolled donation after circulatory death; SCD, standard-criteria brain-dead donors; ECD, expanded-criteria brain-dead donors; IFTA, interstitial fibrosis and tubular atrophy; TMA, thrombotic microangiopathy; SE, standard error.
[a]Recipients with primary nonfunction excluded.
[b]$P < .001$ versus uDCD.
[c]$P = .021$ versus uDCD.
[d]$P < .021$ uDCD versus ECD; $P = .004$ SCD versus uDCD.
[e]$P = .001$ SCD versus ECD; $P < .001$ uDCD versus ECD.
[f]$P = .997$ SCD versus uDCD; $P < .001$ SCD versus ECD; $P < .001$ uDCD versus ECD.

Network/Scientific Registry for Transplant Recipients (OPTN/SRTR) 2015 Report, 47.8% of patients waiting for transplant would accept an ECD kidney.[1] Considering our graft survival rates in the uDCD kidney recipients, accepting an uDCD kidney could be a feasible option to reduce a patient's waiting time.

Our data indicate worse graft survival and kidney function rates for uDCD transplants than for SCD transplants. However, these rates were at least comparable to those observed for ECD transplants. Graft survival in our ECD recipients may seem low compared to recent data, though we should underscore that this is a historic series dating back to 1996. In the past few years, 1-year graft survival (death censored) at our center in recipients of grafts from ECD has improved (Table S2). In a recent meta-analysis [31] comparing ECD and SCD transplants, pooled graft survival probabilities (death not censored) were 59.2% and 75.1% at 5 years, respectively. Our results for both uDCD and ECD are improved over these reported figures: 71.1% and 64.4%, respectively, and similar to the 5-year survival for ECD transplants of about 64% quoted in the OPTN/SRTR 2013 Annual Data Report.[32]

Our worse outcomes for uDCD compared SCD transplants can be attributed to more PNF. Reported kidney graft PNF rates in uDCD transplant recipients in the larger patient series range from 1.8% [26] to 20%.[23,24] Our PNF rate was 12% and 5 and 10 year graft survival rates were 78% and 72%, ie, higher than published rates.[23,24,26] If we compare our data with the DCD donor transplant results provided in the OPTN/SRTR 2016 Report [33] (mostly controlled DCD), our survival rates for uDCD transplants were initially lower though comparable at 5 years (75% vs 78.1%).

The main cause of graft lost in our cohort of uDCD recipients was PNF. Hence, excluding transplants showing PNF, graft survival rates were comparable (Table 2). It therefore seems that uDCD kidneys could be a valuable contribution to the donor pool if this high PNF rate were somehow improved. Research efforts assessing this type of donation should try to identify risk factors for PNF. PNF secondary to glomerular, arteriolar, and arterial thrombosis with fibrinoid necrosis was described from the start of uDCD programs.[34] We suggest ischemia reperfusion injury as a likely cause, as this lesion usually appears immediately after reperfusion and

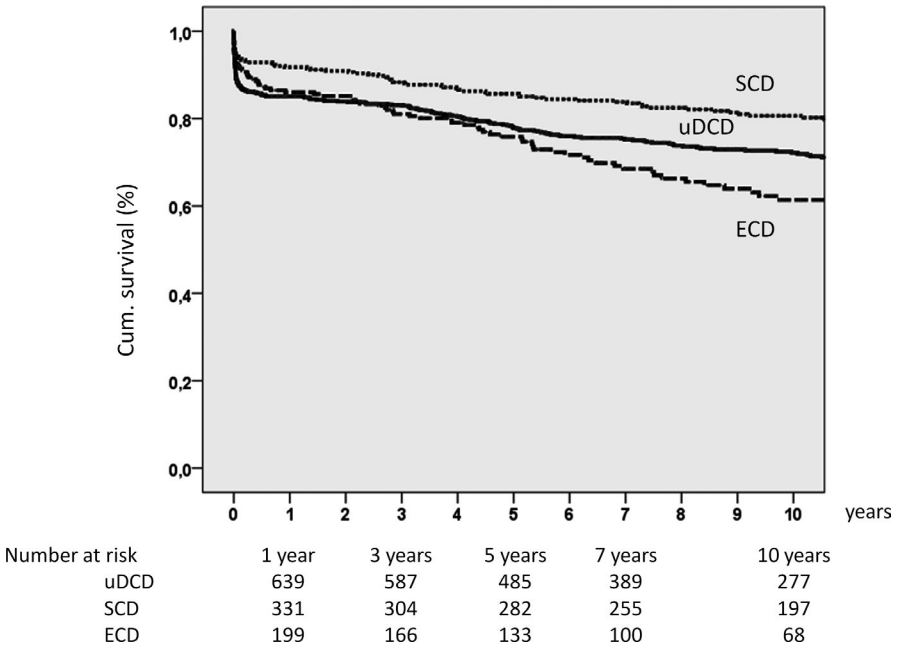
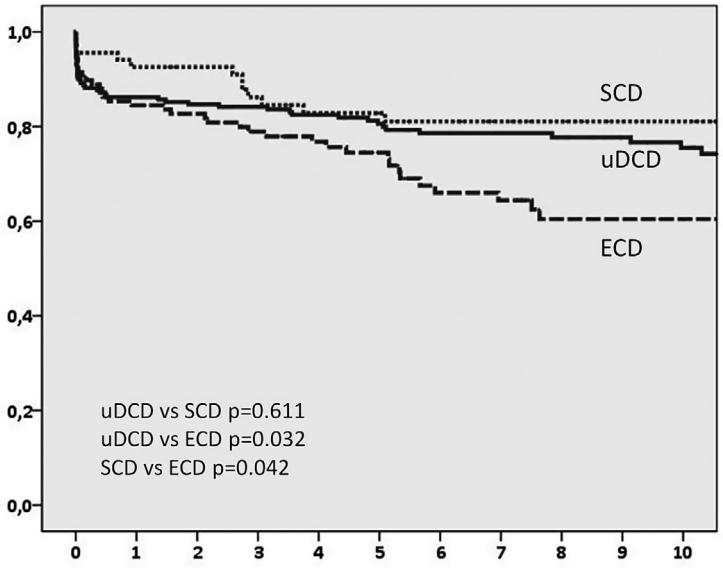
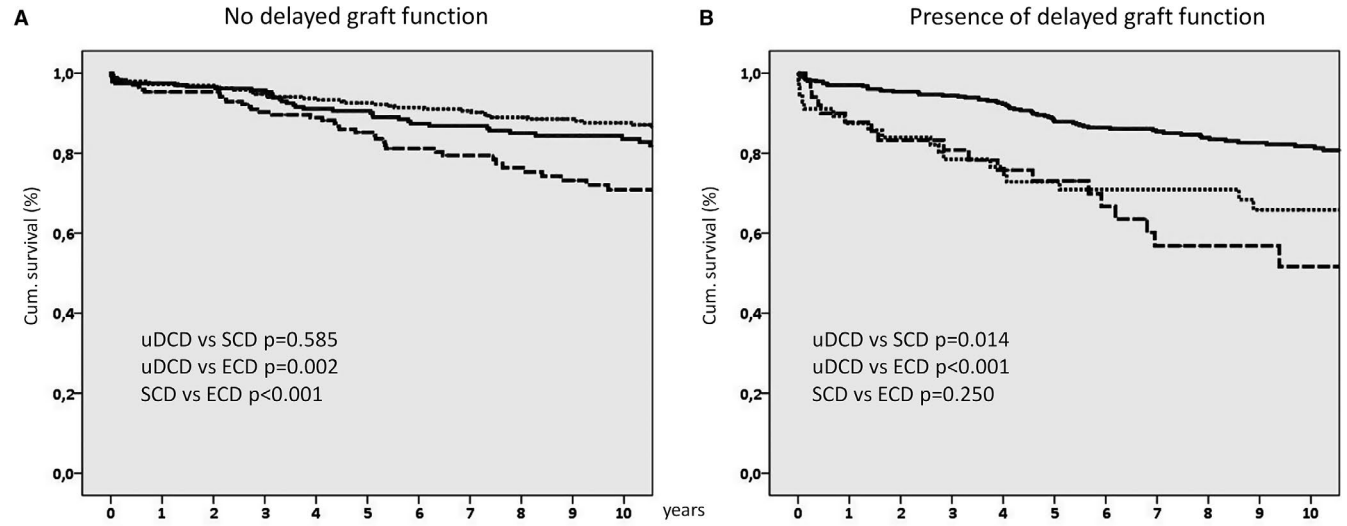


FIGURE 6 Actuarial graft survival in renal transplants according to donor type. uDCD, uncontrolled donation after circulatory death (solid line); SCD, standard-criteria brain-dead donors (dotted line); and ECD, expanded-criteria brain-dead donors (broken line). The log-rank test was used to calculate *P* values. Data were obtained from our center over the period January 1996 to December 2015. The log-rank test was used to calculate *P* values. uDCD vs ECD $P < .021$; SCD vs uDCD $P = .004$



Number at risk	1 year	5 years	10 years
uDCD	172	124	65
SCD	62	47	24
ECD	95	55	22

FIGURE 7 Actuarial graft survival (death censored) in recipients ≥60 years. uDCD, uncontrolled donation after circulatory death (solid line); SCD, standard-criteria brain-dead donors (dotted line); and ECD, expanded-criteria brain-dead donors (broken line). The log-rank test was used to calculate *P* values. uDCD vs SCD *P* = .611; uDCD vs ECD *P* = .032; SCD vs ECD *P* = .042



Number at risk	1 year	5 years	10 years
uDCD	226	177	106
SCD	282	244	174
ECD	160	108	58

Number at risk	1 year	5 years	10 years
uDCD	413	308	171
SCD	49	38	23
ECD	39	25	10

FIGURE 8 Actuarial graft survival in renal transplants according to the presence or absence of delayed graft function. A, Actuarial graft survival in kidney transplants without delayed graft function. B, Actuarial graft survival in kidney transplants with delayed graft function. Comparison of graft survival in the absence of delayed graft function uDCD vs SCD *P* = .585; uDCD vs ECD *P* = .002; SCD vs ECD *P* < .001. Comparison of graft survival in the presence of delayed graft function uDCD vs SCD *P* = .014; uDCD vs ECD *P* < .001; SCD vs ECD *P* < .250. Comparison of graft survival in recipients with and without delayed graft function: uDCD *P* = .324, SCD *P* < .001, ECD *P* = .012. uDCD, uncontrolled donation after circulatory death (solid line); SCD, standard-criteria brain-dead donors (dotted line); and EDCD, expanded-criteria brain-dead donors (broken line). The log-rank test was used to calculate *P* values

in both grafts of a single donor. Moreover, we carefully reviewed medical records and histological findings in nephrectomy specimens to rule out the possibility of rejection or primary disease recurrence. It is known that the endothelium is a target of choice for injury by ischemia reperfusion.[35] In experimental models of ischemia reperfusion injury, renal perfusion in peritubular capillaries is compromised within minutes of unclamping.[36] Endothelial dysfunction/injury and apoptosis compromise microcirculatory renal blood flow through decreased vasodilatory capacity, coagulation activation and the formation of microvascular thrombi, and increased rolling/adhesion of inflammatory cells.[37,38] Kwon et al[39] assessed intraoperative graft biopsies after reperfusion in 21

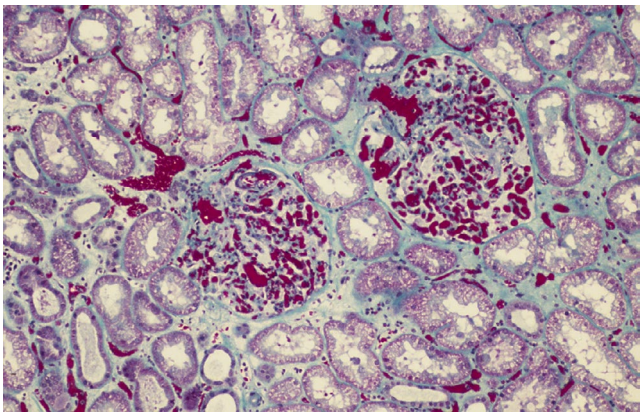


FIGURE 9 Glomeruli with erythrocyte congestion, fibrin thrombi, and fibrinoid necrosis in the arteriole (Masson's trichrome, ×200) [Color figure can be viewed at wileyonlinelibrary.com]

deceased donor renal allografts using fluorescence microscopy to examine vascular smooth muscle and endothelial cell integrity as well as peritubular interstitial pericytes in the biopsies. The reperfused, transplanted kidneys exhibited postischemic injury to the renal vasculature, as demonstrated by disorganization/disarray of the actin cytoskeleton in vascular smooth muscle cells and disappearance of von Willebrand factor from vascular endothelial cells. Damage to peritubular capillary endothelial cells was more severe in subjects who were to suffer acute renal failure than in those rapidly recovering their graft function. Endothelial integrity of peritubular capillaries was better preserved, and pericytes were more pronounced in patients who would show recovery of their graft function compared with those showing delayed graft function. In addition, ischemia-reperfusion injury can increase complement-associated injury through complement activation.[40] Accordingly and considering that DCD organs sustain an inevitable period of warm ischemia after circulatory arrest (between cessation of cardiopulmonary function and onset of preservation), we hypothesize that following reperfusion, endothelial damage takes place with serious repercussions on graft function after transplantation. Warm ischemia time is much longer for uDCD than cDCD grafts. Although our inclusion criteria for donor candidates were rigorous (cardiac arrest and CPR times), we had no variable available to monitor the effectiveness of CPR. At present, we are testing the use of capnography for this purpose. In our study, as variables predictive of PNF, we identified prolonged warm ischemia, donor death secondary to pulmonary embolism, and era. In donors dying from pulmonary embolism, CPR maneuvers would likely be less efficient at maintaining organs adequately oxygenated. A negative result of our study is the higher number of grafts lost to PNF in the medium-final stages than in the initial stages of our program. Thus, most of these losses occurred in the period 2006-2010 with respect to 1996-2000. By analyzing the data it emerges that these losses were associated with a slightly older donor age and suffering longer warm ischemia times, likely explaining the worse outcomes. Accordingly, we believe the strict surveillance of protocols is essential both those implemented by the outside and in-hospital teams to ensure proper donor management and optimal organ protection and preservation. Hence, individuals whose cause of death is pulmonary embolism need to be meticulously assessed and efforts made to shorten warm ischemia time. In DCD kidney transplantation multivariate risk studies including data from a large national database, donor age was identified as an independent risk factor for PNF (reviewed in Ref.[41]). Donor age was not related here to an independent risk of PNF. The explanation for this difference could be first that our donors were younger, and second that most studies have focused on cDCD. Recently, Peters-Sengres et al[23] compared using data from the Dutch Organ Transplantation Registry, 97 recipients of uDCD kidneys with 1441 recipients of cDCD kidneys. These authors observed a greater rate of nonviability (19.6% vs 9.6%), higher incidence of DGF, and worse survival in the uDCD graft recipients. They also found that donor age and warm/cold ischemia times were linked to PNF in these uDCD recipients. These results confirm earlier findings by Hoogland et al[24]

Brook et al[42] found that in patients with DGF, graft survival was better for DCD than DBD kidneys. The reasons for the higher rate of graft survival in DBD recipients are not clear although the authors hypothesized they may be related to the absence in DCD of the complex events associated with brain death. The link between DGF and graft outcome in DCD kidney transplants is unclear and some studies have identified worse graft outcomes in recipients showing DFG[20,21] whereas others have not.[13] Here, DGF was not found to confer a worse prognosis in recipients of uDCD kidneys, in line with our prior experience[4,27] and with Spanish[43] experience in general, whereas DGF did determine a worse prognosis in recipients of DBD grafts.

Of note, we should mention the large number of grafts from uDCD donors that were rejected (see Figure 1). Among the most frequent causes was the poor perfusion of the procured graft, which likely reflects inadequate CPR. The other two more common causes were histologic findings (high Remuzzi score) and severe donor atheromatosis, which is not unexpected considering the leading cause of death was heart disease. Notwithstanding, our fast approach to donor candidates designed to cut down the duration of warm ischemia leaves little time for donor data collection. This determines that donors with infectious diseases or with a history of drug abuse or a kidney condition (polycystosis, multicystosis, pyelonephritis) and other disorders that encompass what we describe in Figure 2 as a poor macroscopic appearance of the graft could initially enter our fast-track protocol. Current donation rates in our country are 25.7% for deceased donors and 26.8% for DCD though we lack specific data for uDCD.[44] Donor rejection rates provided in the OPTN/SRTR 2016 Report[33] are >60% of kidneys recovered from donors ≥65 years and >50% for donors aged 50-64 years, although rates of kidneys recovered from DCD donors and not transplanted are better than ours (ie, lower). However, most of these were from cDCD.[33]

We are aware that some will have ethical concerns about uncontrolled donation and would like to highlight two points

TABLE 3 Univariate and multivariate logistic regression for primary nonfunction in uncontrolled donation after circulatory death kidney transplants

	Univariate (N = 774 transplants)				Multivariate (N = 774 transplants)	
	Viable transplants (N = 678)	PNF (N = 96)	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Cause of death, N (%)				.002		.005
Trauma	80 (11.8)	14 (14.6)	1.38 (0.75-2.56)	.303	1.73 (0.89-3.34)	.103
Pulmonary embolism	13 (1.9)	8 (8.3)	4.84 (1.95-12.13)	.001	4.31 (1.65-11.23)	.003
Other	585 (86.3)	74 (77.1)	1		1	
Donor age, mean (SD)	40.5 (11.0)	40.1 (10.2)	1.00 (0.98-1.02)	.767		
Donor sex male, N (%)	587 (86.6)	78 (81.3)	0.67 (0.38-1.17)	.162		
Cardiac arrest time, N (%)				.449		
<13 min	498 (73.5)	74 (77.1)	1			
≥ 13 min	180 (26.5)	22 (22.9)	0.82 (0.50-1.36)			
Extrahospital CPR time, N (%)				.068		.010
<75 min	492 (72.6)	61 (63.5)	1		1	
≥75 min	186 (27.4)	35 (36.5)	1.52 (0.97-2.38)		1.94 (1.18-3.22)	
In-hospital CPR time ≥ 50 min, N (%)				.024		.021
<50 min	480 (70.8)	57 (59.4)	1		1	
≥50 min	198 (29.2)	39 (40.6)	1.66 (1.07-2.59)		1.79 (1.09-2.93)	
Regional perfusion				.836		
Normothermic	24 (3.5)	3 (3.1)	1			
Hypothermic	654 (96.5)	93 (96.9)	0.88 (0.26-2.98)			
Bypass time, N (%)				.058		
<215 min	512 (75.5)	81 (84.4)	1			
≥215 min	166 (24.5)	15 (15.6)	0.57 (0.32-1.02)			
Cold ischemia time min, mean (SD)	17.4 (3.3)	17.3 (3.4)	0.99 (0.93-1.06)	.763		
Use of perfusion machine, N (%)	248 (36.6)	35 (36.5)	1.00 (0.64-1.55)	.982		
Recipient age, mean (SD)	50.7 (13.1)	49.3 (13.7)	0.99 (0.98-1.01)	.337		
Recipient sex male, N (%)	438 (64.6)	65 (67.7)	1.15 (0.73-1.81)	.551		
Cause of end-stage renal disease, N (%)				.797		
Glomerulonephritis	221 (32.6)	25 (26.0)	1			
Diabetes mellitus	72 (10.6)	9 (9.4)	1.11 (0.49-2.48)	.808		
Adult polycystic kidney disease	99 (14.6)	14 (14.6)	1.25 (0.62-2.51)	.530		
Chronic interstitial disease	104 (15.3)	20 (20.8)	1.70 (0.90-3.20)	.100		
Nephroangiosclerosis	113 (16.7)	17 (17.7)	1.33 (0.69-2.56)	.395		
Other	22 (3.2)	4 (4.2)	1.61 (0.51-5.04)	.416		
Unknown	47 (6.9)	7 (7.3)	1.32 (0.54-3.22)	.547		
Transplant era, N (%)				.002		.001
1996-2000	107 (15.8)	5 (5.2)	1		1	
2001-2005	210 (31.0)	31 (32.3)	3.16 (1.19-8.36)	.020	2.56 (0.94-6.96)	.069
2006-2010	191 (28.2)	43 (44.8)	4.82 (1.85-12.53)	.001	4.64 (1.75-12.32)	.002
2011-2015	170 (25.1)	17 (17.7)	2.14 (0.77-5.97)	.146	1.82 (0.62-5.36)	.275
Previous transplantation, N (%)				.337		
No	583 (86.0)	79 (82.3)	1			
Yes	95 (14.0)	17 (17.7)	1.32 (0.75-2.33)			

(Continues)

TABLE 3 (Continued)

	Univariate (N = 774 transplants)				Multivariate (N = 774 transplants)	
	Viable transplants (N = 678)	PNF (N = 96)	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Preformed anti-HLA antibodies, N (%)				.660		
0%	583 (86.0)	79 (82.3)	1			
1%-19%	50 (7.4)	10 (10.4)	1.48 (0.72-3.03)	.280		
20%-49%	20 (2.9)	4 (4.2)	1.48 (0.49-4.43)	.487		
≥50%	25 (3.7)	3 (3.1)	0.89 (0.26-3.00)	.845		
HLA A and B mismatch, N (%)				.504		
0	0	0				
1-2	199 (29.4)	25 (26.0)	1			
3-4	479 (70.6)	71 (74.0)	1.18 (0.73-1.92)			
HLA-DR mismatch, N (%)				.350		
0	79 (11.7)	14 (14.6)	1			
1	349 (51.5)	42 (43.8)	0.68 (0.35-1.30)	.245		
2	250 (36.9)	40 (41.7)	0.90 (0.47-1.75)	.761		
Use of calcineurin inhibitor pretransplantation, N (%)				.231		
No	281 (41.4)	46 (47.9)	1			
Yes	397 (58.6)	50 (52.1)	0.77 (0.50-1.18)			

Cutoff cardiac arrest and CPR times were based on the 75th percentile of the sample. Area under the multivariate analysis curve = 0.68 (95%CI 0.62-0.74). Hosmer-Lemeshow test *P* = .516.
PNF, primary nonfunction; CPR, cardiopulmonary resuscitation.

related to this issue. First, the determination of death always occurs in an in-hospital setting and is conducted by a physician outside the donation team and team originally responsible for the advanced CPR. Lack of cardiocirculatory function is assessed during a 5-minute period of observation. Immediately after this, cardiac compression and mechanical ventilation are resumed to ensure organ viability, and this is followed by regional abdominal perfusion with oxygenated blood.[45] The second point is that the mean time between initial cardiac arrest and balloon placement in the aorta was 116 minutes in our study. Thus, there is no doubt as to the neurologic situation of the patient at this point and its irreversibility.[45]

The main limitation of this study is that it was based on real-world and not randomized data. In effect, some transplants were performed almost 30 years ago, during which time donor acceptance criteria and immunosuppressive treatments have varied. Nevertheless, we considered we should describe the whole patient cohort in order to detect the factors that could lead to a worse prognosis in uDCD graft recipients. At our center it is common practice to allocate kidneys from aged donors to older recipients and we apply different immunosuppression regimens to the different transplant types as we feel that treatment should be tailored to suit the characteristics of both recipient and donor. These differences will lead to biases capable of explaining some differences in results. This is why we separately examined graft survival in recipients of 60 years or older and provide survival data for the different eras. Another limitation is that it was a single-center study though with much experience with managing this type of transplant. We also lacked external validation. We should highlight that the cohort of patients examined was prospectively collected using a well-defined follow-up protocol in which losses were few. Regardless of these limitations, the main goal of our study was to show that uDCD donors could be an adequate source of kidneys for transplant and to identify risk factors in the uDCD donors for nonviability.

According to the outcomes of our long-standing deceased-donor kidney transplantation program, donation after uncontrolled circulatory death could be a viable option to expand the kidney donor pool. This is important because transplantation has both financial and life year advantages over dialysis in that it adds about 5 quality-adjusted years of life compared with dialysis.[46] We should stress that not only the transplantation team but also the emergency services have the opportunity to play a key role in creating an effective uDCD program and thus help shorten the waiting list.

DISCLOSURE

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

ORCID

Ana I. Sánchez-Fructuoso https://orcid.org/0000-0001-7017-9729

REFERENCES

1. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2015 annual data report: kidney. *Am J Transplant*. 2017;17(suppl 1):21-116.
2. 2017 Annual ONT report on kidney transplantation. http://www.ont.es/infesp/Memorias/Memoria%20Renal%202017_para%20colgar.pdf. Accessed May 16, 2018.
3. Kootstra G, Daemen JH, Oomen AP. Categories of nonheart-beating donors. *Transplant Proc*. 1995;27:2893-2894.
4. Sánchez-Fructuoso A, Prats D, Naranjo P, et al. Renal transplantation from non-heart-beating donors: a promising alternative to enlarge the donor pool. *J Am Soc Nephrol*. 2000;11(2):350-358.
5. Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential improvements. *Transplantation*. 2014;97(3):258-264.
6. Locke JE, Segev DL, Warren DS, et al. Outcomes of kidneys from donors after cardiac death: implications for allocation and preservation. *Am J Transplant*. 2007;7(7):1797-1871.
7. Barlow AD, Metcalfe MS, Johari Y, et al. Case-matched comparison of long-term results of non-heart beating and heart-beating donor renal transplants. *Br J Surg*. 2009;96(6):685-691.
8. Snoeijs MG, Winkens B, Heemskerk MB, et al. Kidney transplantation from donors after cardiac death: a 25-year experience. *Transplantation*. 2010;90(10):1106-1112.
9. Summers DM, Johnson RJ, Allen J, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet*. 2010;376(9749):1303-1311.
10. Summers DM, Johnson RJ, Hudson A, et al. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. *Lancet*. 2013;381(9868):727-734.
11. Pine JK, Goldsmith PJ, Ridgway DM, et al. Comparable outcomes in donation after cardiac death and donation after brainstem death: a matched analysis of renal transplants. *Transplant Proc*. 2010;42(10):3947-3950.
12. Bellingham JM, Santhanakrishnan C, Neidlinger N, et al. Donation after cardiac death: a 29-year experience. *Surgery*. 2011;150(4):692-702.
13. Singh RP, Farney AC, Rogers J, et al. Kidney transplantation from donation after cardiac death donors: lack of impact of delayed graft function on post-transplant outcomes. *Clin Transplant*. 2011;25(2):255-264.
14. Van Arendonk KJ, James NT, Locke JE, et al. Late graft loss among pediatric recipients of DCD kidneys. *Clin J Am Soc Nephrol*. 2011;6(11):2705-2711.
15. Kosmoliaptsis V, Salji M, Bardsley V, et al. Baseline donor chronic renal injury confers the same transplant survival disadvantage for DCD and DBD kidneys. *Am J Transplant*. 2015;15(3):754-763.
16. Singh SK, Kim SJ. Does expanded criteria donor status modify the outcomes of kidney transplantation from donors after cardiac death? *Am J Transplant*. 2013;13(2):329-336.
17. Jochmans I, Darius T, Kuypers D, et al. Kidney donation after circulatory death in a country with a high number of brain dead donors: 10-year experience in Belgium. *Transpl Int*. 2012;25(8):857-866.
18. Hamed MO, Chen Y, Pasea L, et al. Early graft loss after kidney transplantation: risk factors and consequences. *Am J Transplant*. 2015;15(6):1632-1643.
19. Summers DM, Watson CJ, Pettigrew GJ, et al. Kidney donation after circulatory death (DCD): state of the art. *Kidney Int*. 2015;88(2):241-249.
20. Lim WH, McDonald SP, Russ GR, et al. Association between delayed graft function and graft loss in donation after cardiac death kidney transplants - a paired kidney registry analysis. *Transplantation*. 2017;101(6):1139-1143.
21. Nagaraja P, Roberts GW, Stephens M, et al. Influence of delayed graft function and acute rejection on outcomes after kidney transplantation from donors after cardiac death. *Transplantation*. 2012;94:1218-1223.
22. Demiselle J, Augusto JF, Videcoq M, et al. Transplantation of kidneys from uncontrolled donation after circulatory determination of death: comparison with brain death donors with or without extended criteria and impact of normothermic regional perfusion. *Transpl Int*. 2016;29(4):432-442.
23. Peters-Sengers H, Homan van der Heide JJ, Heemskerk MB, et al. Similar 5-year estimated glomerular filtration rate between kidney transplants from uncontrolled and controlled donors after circulatory death-A Dutch cohort study. *Transplantation*. 2017;101(6):1144-1151.
24. Hoogland ERP, Snoeijs MGJ, Winkens B, et al. Kidney transplantation from donors after cardiac death: uncontrolled versus controlled donation. *Am J Transplant*. 2011;11(7):1427-1434.
25. Viglietti D, Abboud I, Hill G, et al. Kidney allograft fibrosis after transplantation from uncontrolled circulatory death donors. *Transplantation*. 2015;99(2):409-415.
26. Gagandeep S, Matsuoka L, Mateo R, et al. Expanding the donor kidney pool: utility of renal allografts procured in a setting of uncontrolled cardiac death. *Am J Transplant*. 2006;6(7):1682-1638.
27. Sánchez-Fructuoso AI, Marques M, Prats D, et al. Victims of cardiac arrest occurring outside the hospital: a source of transplantable kidneys. *Annals Intern Med*. 2006;145(3):157-164.
28. Rao PS, Ojo A. The alphabet soup of kidney transplantation: SCD, DCD, ECD–fundamentals for the practicing nephrologist. *Clin J Am Soc Nephrol*. 2009;4(11):1827-1831.
29. Levey A, Greene T, Kusek J, Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine (abstr). *J Am Soc Nephrol*. 2000;11:A0828.
30. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant*. 2018;18(2):293-307.
31. Querard AH, Foucher Y, Combescure C, et al. Comparison of survival outcomes between expanded criteria donor and standard criteria donor kidney transplant recipients: a systematic review and meta-analysis. *Transpl Int*. 2016;29(4):403-415.
32. Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2013 annual data report: kidney. *Am J Transplant*. 2015;15(suppl 2):1-34.
33. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2016 annual data report: kidney. *Am J Transplant*. 2018;18(suppl 1):18-113.
34. Schlumpf R, Candinas D, Zollinger A, et al. Kidney procurement from non-heartbeating donors: transplantation results. *Transpl Int*. 1992;5(suppl 1):S424-S428.
35. Cardinal H, Dieudé M, Hébert MJ. Endothelial dysfunction in kidney transplantation. *Front Immunol*. 2018;23(9):1130.
36. Yamamoto T, Tada T, Brodsky SV, et al. Intravital videomicroscopy of peritubular capillaries in renal ischemia. *Am J Physiol Renal Physiol*. 2002;282:F1150-F1155.
37. Molitoris BA. Therapeutic translation in acute kidney injury: the epithelial/endothelial axis. *J Clin Invest*. 2014;124:2355-2363.
38. Goligorsky MS, Brodsky SV, Noiri E. NO bioavailability, endothelial dysfunction, and acute renal failure: new insights into pathophysiology. *Semin Nephrol*. 2004;24:316-323.

39. Kwon O, Hong SM, Sutton TA, Temm CJ. Preservation of peritubular capillary endothelial integrity and increasing pericytes may be critical to recovery from postischemic acute kidney injury. *Am J Physiol Renal Physiol*. 2008;295(2):F351-F359.
40. de Vries DK, van der Pol P, van Anken GE, et al. Acute but transient release of terminal complement complex after reperfusion in clinical kidney transplantation. *Transplantation*. 2013;95:816-820.
41. van Heurn LW, Talbot D, Nicholson ML, et al. Recommendations for donation after circulatory death kidney transplantation in Europe. *Transpl Int*. 2016;29(7):780-789.
42. Brook NR, White SA, Waller JR, Veitch PS, Nicholson ML. Non-heart beating donor kidneys with delayed graft function have superior graft survival compared with conventional heart-beating donor kidneys that develop delayed graft function. *Am J Transplant*. 2003;3:614-618.
43. Sánchez-Fructuoso A, Prats Sánchez D, Marqués Vidas M, et al. Non-heart beating donors. *Nephrol Dial Transplant*. 2004;19(suppl 3):iii26-31.
44. 2016 Annual ONT report on kidney transplantation. http://www.ont.es/infesp/Memorias/Memoria%20Renal.pdf. Accessed May 16, 2018.
45. Matesanz R, Coll E, Domínguez-Gil B. Organización Nacional de Trasplantes for the Spanish Group for Donation after Circulatory Death. Response to circulatory death determination in uncontrolled organ donors: a panel viewpoint. *Ann Emerg Med*. 2014;63(1):87-89.
46. Held PJ, McCormick F, Ojo A, Roberts JP. A cost-benefit analysis of government compensation of kidney donors. *Am J Transplant*. 2015;16:877-885.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Sánchez-Fructuoso AI, Pérez-Flores I, Del Río F, et al. Uncontrolled donation after circulatory death: A cohort study of data from a long-standing deceased-donor kidney transplantation program. *Am J Transplant*. 2019;19:1693-1707. https://doi.org/10.1111/ajt.15243