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Kidney Transplants in Controlled Donation Following Circulatory Death, or Maastricht Type III Donors, With Abdominal Normothermic Regional Perfusion, Optimizing Functional Outcomes

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Background. Warm ischemia time and ischemia-reperfusion damage result in higher rates of delayed graft function and primary nonfunction in kidney transplants (KTs) from controlled donation after circulatory death (cDCD). This study aimed to assess early and late kidney function and patient and graft survival of KT from cDCD preserved with normothermic regional perfusion (NRP) and to compare with KT from brain death donors (DBDs) and cDCD preserved with rapid recovery (RR). **Methods.** Patients who received a KT at our institution from 2012 to 2018 were included, with a minimum follow-up period of 1 y. They were categorized by donor type and conditioning methods: DBD, cDCD with NRP, and cDCD with RR. Early and late graft function, along with patient and graft survival were analyzed in all groups. **Results.** A total of 182 KT recipients were included in the study (98 DBD and 84 cDCD). Out of the cDCDs, 24 kidneys were recovered with the use of NRP and 62 with RR; 22 of the 24 kidneys were ultimately transplanted. The cDCD using NRP group showed lower rates of delayed graft function compared with the cDCD with RR group (36.3% versus 46.7%, $P=0.01$). Also, primary nonfunction rates were lower in the cDCD using NRP group (4.5% versus 6.4% cDCD-RR and 10.2% DBD). Patient survival rates were >90% in all groups. No differences were found in graft survival rates at 1 y. **Conclusions.** The use of abdominal NRP improves early function recovery of KT from cDCD, making their outcomes comparable with those of DBD.

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INTRODUCTION

Chronic kidney disease has increased its prevalence in recent years and has become one of the most frequently occurring diseases in Europe.¹ Kidney transplant (KT) has proven to be an effective renal replacement therapy for improving the quality of life and survival of patients compared with classic renal replacement therapies, such as hemodialysis (HD) and peritoneal dialysis, which has led to an increase in KT rates in the past years.^{2,3}

In 2011, a stabilization of the number of brain death donors (DBDs) occurred, which, combined with the growing global demand for organs, has pushed the field of transplantation toward the search for new donor sources and reviewing modified kidney preservation techniques. In the past decade, the kidney deficit has led to an increased use of organ controlled donation after circulatory death (cDCD) or Maastricht type III donors, which was initiated in Spain in 2012, under

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a legal and ethical framework.⁴ Subsequently, an exponential increase in donations was experienced.^{5,6} As a matter of fact, this donation model had already been successfully established in several European countries.^{7,8}

However, limitations in donation after circulatory death (DCD) include warm ischemia time (WIT)⁹ and ischemia-reperfusion injury.¹⁰ These phenomena lead to higher rates of primary nonfunction (PNF) or delayed graft function (DGF), compared with DBD grafts.¹¹

Kidney grafts that suffer from a prolonged WIT are more susceptible to damage from hypothermic preservation; therefore, the classic *in situ* cold perfusion (ICP) is especially suboptimal for DCD grafts.¹² Thus, alternative *in situ* preservation techniques have emerged, such as abdominal normothermic regional perfusion (NRP) with extracorporeal membrane oxygenation (ECMO).^{13,14} The main role of this method is to restore warm oxygenated blood flow into the abdominal organs upon determination of death, occurring after the withdrawal of life-sustaining treatments (WLSTs) and before organ recovery.

To date, there are limited publications that explore the results of kidney grafts retrieved from cDCD with the use of NRP, and to our knowledge, there are no studies that compare DBD, cDCD with NRP, and cDCD without NRP.

The main objective of this study was to analyze the clinical results of graft survival and function in controlled asystole donors recovered with the use of NRP, compared with cDCD preserved with rapid recovery (RR) and to DBD, ultimately describing the protocol used in our hospital.

MATERIALS AND METHODS

Study Design and Study Population

This is a single-center observational cohort study based on retrospective data collection. This study was approved by the Ethics Committee of Puerta de Hierro-Majadahonda University Hospital upon initiation (CEI-86-1611). Study population comprised consecutive patients who had received a KT at our institution from January 2012 to December 2018, with a minimum follow-up of 1 y.

Outcomes and Covariates

The main goal of this study was to validate the results of the kidney grafts retrieved from cDCD when comparing RR and NRP techniques as a possible solution to reduce potential donor risks.

For this aim, we included both cDCD and DBD procedures, and within the cDCD procedures, both RR and NRP methods were considered. NRP was performed in abdominal multiorgan recovery, especially when liver recovery was involved. Given that most of the donors from our institution are multiorgan donors, RR was the technique of choice in those few cases of exclusive renal donors.

Controlled DCD was performed in patients with severe conditions such as irreversible brain damage, chronic neurodegenerative diseases, cardiovascular disease, or chronic respiratory disease in a terminal condition. DBDs were considered when irreversible cessation of all intracranial neurological functions was confirmed in both cerebral hemispheres and in the brainstem.¹⁵ Both expanded criteria donors (ECDs) and standard criteria donors were included.^{16,17}

The decision on suitability for transplantation was taken after careful assessment of the kidney allograft and an exhaustive review of donor and recipient factors. Patients with graft anatomical abnormalities and donors with advanced age, past history of hypertension, diabetes mellitus, cardiovascular diseases, or poor organ perfusion and the Remuzzi score¹⁸ were excluded.

Definitions

DGF was defined as the need for HD in the first postoperative week.¹⁹ Additionally, PNF was defined as the failure of the graft to ever function up to 30 d posttransplantation, in need of continuous maintenance of HD.²⁰ Of note, this term has also been referred to as early graft loss in other publications.²¹ Its incidence was approximately 5% of the KT,²² mostly caused by vascular thrombosis,²³ followed by immunological causes and primary graft failure. The latter was considered when an initial nonfunctioning graft obtained good perfusion observed by Doppler ultrasound without other alterations and other causes were ruled out in biopsy tissue.²¹

ECDs were defined using the criteria suggested by the United Network for Organ Sharing.^{16,17} According to United Network for Organ Sharing, ECDs should include patients over 60 y of age, or those aged 50–59 y, with at least 2 of the following conditions: death from stroke, history of hypertension, or serum creatinine levels >1.5 mg/dL. Standard criteria donors were defined as those under 50 y of age who did not meet the ECD criteria.

WIT was defined as the time from the initiation of WLST to organ perfusion. Functional warm ischemic time was defined as the time from systolic blood pressure <60 mm Hg to the initiation of NRP (5 min of nontouch period was included).

Surgical Techniques

First, the decision of WLSTs on the grounds of futility is taken by the intensive care team responsible for the patient, according to the preestablished protocol at the Puerta de Hierro-Majadahonda University Hospital.^{24,25} Once communicated to and accepted by the family, the Transplant Coordination team is contacted to raise the possibility of organ donation. After signing the corresponding informed consents, especially those regarding premortem interventions, several tests are run before donation. Premortem cannulation is performed in the intensive care unit and a bolus dose of 60 IU/kg of unfractionated heparin is administered, which is deducted from the total heparin administered in the cDCD protocol.

The introducer for the aortic occlusion catheter is placed in the contralateral femoral artery. A fluoroscopy confirmation is performed to assure the placement of the catheters and the aortic occlusion balloon in the descending thoracic aorta. The volume of occlusion of the aortic balloon is also checked and the balloon is adjusted accordingly. The patient is then transferred to the operating room, where the arterial and venous cannulas are connected to the ECMO device and fixed with flanges. The cannulas remain clamped until the initiation of the NRP. The preservation solution (Celsior) is connected and administered via the arterial cannula when the NRP is finished.

Following WLST and once determination of death is established, there is a 5-min “no-touch” period without spontaneous circulation or with respiration cessation.²⁶ The aortic occlusion balloon is then filled to avoid encephalic and coronary

perfusion, and the cannulas are unclamped, commencing the NRP with an initial flow of 1 lpm and 2–3 lpm of oxygen ($\text{FiO}_2 = 1$, subject to flow adjustments depending on Pco_2).

A sufficient flow for abdominal perfusion is maintained, normally achieved with a mean arterial pressure of 60 mm Hg and 1.5–3 lpm flows. Flows are modified depending on the in situ macroscopic perfusion aspect of the organs. According to the gasometry performed every 30 min, oxygen and scrubbing gas are adjusted. The average duration of the NRP performed at our institution ranges between 60 and 90 min.

The macroscopic and functional evaluation of the organs before their recovery requires maintaining NRP for at least 1 h for biochemical and hematological parameters determination (blood gas, lactate, transaminases, and hematocrit) in blood samples. During the NRP duration, preliminary dissection of the liver is performed, leaving a well-prepared surgical field for kidney retrieval. Once the NRP is completed, the extracorporeal circulation is stopped while cold preservation solution is perfused through the arterial cannula, and the venous cannula is freed to allow drainage. After complete infusion of the preservation solution, the ECMO device is disconnected and the cannulas are removed. The process terminates with the abdominal organ recovery procedure.

Statistical Analysis

A descriptive analysis of the categorical variables was performed using absolute and relative frequencies. For the numerical variables, mean and SD or median and 25th and 75th percentiles were applied, according to compliance with the assumption of normality.

Univariate analysis was performed with the Mann-Whitney U test to contrast numerical variables and chi-square test or Fisher exact statistic to test hypotheses of categorical variables, as appropriate. Survival analysis was obtained using the Kaplan-Meier method, comparing the survival curves with the log-rank test. In the overall survival analysis, the follow-up time has been truncated to 15 mo for all patients.

To assess graft survival, 2 strategies have been used: on the one hand, logistic regression was performed, in which the event of interest is the loss of the graft or death before 15 mo; on the other hand, survival analysis was performed considering death as a competitive event. In this second analysis, the cumulative incidence function was estimated²⁷ and the regression models followed the strategy described by Fine and Gray.²⁸ In this model, the subhazard ratio was estimated instead of the hazard ratio, with their respective 95% confidence intervals. In the graft survival analysis, patient's death is not censored, as recommended.²⁹ The results regarding the maturity of the data according to the follow-up time were: 96% maturity at 15 mo, 82% maturity at 36 mo, 70% maturity at 60 mo, and 38% maturity at 80 mo. In view of these results, 15 mo was the follow-up time of choice, given its high maturity percentage.³⁰ The significance level was set at 0.05. Statistical analysis was performed using the Stata/IC v.16 package (StataCorp LLC, College Station, TX).

RESULTS

A total of 182 KT recipients who met inclusion criteria were included in the study (98 DBDs and 84 cDCDs) during the specified time period. Out of the cDCD group, 24 kidneys were recovered after NRP preservation and 62 using

RR technique. Of these 24 kidneys, 22 were eventually transplanted (Table 1).

To assess the advantage of the NRP preservation, cDCD grafts with NRP preservation were compared with those recovered with RR and cold in situ perfusion (ISP), along with grafts from DBD donors. The main donor and recipient characteristics are noted in Tables 2 and 3. The cohorts were homogeneous and no confounding variables influence the results.

Early Graft Function

In the first week of graft evaluation postimplantation, the cDCD with NRP group showed lower rates of DGF compared with the cDCD with RR group (36.3% versus 46.7%, $P = 0.01$). However, the DBD group presented a lower rate of DGF (20%). In contrast, the cDCD with NRP group had the lowest rates of PNF (4.5% versus 6.4% in the cDCD with RR group and 10.2% in the DBD group). The DBD group, however, obtained better results compared with the initial function globally, despite the high rates of PNF (Table 4).

This result is related to our definition of PNF, stating that PNF is considered as loss of the kidney graft in the first 30 d implying the never function of the graft. This loss can be due to multiple causes: thrombotic, ischemic, surgical complications, etc and not only due to those grafts that, without apparent cause, never work (ie, grafts with normal echography and a biopsy that shows no rejection²¹). In fact, the 10 cases of PNF of the DBD grafts in our series were due to thrombotic causes.

In the 1-y graft function analysis, PNF was included, with a clear impact on results. The highest rates of functioning grafts were obtained by the cDCD-NRP group (90%), although the results did not reach statistical significance (Table 5).

Evolution of Posttransplant Kidney Function

Evolution of creatinine levels was monitored over time, from the first week to the first year. Patients who presented better median outcomes were from the DBD group, followed by the cDCD with NRP group. Although the cDCD with RR group had initial higher creatinine levels, they matched the levels of the DBD and cDCD-NRP groups at 3 mo (Figure 1A and B). DBD donors were considered the reference category. cDCD-NRP donors preservation presented average creatinine values 0.460 mg/dL (95% confidence interval [CI], 0.145–0.776) higher than DBD ($P = 0.004$), whereas cDCD-RR donors presented 0.784 (95% CI, 0.562–1.000) higher than DBD donors ($P < 0.001$).

Patient Survival

Patient survival rates were >90% in all groups (DBD: 94%, cDCD-NRP: 100%, and cDCD-RR: 93%). In the log-rank

TABLE 1.
Distribution of the study cohort

Donor type	N	Conditioning methods (N)	
		NRP	RR
DBD	98		
cDCD	84	22	62

cDCD, controlled donation after circulatory death; DBD, brain death donor; NRP, normothermic regional perfusion; RR, rapid recovery.

TABLE 2.**Donor characteristics**

Donors	cDCD-NRP (n = 22)	cDCD-RR (n = 62)	DBD (n = 98)	P
Age ^a	59 (46–64)	57 (50–66)	57 (45–68)	0.851
Days in ICU ^a	8 (6–17)	9 (6–12)	2 (2–6)	<0.001
Creatinine in ICU ^a	0.6 (0.4–0.7)	0.6 (0.4–0.7)	0.79 (0.6–1.04)	<0.001
CIT (min) ^a	600 (240–1050)	420 (270–720)	720 (360–915)	0.011
WIT (min) ^a	10 (10–35)	15 (11–28)	0	<0.001
SCD ^b	13 (59.09%)	25 (45.45%)	42 (43.75%)	0.42
ECD ^b	9 (40.91%)	30 (54.55%)	54 (56.25%)	0.42
HTA ^b	12 (55%)	17 (32.08%)	34 (36.56%)	0.18
DM ^b	0	6 (11.32%)	9 (9.68%)	0.27
Dyslipidemia ^b	7 (31.82%)	11 (20.75%)	18 (19.35%)	0.43
Cardiovascular disease ^b	2 (9.09%)	12 (22.64%)	21 (22.58%)	0.34
Cerebrovascular disease ^b	2 (9.09%)	5 (9.43%)	14 (15.05%)	0.53
Peripheral artery disease ^b	0	0	3 (3.23%)	0.29
Graft obtained in our center ^b	20 (90.91%)	57 (91.94%)	59 (60.20%)	0.0001
Graft obtained outside our center ^b	2 (9.09%)	5 (8.06%)	39 (39.80%)	0.0001
Good graft perfusion ^b	22 (100%)	61 (98.39%)	93 (94.9%)	0.31

^aP50 (p25–p75).^bFrequencies (%).

cDCD, controlled donation after circulatory death; CIT, cold ischemia time; DBD, brain death donor; DL, dyslipidemia; DM, diabetes mellitus; ECD, extended criteria donor; HTA, hypertension; ICU, intensive care unit; NRP, normothermic regional perfusion; RR, rapid recovery; standard SCD, criteria donor; WIT, warm ischemia time.

TABLE 3.**Recipient characteristics**

Recipients	cDCD-NRP	cDCD-RR	DBD	P
Age at KT ^a	52 (45–60)	57 (47–67)	56 (43–66)	0.268
HTA ^b	20 (90.91%)	60 (96.77%)	86 (87.76%)	0.14
DM ^b	1 (4.55%)	16 (25.81%)	30 (30.61%)	0.04
DL ^b	11 (50%)	32 (51.61%)	51 (52.04%)	0.98
Cardiovascular disease ^b	5 (22.73%)	18 (29.03%)	36 (36.7%)	0.35
Cerebrovascular disease ^b	2 (9.09%)	6 (9.68%)	12 (12.24%)	0.84
Peripheral artery disease ^b	3 (13.64%)	10 (16.13%)	16 (16.33%)	0.95
Previous KT ^b	4 (18.18%)	13 (20.97%)	11 (1.22%)	0.23
High immune risk ^b	6 (27.27%)	15 (24.19%)	23 (23.47%)	0.93
Cause of death ^b				
TBI	0	2 (3.64%)	11 (11.83%)	0.0001
Cardiovascular	6 (27.27%)	19 (34.55%)	15 (16.13%)	0.0001
Encephalic	6 (27.27%)	16 (29.09%)	62 (66.67%)	0.0001
Anoxic encephalopathy (respiratory origin)	10 (45.45%)	16 (29.09%)	4 (4.3%)	0.0001

^aP50 (p25–p75).^bFrequencies (%).

cDCD, controlled donation after circulatory death; DBD, brain death donor; HTA, hypertension; DL, dyslipidemia; DM, diabetes mellitus; KT, kidney transplant; NRP, normothermic regional perfusion; RR, rapid recovery; TBI, traumatic brain injury.

test, no differences were found between groups ($Pr > \chi^2 = 0.50$) (Figure 2).

Graft Survival

In the graft survival analysis censored at 15 mo, graft loss rates ranged from 9% to 15% (DBD: 15.6%, cDCD-NRP: 9%, and cDCD-RR: 13%). One-year graft survival was 84.4% in the DBD group, 91% in the cDCD-NRP group, and 87% in the cDCD-RR group. Elevated PNF rates in the DBD group significantly affected 1-y graft survival.

These data are shown in the cumulative incidence function graph (Figure 3). According to the Fine and Gray model elaborated for this analysis, the subhazard ratio did not reach statistical significance, meaning that there is no association between the type of donor, preservation method, and graft loss at 15 mo.

DISCUSSION

Literature concerning KT after NRP is scarce. To our knowledge this is the first study performed to date describing the use of NRP in cDCD comparing it with RR in cDCD and with DBD.

The main findings of our study include a higher DGF rate in the cDCD-RR group compared with cDCD-NRP and DBD (46%, 36%, and 20%, respectively; $P = 0.01$).

The NRP technique is associated with a lower rate of DGF, which implies an improvement of the early outcomes, allowing us to achieve comparable results with those of the gold standard group (DBD). No improvement was observed in long-term graft survival, probably because of the small sample size of the series. Nevertheless, clear improvements in DGF were observed, therefore entailing both clinical and economic benefits.

TABLE 4.**Early graft function comparing cDCD-NRP and cDCD-RR with DBD**

	GEF	DGF	PNF	Total	DGF vs GEF <i>P</i>	PNF vs GEF <i>P</i>
DBD (ref.) ^a	68 (69.39%)	20 (20.41%)	10 (10.20%)	98 (100%)	Ref. cat.	Ref. cat.
cDCD-NRP ^a	13 (59.09%)	8 (36.36%)	1 (4.55%)	22 (100%)	0.14	0.54
cDCD-RR ^a	29 (46.77%)	29 (46.77%)	4 (6.45%)	62 (100%)	0.001	0.91

Global *P* = 0.012.^aFrequencies (%).

cDCD, controlled donation after circulatory death; DGF, delayed graft function; GEF, good early function; NRP, normothermic regional perfusion; PNF, primary nonfunction; ref. cat., reference category; RR, rapid recovery.

TABLE 5.**Late graft function. Kidney function 12 mo posttransplant**

	Functional	Nonfunctional	<i>P</i>
DBD ^a	81 (82.65%)	17 (17.35%)	
cDCD-NRP ^a	20 (90.91%)	2 (9.09%)	0.14
cDCD-RR ^a	53 (85.48%)	9 (14.52%)	0.001

^aFrequencies (%).*P* = 0.6.

cDCD, controlled donation after circulatory death; DBD, brain death donor; NRP, normothermic regional perfusion; RR, rapid recovery

The first human application of NRP in DCD was in uncontrolled DCD (uDCD) KT.³¹ Previously, several experimental studies had been published.^{32,33} The technique was quickly adopted in different countries, and one of the earliest published retrospective nonrandomized studies with Maastricht type II donors was a series of the Spanish group of Valero and collaborators in 2000.³¹ In this study, NRP, ISP, and total body cooling were compared. The results showed that NRP preservation had lower rates of PNF and DGF, compared with hypothermic preservation techniques (NRP: PNF 0%, DGF 13%; ISP: PNF 23%, DGF 55%; total body cooling PNF 0%, DGF 75%; *P* < 0.01). Similarly, La Pitié-Salpêtrière¹³ group in Paris also published a series with Maastricht type II donors comparing ISP and NRP, observing better kidney function 1 mo after transplantation in the NRP group.

Several studies have proven the good results of this technique.³⁴⁻³⁷ One of the first groups to publish their experience of cDCD preserved with NRP was Oniscu et al³⁶ in 2014. This English series presented the results from 21 donors from whom 32 kidneys were transplanted, of which 13 (40%) had DGF and 4 (12.5%) were lost due to thrombotic events.

In the study published by the University of Wisconsin³⁷ cDCD and DBD were compared. No statistically significant differences were observed in DGF rates between KT from cDCD with ECMO-supported protocol (n = 24) compared with the DBD group (n = 100) (8.3% versus 24%, respectively; *P* = 0.1).

Recently, Miñambres et al⁹ published the first Spanish series using NRP preservation in cDCD. Of the 37 kidneys procured, 27% presented DGF and 5% PNF, finding no statistically significant differences when comparing it with the DBD group (*P* = 0.55). Nevertheless, The Spanish National Transplant Organization data showed statistically significant differences in terms of type of preservation used, thus proving the advantage of the NRP protocol over the cold ISP, as NRP showed lower rates of DGF and PNF (*P* < 0.001 and *P* = 0.014, respectively).³⁸

The largest study published to date compares 92 cDCD KTs preserved with NRP and subsequent hypothermic machine perfusion (HMP) with 5176 DBD. Despite showing lower rates of DGF in the cDCD group (9% versus 19%, *P* < 0.05),³⁹ the lower rates of DGF could be due to the NRP, the HMP, or both.

Comparative results of the main series of cDCD with NRP are shown in Table 6.

In our series, we observed that the group of cDCD preserved with NRP had lower rates of DGF compared with cDCD with RR group (36.3% versus 46.7%. *P* = 0.01). However, the DBD group had overall better results in the early graft function, despite the PNF rate in this group being higher (10%).

The PNF rate is higher in the DBD group because of the loss of 10 KT in the first 30 d posttransplant. After carefully evaluating these patients, we observed that they all belong to ECDs and were extracted in other centers. Additionally, these organs were lost because of thrombotic events that were mostly justified by clinical circumstances unrelated to the surgical technique, such as antiphospholipid syndrome, prothrombin factor II mutation, or loss of previous KTs due to thrombosis, among other risk factors. Yet, in other cases, thromboses were secondary to complex surgery related to the vascular anatomy of the receptors (Table S1, SDC, <http://links.lww.com/TXD/A339>).

Also of note, the initial levels of creatinine were better in the cDCD group with NRP, compared with the cDCD-RR group; yet, all 3 groups showed equivalent function at 3 mo.

Regarding graft survival, there are studies showing better survival rates in uDCD KTs with NRP compared with those preserved with cold ISP.^{38,40} A recent Spanish publication on uDCD KT highlights the superiority of NRP preservation on graft survival.⁴⁰ However, other studies like the one published by Demiselle et al showed no differences in graft survival rates between NRP-uCDC, ICP-uDCD and ECD.^{41,42}

On the other hand, results on graft survival observed in our series align with several studies^{9,38,43} with cDCD donors that compared different preservation and procurement techniques, and found no differences in long-term kidney graft survival, compared with DBD donors.

Recently, Lomero et al published the differences in the cDCD protocols between European countries.⁴⁴ To date, RR is the most popular organ recovery modality. Since the cDCD program was initiated in our institution in 2012, different recovery techniques have been used. Initially, RR with direct cannulation of the aorta and, in some cases, double-balloon triple-lumen catheter cannulation was performed. Since 2013, NRP has progressively replaced RR with ICP as the main preservation modality and was implemented in our hospital with few difficulties due to the

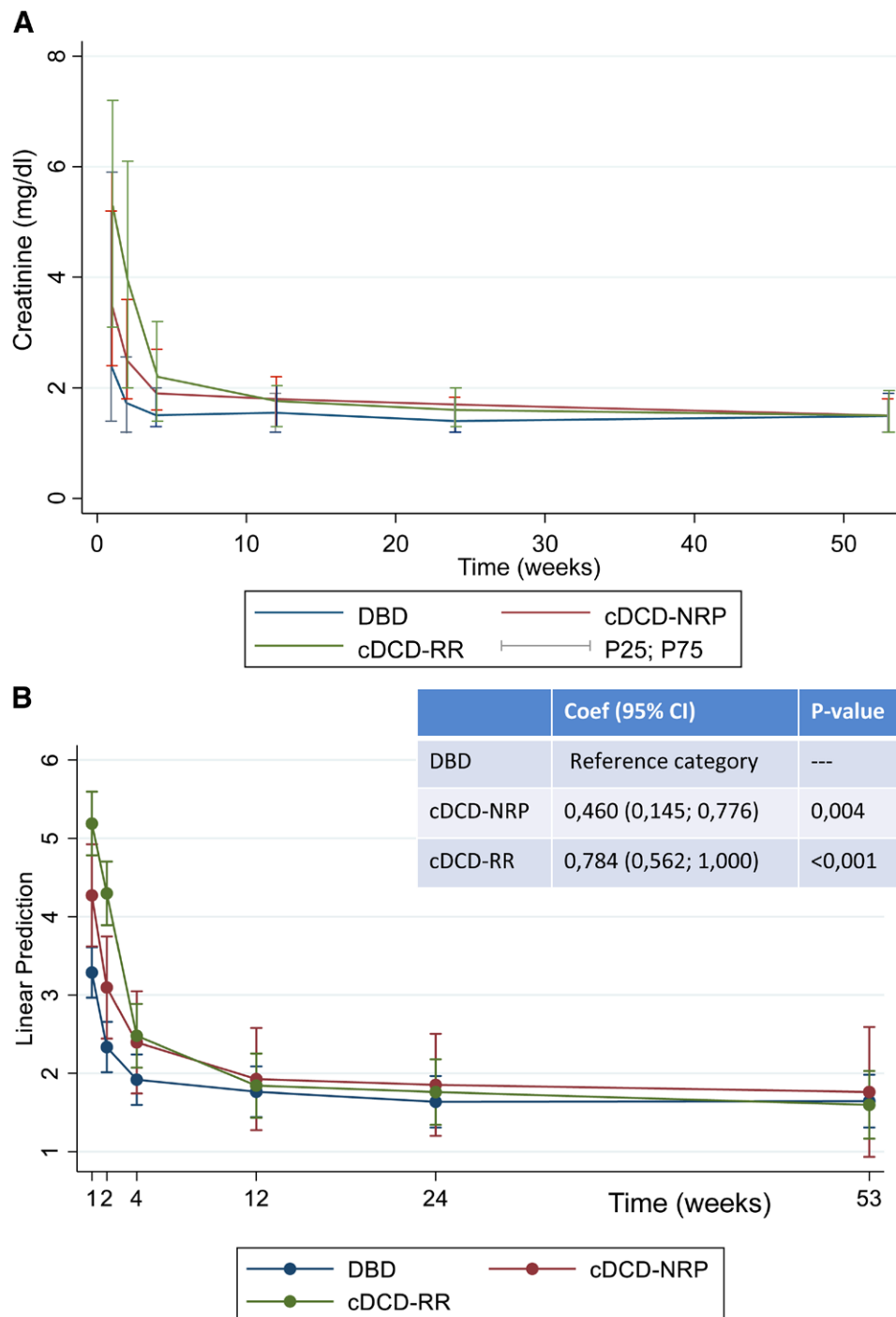


FIGURE 1. A, Posttransplant kidney function in a descriptive graph. This graph represents the medians of creatinine levels of the 3 groups over time. The bars indicate the 25th and 75th percentiles. B, Linear prediction for creatinine over the time, at 1, 2, 4, 12, 24, and 53 wk posttransplant according to the type of donor and type of preservation. The bars indicate 95% CI. cDCD, controlled donation after circulatory death; CI, confidence interval; DBD, brain death donor; NRP, normothermic regional perfusion; RR, rapid recovery.

experienced intensive care unit team with therapeutic ECMO and the long experienced transplantation team.

There are several advantages to this technique. First, pre-mortem cannulation is performed, in accordance with current Spanish legislation, which makes organ procurement an elective procedure, avoiding the possible damages that can occur during the RR.⁴⁵ Furthermore, macroscopic and functional evaluation of the organs before their recovery is feasible, which allows for a better organ selection.^{46,47} Despite these theoretical

benefits, most Spanish hospitals with cDCD protocols perform RR.⁴⁸ In the past few years, however, organ procurement using NRP with ECMO has increased,³⁸ currently representing 50% of the DCD procedures in Spain. Regarding the duration of the NRP, the limit is set in 4 h, although in our series and in most relevant publications, it ranges between 90 and 120 min.^{9,34-36,38.}

Functional and morphological evaluation is performed before organ procurement, which results in a better organ selection and permits us to expand donor criteria more safely.

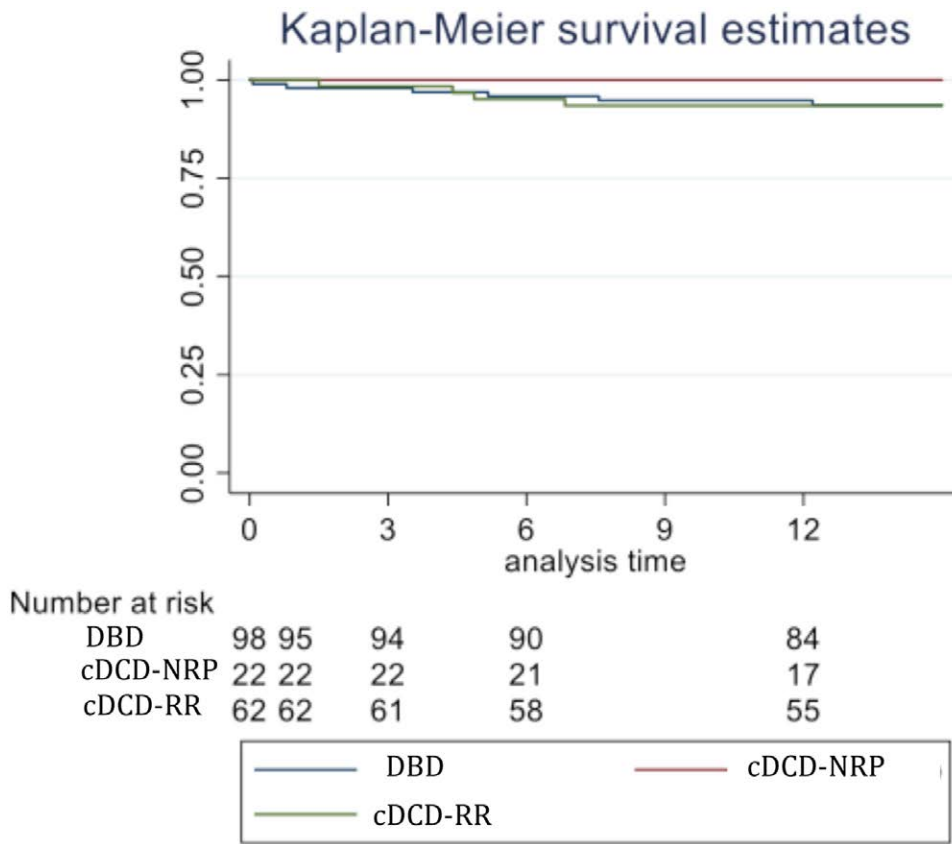


FIGURE 2. Kaplan-Meier survival curves for the 3 groups. Time is represented in months. Log-rank test for equality of survivor functions is $P=0.3062$. cDCD, controlled donation after circulatory death; DBD, brain death donor; NRP, normothermic regional perfusion; RR, rapid recovery.

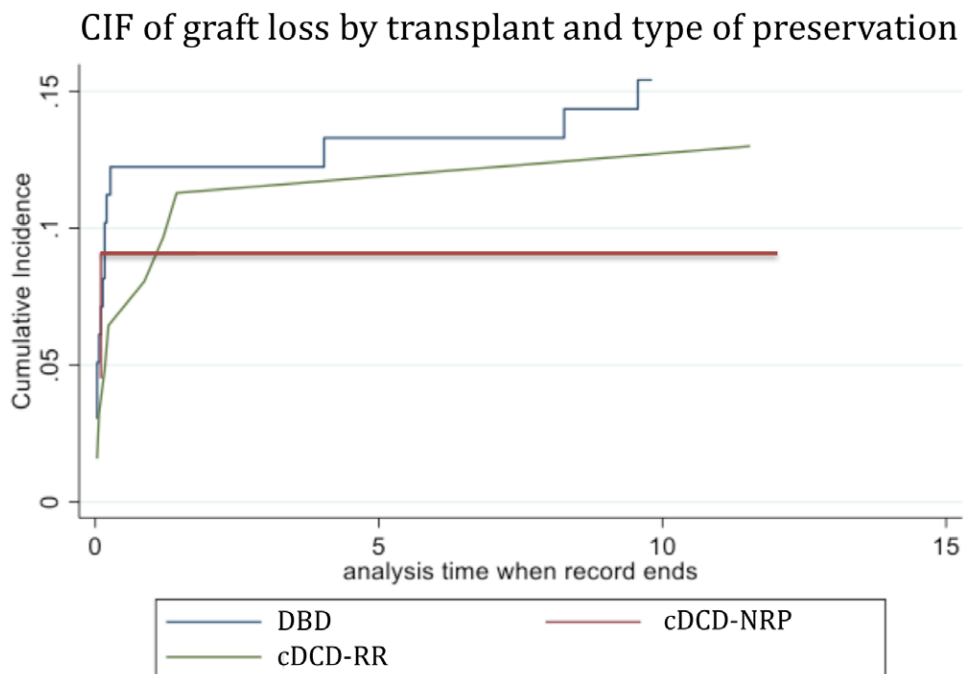


FIGURE 3. Graft survival curves truncated to 15 mo for all patients. cDCD, controlled donation after circulatory death; CIF, cumulative incidence function; DBD, brain death donor; NRP, normothermic regional perfusion; RR, rapid recovery.

There are several limitations to the implementation of NRP with ECMO. The technique presents new ethical and legal challenges, especially for pre-mortem maneuvers. One

limitation is the possibility of resuscitating the patient by restoring intracerebral flow if the aortic occlusion balloon does not function correctly.⁴⁹ For this matter, only United

TABLE 6.
Series of NRP in controlled donation after circulatory death

	No. kidneys	Age	Early graft function		
			PNF	DGF	GEF
Oniscu et al ³⁶	32	46 (16–74) ^a	4 (12.5%)	13 (40%)	15 (46.8%)
Rojas Peña et al ³⁵	48	39 (9–65) ^a	1 (3.5%)	9 (31%)	19 (66%)
Butler et al ³⁴	14	53 (22–74) ^b	2 (14%)	2 (14%)	10 (71.4%)
Miñambres et al ⁹	37	58 (50–67) ^c	2 (5%)	10 (27%)	25 (67.5%)
Ramirez et al	22	59 (46–67) ^c	1 (4.5%)	8 (36.3%)	13 (59%)

^aMedian (min–max).

^bMean (min–max).

^cMedian (p25–p75).

DGF, delayed graft function; GEF, good early function; PNF, primary nonfunction.

Kingdom and Spain have proposed methods to avoid the possibility of brain reperfusion.^{9,50,51} Additionally, there are organizational barriers to overcome. However, because of the development of new initiatives such as the mobile ECMO,⁵² the technique may be expanded to multiple hospitals in Spain where RR is the main organ recovery technique.

There are many publications regarding different methods of in situ regional perfusion in the donor and ex situ machine perfusion of individual organs. This wide range of regimens makes the preservation sequence more complicated to choose. There have been publications regarding NRP followed by ex situ HMP,^{53,54} but to our knowledge, no studies regarding NRP followed by ex situ normothermic machine perfusion have been published to date.

The main goal of the abdominal NRP preservation is to reduce WIT and therefore improve graft quality.⁵⁵ In this sense, the results of our study suggest that NRP improves early function recovery of cDCD grafts and that their results are comparable with the DBD KT.

In view of these results, we consider that this protocol is suitable for implementation in similar institutions with donation in controlled asystole. This technique has proven that, although it does not influence long-term survival, higher rates of DGF have a negative impact on length of hospital stays and with it an increase in hospital expenditure, which could be prevented. Despite the good results, we concede some limitations in our study. The main limitation may have been the small sample size, which may have limited showing some expected significant differences among the groups. An important matter is the potential problem of the DBD control group, regarding the high rate of primary graft nonfunction as previously described. Furthermore, there is a great limitation when comparing studies due to the definition of DGF because the need to dialyze the patient during the first postoperative week may be required in situations such as poor management of postoperative intravascular volume and not to a real acute tubular necrosis. Additionally, HD criteria are not always shared between institutions.

The published results are promising thus far, but prospective clinical trials comparing the different preservation techniques and their combinations are necessary to find the best combination model for each donor–recipient match.

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