



## ORIGINAL ARTICLE

# Kidney transplant outcomes in elderly recipients with controlled donation after circulatory death or donation after brain death donors: a registry cohort study

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## SUMMARY

The number of kidney transplant (KT) procedures with controlled donation after circulatory death (cDCD) donors has exponentially increased in Spain in recent years, with a parallel increase in donor and recipient acceptance criteria. The outcomes of cDCD-KT have been reported to be comparable to those of KT with donation after brain death (DBD) donors. However, studies in elderly recipients have yielded contradictory results. We performed a registry analysis of 852 KT recipients aged  $\geq 65$  years (575 in the DBD-KT group, 277 in the cDCD-KT group) in Catalonia, Spain. Clinical outcomes and survival were compared between DBD-KT and cDCD-KT recipients. The donor and recipient ages were similar between the two groups ( $71.5 \pm 8.7$  years for donors,  $70.8 \pm 4.1$  years for recipients). Delayed graft function (DGF) was more frequent among cDCD-KT recipients, without a difference in the rate of primary nonfunction. The 3-year patient and death-censored graft survival rates were similar between DBD-KT and cDCD-KT recipients (78.8% vs. 76.4% and 90.3% vs. 86.6%, respectively). In multivariable analysis, previous cardiovascular disease and DGF were independent risk factors for patient death. The type of donation (cDCD vs. DBD) was not an independent risk factor for patient survival or graft loss. cDCD-KT and DBD-KT provide comparable patient and graft survival in elderly recipients.

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## Key words

controlled circulatory death, donors, elderly, kidney transplantation

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## Introduction

The proven benefit of kidney transplant (KT) compared with dialysis [1,2] has recently been questioned when considering elderly recipients [3–5]. Recipient acceptance criteria have expanded in recent years [6,7]; however, the potentially higher comorbidity burden and

frailty of elderly patients may increase their vulnerability to poor outcomes and death after the transplant procedure [8,9]. A few recent European publications have suggested that recipients aged  $>65$  years may not obtain a survival benefit from KT compared with remaining on dialysis [3,4]. In contrast, other studies have reinforced the benefit of transplantation among elderly candidates

aged >60 years [10], 70–75 years [11,12], and even 80 years [13].

Elderly recipients have fewer chances to be listed as KT candidates and, after being listed, have fewer chances to receive a kidney [14]. Old-for-old allocation policies determine the likelihood of receiving an organ from an expanded criteria donor, which implies poorer results in terms of patient and graft outcomes [15]. This becomes especially relevant in KT with donation after circulatory death (DCD) donors [3,4], as this type of organ donation has been associated with poorer graft outcomes [15]. Several studies in large cohorts have reported similar results between DCD-KT and KT with donation after brain death (DBD) donors [16–20]. However, elderly recipients may not be sufficiently represented in these cohorts, and the studies were not designed to analyze results in this specific patient population.

Since Spain launched the controlled DCD (cDCD) transplant program in 2012, the number KT procedures with cDCD donors has dramatically increased, with cDCD-KT representing almost 30% of all KT procedures performed in 2019 in Spain [21]. Meanwhile, >35% of KT recipients in Catalonia are >65 years of age [22]. Our group has previously investigated the benefit of KT using grafts from elderly donors based on data from the Catalan Renal Registry (RMRC) [10,23,24], with special interest in elderly recipients [10,24]. However, the cDCD-KT results were not evaluated in these studies. Although most of the available evidence supports the practice of KT for elderly recipients [10–13], concerns have been raised about outcomes when using organs from cDCD donors in this population [3,4]. Thus, an analysis of the results is needed.

The aim of this study was to compare the outcomes of DBD-KT and cDCD-KT in elderly recipients (aged ≥65 years), to aid in the establishment of proper allocation policies.

## Methods

We used data from the RMRC, which is a mandatory population-based registry covering 7.5 million people. The RMRC collects information on all patients with end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) in Catalonia. At the start of RRT, a registration form is filled in for each patient. The patient's status is updated and sent to the RMRC every year until the withdrawal of RRT, death of the patient, or loss of the patient to follow-up.

This study followed the principles of the World Medical Association Declaration of Helsinki and relied only on

the official database. As data were retrospectively obtained from the RMRC, informed consent and institutional ethics board review were not required for this study.

Between 2013 and 2018, a total of 1284 patients aged ≥65 years underwent a KT in Catalonia. Patients who underwent multiorgan transplant ( $n = 10$ ), dual KT ( $n = 2$ ), living-donor KT ( $n = 115$ ), and KT with an uncontrolled DCD donor ( $n = 12$ ) were excluded from the study. In addition, 293 recipients who underwent KT in Catalonia but received an organ from non-Catalan donors were excluded owing to lack of information. Finally, 852 KT recipients aged ≥65 years, of whom 575 underwent DBD-KT and 277 underwent cDCD-KT, were included in the analysis. The patients were followed up until death, follow-up loss, or December 31, 2018. The median follow-up duration of the entire cohort was 22.3 months, with a maximum follow-up duration of 72.4 months.

The donor variables considered in this study were age, sex, cause of death, multiorgan donation, and number of days in the intensive care unit before donation. The recipient variables were age, sex, cause of ESRD, maximum panel reactive antibody (PRA), time on dialysis before KT, and comorbidities. The transplant variables were cold and warm ischemia times, method of organ preservation or retrieval, delayed graft function (DGF; defined as the need for dialysis within the first week after KT), and induction and maintenance immunosuppression. The outcomes were patient survival and graft survival (including death-censored graft survival), cause of graft loss, and estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.

Continuous variables are expressed as mean ± standard deviation or median and interquartile range, according to their distribution (normal or non-normal). Categorical data are expressed as percentages. Baseline characteristics were compared between the two groups using the chi-squared test or Fisher's exact test for categorical variables, Student's *t*-test for continuous variables with a normal distribution, and the Mann–Whitney test for nonparametric variables. Patient and graft survival rates were estimated using Kaplan–Meier curves with a log-rank test. Cox regression was used to estimate the hazard ratios (HRs) and confidence intervals (CIs) for patient mortality and graft loss. Multivariable analysis was performed based on saturated models, including all variables that were considered clinically significant, according to previous studies from our group [10,23,24]. Statistically nonsignificant variables

were progressively eliminated, and only those that showed significance are shown in addition to recipient age, recipient sex, and type of donor. Statistical analysis was performed using STATA software (version 13; Stata-Corp LLC, College Station, TX, USA).

## Results

The baseline recipient, donor, and transplant characteristics are shown in Table 1. The recipient and donor ages were similar between the DBD-KT and cDCD-KT groups (70.8 years for recipients and 71.5 years for donors). The comorbidities did not differ between DBD-KT and cDCD-KT recipients, with a high prevalence of diabetes (39.1%) and coronary artery disease (25.7%) in the entire cohort. We observed a higher degree of sensitization among cDCD-KT recipients than among DBD-KT recipients (percentage of patients with PRA >50%: 19.9% vs. 12.2%). cDCD donors were more frequently male (57.4% vs. 48.4%), less frequently multiorgan donors (17% vs. 79.7%), and less frequently died of stroke (43.3% vs. 77.6%). The cold ischemia time was shorter among cDCD-KT recipients (11.1 vs. 16.4 h); however, they presented with higher rates of DGF (42.5% vs. 24.4%). Only 10.2% of kidney grafts from cDCD donors were retrieved with normothermic regional perfusion. In terms of immunosuppression, cDCD-KT recipients more frequently received thymoglobulin as induction therapy (60.6% vs. 34.5%).

With respect to graft function, similar eGFR (based on the CKD-EPI equation) was observed between DBD-KT and cDCD-KT recipients both in the short term (37.8 ml/min at a mean of 7.8 months after transplant) and long term (40 ml/min at a mean of 20.5 months after transplant, Table 1). In addition, the proportion of recipients with poor kidney function (eGFR <30 ml/min) was also similar between the groups. The rate of primary nonfunction (PNF; including vascular or surgical problems that resulted in graft loss) was slightly higher in DBD-KT recipients, although the difference was not statistically significant (8.1% vs. 4.8%, Table 1). Thirty-seven KT recipients from the DBD-KT group experienced PNF, two of whom experienced PNF twice ( $n = 39$  transplants). Of the patients with PNF, 10 received a second transplant and 13 died on dialysis within a median time of 335 (160–531) days. Of the cDCD-KT recipients, 11 had PNF, two of whom underwent re-transplantation and three died after a median time of 464 (13–1267) days.

The 1-, 2-, and 3-year patient survival rates were comparable between DBD-KT and cDCD-KT recipients

(91% vs. 87%, 86.3% vs. 82.5%, and 78.8% vs. 76.4%, respectively; Fig. 1). In the multivariable analysis, the presence of any cardiovascular disease (HR 2.16, 95% CI 1.45–3.22) and DGF (HR 1.89, 95% CI 1.35–2.65) were predictors of mortality; however, donor type did not affect patient survival (Table 2). Meanwhile, the graft survival and death-censored graft survival rates were also similar between the two groups, reaching 90.3% for DBD grafts and 86.6% for cDCD grafts at 3 years after transplant (Fig. 1).

## Discussion

In this registry cohort study, we compared the outcomes of KT recipients aged  $\geq 65$  years who received an organ from either a DBD or a cDCD donor. The 3-year patient survival rate was >75% in both the DBD-KT and cDCD-KT groups, without a significant difference. The overall graft survival was also similar and was approximately 70% at 3 years. Donor type was not a risk factor for patient death or graft loss in our cohort.

Although studies in the last 10 years have shown similar results between DBD-KT and DCD-KT, even with kidneys from expanded criteria donors [16–20], concerns have emerged about the benefits of KT in elderly recipients [3,4]. The percentage of elderly KT candidates and recipients has increased in recent years [6,7,22]; therefore, this population is usually underrepresented in earlier studies, which commonly analyzed historic cohorts. With the age of recipients being between 50 and 55 years in previous studies [16,17,19,20], comparisons of outcomes between DBD-KT and DCD-KT have not provided any specific conclusion about patient and graft survival rates in elderly recipients [16,17,19,20]. Two recent studies in Dutch and British DCD-KT cohorts reported no survival benefit among recipients aged  $\geq 65$  years who received a kidney from an elderly DCD donor compared with those who remained wait-listed on dialysis [3,4]. However, the actual number of patients in this group was small, being <150 patients in the larger study [3]. These two studies reported a 3-year patient survival probability of 75–70% in the elderly DCD donor–elderly recipient group [3,4], with a mean donor age of 67 years and a mean recipient age of 68 years [3].

The survival benefit of DBD-KT over dialysis among elderly recipients has generally been established in previous studies from our group [10,23,24]. In the present study, we aimed to analyze whether the outcomes of DBD-KT differ from those of cDCD-KT. The mean age of both donors and recipients in our cohort was

**Table 1.** Baseline characteristics and graft outcomes in DBD-KT and cDCD-KT recipients.

	DBD (n = 575)	cDCD (n = 277)	All (n = 852)	P-value
<b>Recipient characteristics</b>				
Age (years), mean (SD)	70.9 (4.2)	70.6 (4.2)	70.8 (4.2)	0.925
Sex (male), n (%)	365 (63.5)	188 (67.9)	553 (64.9)	0.208
Hypertension (yes), n (%)	534 (95)	255 (93.8)	789 (94.6)	0.447
Diabetes mellitus (yes), n (%)	210 (37.4)	116 (42.7)	326 (39.1)	0.148
Coronary artery disease (yes), n (%)	141 (25)	74 (27.2)	215 (25.7)	0.494
Cerebrovascular disease (yes), n (%)	63 (11.2)	41 (15.1)	104 (12.5)	0.111
Any cardiovascular disease* (yes), n (%)	336 (61.3)	169 (64.3)	505 (62.3)	0.418
Renal replacement therapy modality (HD), n (%)	456 (79.6)	229 (82.7)	685 (80.6)	0.565
Time on dialysis (months), median [IQR]	26.3 [13.9–42.9]	26.4 [15.2–44.9]	26.4 [14.3–43.5]	0.550
Re-transplant (yes), n (%)	63 (11)	37 (13.4)	127 (14.9)	0.565
PRA (>50%), n (%)	70 (12.2)	55 (19.9)	125 (14.7)	0.003
Follow-up (months), median [IQR]	26.2 (8.8–43.7)	14.8 (5.1–28.4)	22.3 (7.1–36.8)	<0.001
<b>Donor characteristics</b>				
Age (years), mean (SD)	71.8 (8.8)	70.9 (8.4)	71.5 (8.7)	0.144
Age <60 years, n (%)	63 (10.9)	28 (10.1)	91 (10.7)	0.141
Sex (male), n (%)	278 (48.4)	159 (57.4)	437 (51.3)	0.013
Multiorgan donor (yes), n (%)	458 (79.7)	47 (17)	505 (59.3)	<0.001
Cause of death (stroke), n (%)	446 (77.6)	120 (43.3)	566 (66.4)	<0.001
ICU stay (days), median [IQR]	2 [1–3]	6 [2–10]	2 [1–5]	<0.001
Total warm ischemia time (min), mean (SD)	NA	25.3 (10.9)	NA	NA
Normothermic regional perfusion (yes), n (%)	NA	21 (10.1)	NA	NA
Pulsatile preservation (yes), n (%)	NA	25.6 (41)	NA	NA
<b>Transplant characteristics</b>				
Cold ischemia time (h), mean (SD)	16.4 (5.8)	11.1 (5.7)	14.6 (6.2)	<0.001
Delayed graft function (yes), n (%)	132 (24.4)	111 (42.5)	243 (30.3)	<0.001
Induction immunosuppression (thymoglobulin), n (%)	181 (34.5)	152 (60.6)	333 (42.9)	<0.001
Maintenance immunosuppression (tacrolimus + mycophenolate), n (%)	438 (86.1)	201 (86.6)	639 (86.2)	0.830
<b>Graft function and primary graft loss</b>				
First eGFR based on CKD-EPI (ml/min; at 7.8 months after KT), mean (SD)	38.6 (17.6)	36 (21)	37.8 (18.8)	0.080
Patients with first eGFR based on CKD-EPI <30 ml/min, n (%)	156 (31.8)	84 (36.7)	240 (33.3)	0.330
Second eGFR based on CKD-EPI (ml/min; at 20.5 months after KT), mean (SD)	40.7 (15.6)	38.1 (13.8)	40 (15.2)	0.108
Patients with second eGFR based on CKD-EPI <30 ml/min, n (%)	92 (24.8)	37 (29.8)	129 (26.1)	0.541
Primary nonfunction and thrombosis, n (%)	39 (8.1)	11 (4.8)	50 (7)	0.072

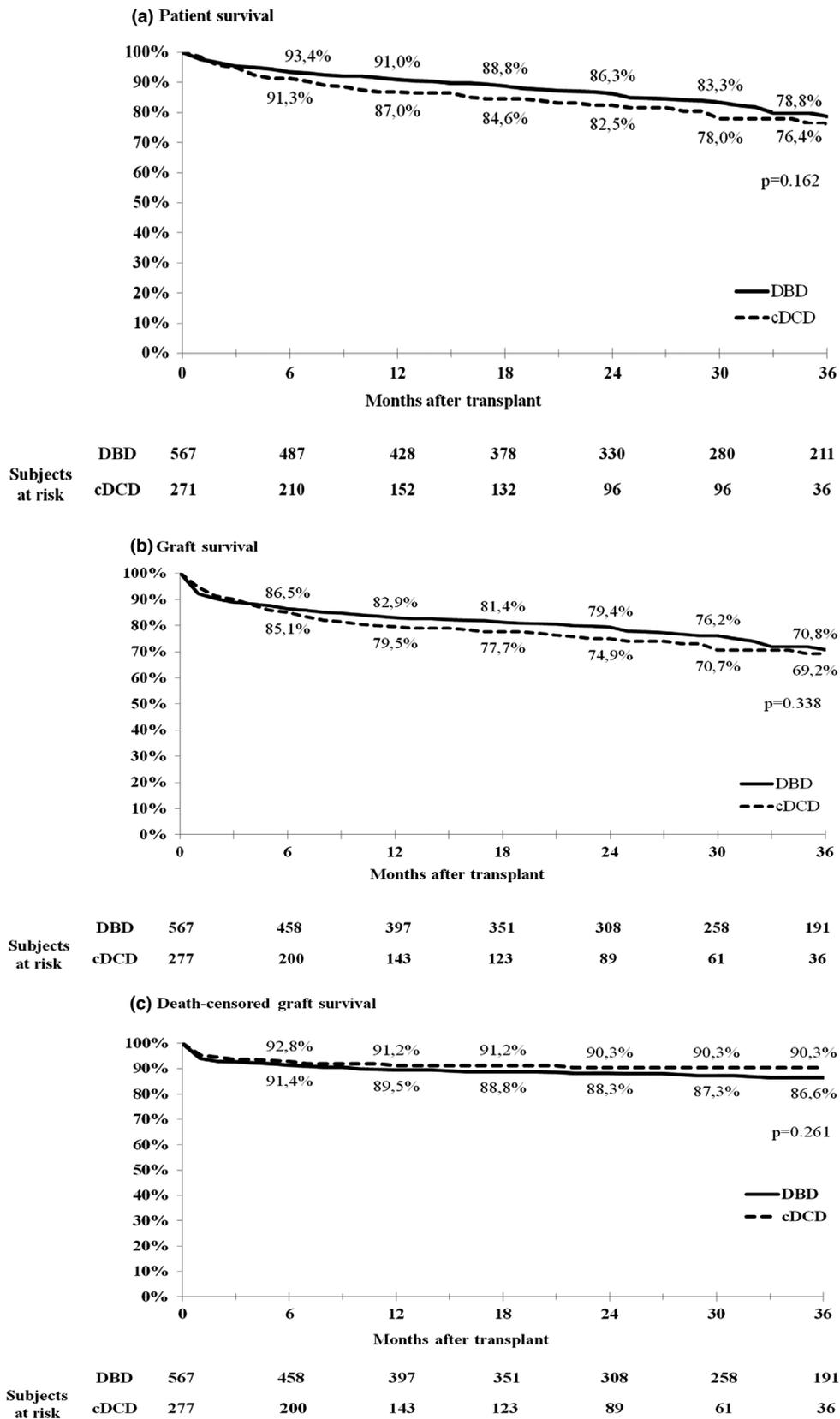
cDCD, controlled donation after circulatory death; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBD, donation after brain death; eGFR, estimated glomerular filtration rate; HD, hemodialysis; ICU, intensive care unit; KT, kidney transplant; NA, not applicable; PRA, panel reactive antibody; SD, standard deviation.

\*“Any cardiovascular disease” included coronary artery disease, cerebrovascular disease, peripheral vascular disease, heart failure, heart rhythm problems, and cardiac surgery.

>70 years. Moreover, the recipients had a high comorbidity burden, with 40% having diabetes mellitus and 25% having coronary artery disease, compared with 17.5% recipients with diabetes in the study by Peters-Sengers *et al.* [3]. The patient survival rates did not differ between the two groups (78.8% and 76.4% in the DBD-KT and cDCD-KT groups at 3 years, respectively).

Donor type did not influence patient survival, whereas previous cardiovascular disease (HR 2.16) and DGF (HR 1.89) were risk factors for recipient death.

In our study, graft survival was determined by patient death, as the 3-year rate of death-censored graft survival remained >85% in the two groups. However, important graft outcomes such as DGF, PNF, and kidney function



**Figure 1** Kaplan–Meier survival curves of the rates of patient, graft, and death-censored graft survival in DBD-KT and cDCD-KT recipients. (a) Patient survival. (b) Graft survival. (c) Death-censored graft survival. cDCD, controlled donation after circulatory death; DBD, donation after brain death; KT, kidney transplant.

**Table 2.** Multivariate analysis of risk factors for patient and graft survival.

	Patient survival HR (95% CI)	Graft survival HR (95% CI)	Death-censored graft survival HR (95% CI)
Recipient sex (female)	1.16 (0.82–1.64)	1.11 (0.82–1.50)	1.22 (0.77–1.95)
Recipient age (>75 years)	1.13 (0.76–1.67)	1.28 (0.91–1.79)	1.62 (0.99–2.66)
Any cardiovascular disease*	<b>2.16 (1.45–3.22)</b>	<b>1.78 (1.29–2.46)</b>	1.51 (0.92–2.47)
Delayed graft function	<b>1.89 (1.35–2.65)</b>	<b>1.61 (1.20–2.17)</b>	1.59 (1.00–2.52)
cDCD	1.24 (0.84–1.82)	1.10 (0.79–1.53)	0.71 (0.41–1.22)

cDCD, controlled donation after circulatory death; CI, confidence interval; HR, hazard ratio.

\*“Any cardiovascular disease” included coronary artery disease, cerebrovascular disease, peripheral vascular disease, heart failure, heart rhythm problems, and cardiac surgery.

Bold values denote statistically significance.

were also assessed in our cohort. In previous studies, the DGF rate was consistently higher in DCD-KT [16,19,20] than in DBD-KT, similar to our result (42.5% in cDCD-KT); however, our cohort had a lower percentage of recipients with DGF than other similar cohorts (up to 74%) [3]. Contradictory results have been reported about the potential impact of DCD-associated DGF on graft survival [25,26]. One study postulated that it could have a negligible negative impact, which is related to donor-type-specific activation of resilience pathways in DCD grafts [26]. Notably, DGF had an impact on patient survival in our study, which might be related to prolonged hospitalization with a consequent higher risk of infections or other complications, as well as poorer kidney function. Although DGF was more frequent among cDCD-KT recipients, only DGF, and not cDCD, was associated with patient mortality in the multivariable analysis. This may be due to a higher impact of DGF among DBD-KT recipients, as previously reported [26]. Surprisingly, donor age had no impact on graft survival. For the analysis, we included donor age in the saturated model, although it was later excluded because it did not reach statistical significance. However, even when donor age was considered a unique covariable for the death-censored graft survival model, we did not observe differences between the groups. This could be explained by the homogeneity of the sample: The percentage of donors aged  $\geq 60$  years was 89.1% in the DBD-KT group and 89.9% in the cDCD-KT group. Meanwhile, only recipients aged  $>65$  years were included in the study, without differences in the mean age between the groups (70.9 vs. 70.6 years). Therefore, the effect of age (in both donors and recipients) might have been diluted by the strong presence of other factors such as DGF or disease burden in recipients.

Other graft outcomes such as PNF and kidney function based on eGFR were also evaluated. In a recent series comparing global results between DBD-KT and DCD-KT recipients, both PNF and kidney function were reported to be similar between the two groups [16,18,19]; however, they were found to be much poorer in elderly DCD-KT recipients than in elderly DBD-KT recipients in another study [3]. In the study by Peters-Sengers *et al.* [3], poor kidney function (eGFR  $<30$  ml/min) was detected in  $>40\%$  of recipients when both elderly DCD donors and elderly recipients were considered. In addition, the authors reported a 12% rate of graft loss due to PNF. We obtained better results in terms of PNF (4.8% in elderly cDCD-KT recipients) and graft function ( $<30\%$  recipients with eGFR  $<30$  ml/min at 20.5 months). Several factors might have contributed to this finding. Both warm [27] and cold [20,28,29] ischemia times have been reported to be important factors affecting graft survival. In our study, the cold ischemia time in the cDCD-KT group was shorter than that previously reported [3] (11.1 vs. 17.5 h), which may explain the better graft outcomes [3]. In fact, we could speculate that DBD-KT recipients with similar cold ischemia time to cDCD-KT recipients (in our cohort, the cold ischemia time was 5 h longer in the DBD-KT group) could have achieved better graft or patient survival. Furthermore, only donors from Catalonia were considered in our study, minimizing external factors that could affect graft outcomes.

Another factor that differed between the two groups was the use of thymoglobulin as induction therapy, which was more frequent in the cDCD-KT group (60.6% vs. 34.5%). Immunosuppressive treatment was freely prescribed according to the protocol of each center. Thymoglobulin is usually administered in sensitized recipients (the percentage of recipients with high PRA

[>50%] was higher in the cDCD-KT group); however, it is also administered if prolonged DGF is expected. Despite this difference in the use of thymoglobulin, we analyzed the impact of the use of thymoglobulin compared with the use of basiliximab as induction therapy and found no impact on transplant outcomes (data not shown).

Lastly, although normothermic regional perfusion has been recently described as a major improvement in cDCD organ retrieval [30], only 10.3% of our grafts were retrieved under this condition, probably because the donors were non-multiorgan donors.

This study had some limitations, including its retrospective nature. In addition, the sample size was moderate and the follow-up duration may not reflect long-term outcomes. In fact, the follow-up duration differed between the groups (shorter in cDCD-KT recipients), and this might have influenced the results. We also excluded donors from other regions of Spain, in an attempt to homogenize the sample and collect as much data as possible. This could have resulted in a selection bias, as grafts retrieved in Catalonia probably had shorter cold ischemia times. The inclusion of kidneys retrieved from donors outside Catalonia could have worsened our study results. However, to our knowledge, this is the largest cohort study thus far to compare elderly cDCD-KT and DBD-KT recipients.

Elderly KT recipients seem to present similar outcomes regardless of donor type. Therefore, elderly cDCD donors may constitute a complementary source of kidneys for elderly recipients. Considering the

negative previous results of the use of elderly cDCD grafts in elderly recipients, as well as the increasing acceptance of marginal donor organs in Europe, this study contributes to clarifying the outcomes of elderly KT candidates with different types of donors, adding some evidence toward the favorable results of cDCD-KT. However, careful recipient evaluation is mandatory to minimize the risks after KT. Further studies with larger sample sizes are required to confirm our results.

## Authorship

MJPS and JP: conceptualized the study, contributed with the study design, data analysis and wrote the manuscript. JJ and AZ: contributed with the study design and data analysis. JC: performed data analysis. JT and RL: gave their insight and contributed to the manuscript development.

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## Conflict of interest

The authors of this study declare no conflict of interest.

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