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ORIGINAL ARTICLE

Deciphering transplant outcomes of expanded kidney allografts donated after controlled circulatory death in the current transplant era. A call for caution

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SUMMARY

Outcomes of kidney transplantation (KT) after controlled circulatory death (cDCD) with highly expanded criteria donors (ECD) and recipients have not been thoroughly evaluated. We analyzed in a multicenter cohort of 1161 consecutive KT, granular baseline donor and recipient factors predicting transplant outcomes, selected by bootstrapping and Cox proportional hazards, and were validated in a contemporaneous European KT cohort (n = 1585). 74.3% were DBD and 25.7% cDCD-KT. ECD-KT showed the poorest graft survival rates, irrespective of cDCD or DBD (log-rank < 0.001). Besides standard ECD classification, dialysis vintage, older age, and previous cardiovascular recipient events together with low class-II-HLA match, long cold ischemia time and combining a diabetic donor with a cDCD predicted graft loss (C-Index 0.715, 95% CI 0.675–0.755). External validation showed good prediction accuracy (C-Index 0.697, 95%CI 0.643–0.741). Recipient older age, male gender, dialysis vintage, previous cardiovascular events, and receiving a cDCD independently predicted patient death. Benefit/risk assessment of undergoing KT was compared with concurrent waitlisted candidates, and despite the fact that undergoing KT outperformed remaining waitlisted, remarkably high mortality rates were predicted if KT was undertaken under the worst risk-prediction model. Strategies to increase the donor pool, including cDCD transplants with highly expanded donor and recipient candidates, should be performed with caution.

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Key words
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Introduction

The persistent shortage of kidney organ donors and the progressive ageing of waitlisted kidney transplant candidates has led transplant physicians to implement strategies that have proven successful in order to maximize the likelihood of kidney transplantation such as transplants retrieved after controlled circulatory death (cDCD) as well as those from expanded criteria kidney organ donors (ECD) [1–3].

Despite the considerable warm ischaemic injury that cDCD kidneys incur, studies assessing midterm graft outcomes between cDCD and DBD donors >60 years showed similar transplant outcomes, [4] although strengthening the importance of shortening cold ischemia times (CIT) and avoiding large age mismatches [5,6]. However, recent reports have challenged this previous data by showing that the utilization of more elderly cDCD donors (>65 years) for similarly senior transplant candidates leads to worse graft and patient outcomes than similarly elder recipients of younger cDCD donors [7]. Notably, this data suggests that not all elderly kidney donors and transplant candidates may be considered with the same associated risk exclusively related to age, but rather to additional biological factors no longer fitting with the classical ECD conception. Thus, a more precise understanding of the benefit/risk of this type of KT is highly needed since poor graft outcomes among this frail patient population may challenge patient survival.

In our transplant region, we are especially well-placed for addressing these questions; on the one hand, it is the largest transplant region in Europe with the highest proportion of cDCD-ECD organs (almost 40%) (http://www.ont.es), and on the other hand, the allocation system is homogeneous and not centre-dependent with all kidneys donors being allocated according to the same organ sharing scheme. Taking advantage of this setting, we designed a retrospective multicentre cohort study aiming to assess the impact of granular risk factors from both donors and recipients defining distinct graft and patient outcomes when undergoing either cDCD or DBD kidney transplantation. To further validate the findings, we explored their impact in a large external contemporary European cohort from the Epidemiology Kidney Transplantation in Europe (EKITE). Finally, the benefit/risk of undergoing kidney transplantation in patients harboring these risk factors were compared with matched active waitlisted patients for KT.

Material and methods

Patients of the study

All consecutive deceased-donor kidney transplants (KT) performed in five main kidney transplant centres in Barcelona (Spain), from January 2013 until December 2017, procured after either DBD or cDCD, were eligible to participate in this study. Out of these 1281 patients, 1161 were recruited because of complete data collection (Bellvitge University Hospital, $n = 352$; Hospital del Mar, $n = 289$; Vall d'Hebrón University Hospital, $n = 243$; Hospital Clínic, $n = 206$; Fundació Puig-Vert, $n = 71$) (Fig. 1). Patients were followed up until death, loss of follow-up, or 31st of December 2019. Median time of follow-up was 33.75 months (interquartile range (IQR): 24.2–47.9). Patient inclusion in the study begun when a new allocation system in Catalonia was implemented, in which all KT are allocated according to a centralized point-based scoring system that prioritizes age matching, time on waiting list, donor/recipient HLA antigen matching, and compatibility (absence of donor-specific alloantibodies [DSA]) and selects the best-match recipient across all centers.

After internal validation, to further evaluate the predictive capacity of most discriminative risk factors building our model, we investigated its impact and accuracy in a large contemporaneous external European kidney transplant cohort ($n = 1585$) within the EKITE, which was set up to combine data of kidney transplant recipients of five French transplantation centres (Nantes, Nancy, Lyon, Necker, Montpellier), Oslo (Norway) and Leuven (Belgium) since 2005 into a single European cohort updated annually [8].

Finally, to assess the benefit/risk of undergoing kidney transplantation with the distinct risk factors as compared with remaining in the waiting list, we used data from our national Catalan Renal Registry (RMRC) with all kidney transplant candidates in the waiting list during the same era of our study ($n = 1342$). In this analysis, patients on the waiting list were censored on the transplant date, and last follow-up date was

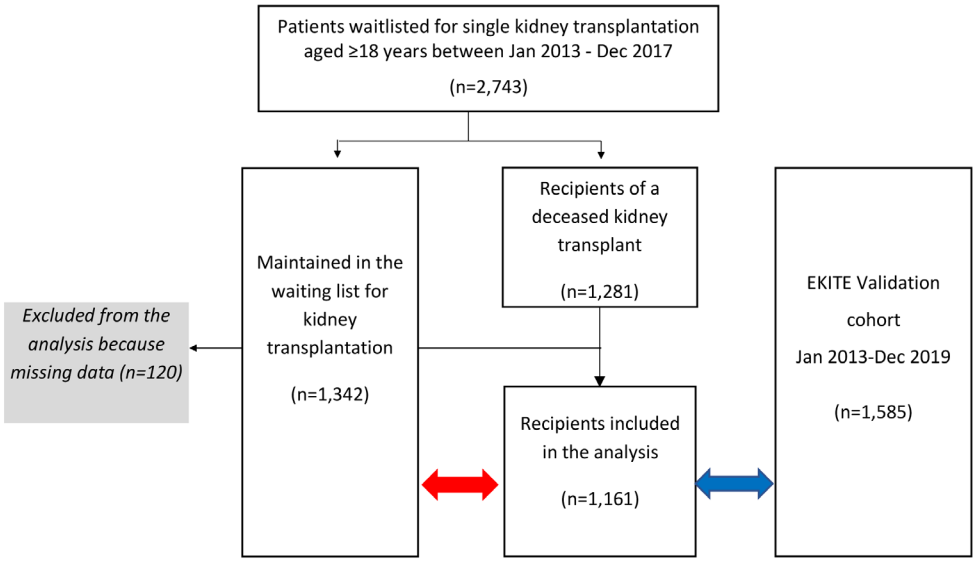


Figure 1 Flow-chart of the included population, the comparison EKITE cohort and waiting list kidney transplant patients.

December 31, 2019. De-listed patients were also followed up, and if death, this event was also taken into account. The RMRC is a mandatory population-based registry covering 7.5 million people that collects information on all patients with End Stage Renal Disease requiring Renal Replacement Therapy in our region in Catalonia (www.trasplantaments.gencat.cat).

The study was performed after obtaining the approval of the Institutional Review Board at each participating centre.

Main end points of the study

The primary objective of the study was to identify granular clinical, demographic, and biological pretransplant characteristics from both donor and recipients, beyond age and the standard quality donor stratification of SCD or ECD, [9] differentiating between different kidney transplant and patient outcomes defined as graft loss and patient death, when undergoing either a DBD or cDCD-KT. Furthermore, we investigated the benefit/risk in terms of patient survival when performing a KT in the presence of these risk factors as compared with remaining in the waiting list.

Graft loss was defined as patient return to any renal replacement therapy including re-transplantation and was censored if patient died.

Primary nonfunctioning graft was defined as those KT that were lost during the first week after transplantation not due to allograft rejection as well as those with prolonged nonfunction that never recovered and it was included in the outcome of graft loss.

Main variables of the study

cDCD was defined as donors suffering cardiac arrest after withdrawal life-supporting treatment in the intensive care unit. All kidney donors were also defined according to the classical criteria of donor kidney risk quality as either SCD or ECD [8–10]. Briefly, ECD were all kidney donors ≥60 years old or donors who were aged 50 to 59 years old and had two of the following three features: hypertension, terminal serum creatinine >1.5 mg/dl, or death from cerebrovascular accident. Additionally, all kidney donors and recipients were further assessed for a number of different demographic, clinical, and immunological variables such as age, gender, body mass index, use of machine perfusion preservation, preimplantation kidney allograft histological scores, and comorbidities such as Hepatitis C Virus, diabetes mellitus (DM), hypertension, and last donor serum creatinine and proteinuria values before retrieval. Transplant recipients and the comparative waitlisted patient cohort at the time of listing for transplantation were evaluated for age, gender, ethnicity, weight, height, etiology of renal disease, number of previous KT, immunological sensitization, and comorbidities such as DM, hypertension, previous cardiovascular events (ischemic heart disease, peripheral arterial disease, stroke, or revascularization procedure), type of dialysis, and dialysis vintage. Transplant variables such as cold and warm ischemia times and HLA mismatches between donor and recipient were also considered.

We followed the TRIPOD Guidelines to report all this information [11].

Statistical analysis

To define cohort characteristics, categorical variables were presented as the number of cases and percentages, while continuous variables were presented as the mean and standard deviation (SD) or median and interquartile range (IQR). Continuous variables were compared using Student's *t*-test or Mann-Whitney U test where appropriate. Fisher's exact test or Pearson's χ^2 test were applied to assess the relationship between categorical variables.

Two different prediction models were estimated using Cox proportional hazards model to predict the risk of death-censored graft failure and the risk of death at 3 years after KT. A set of graft failure and death related predictor variables were prespecified.

The development cohort was sampled by bootstrapping with replacement up to 2000 times. A model was fitted in each sample using stepwise elimination and Akaike Information Criterion. Predictors retained in more than 60% of the models were considered for inclusion in the selected model and also those considered clinically relevant and improved model's predictive capacity. A model with the elected predictors was then estimated and reported as the hazard ratio (HR) and 95% confidence interval. The proportionality of risks in the Cox model was verified graphically and analytically using the Schoenfeld residuals. The model discrimination was reported as Harrel's C statistic. In addition, it was also assessed by estimating the time-to-event area under the receiver operating characteristic (ROC) curve. Calibration was assessed by comparing observed versus expected graft loss/deaths by deciles of predicted risk. An internal validation was performed by bootstrapping on the development sample.

External validation was performed using the EKITE cohort. Using the developed mortality model, several scenarios were generated to compare the observed versus the expected death incidence at 1 and 3 years from KT of waitlisted patients. Data management, statistical analyses, and graphs generation were performed using R Statistical Software version 3.6.3 (cran.r-project.org) (packages: Survival, lmtest, PredictABEL, rms, ROCR).

Results

Baseline donor and recipient characteristics

This multicentric cohort study included 1161 consecutive adult, single, KT patients: 863 (74.3%) recipients of a DBD and 298 (25.7%) of a cDCD (Fig. 1). In line with the classical deceased donor risk classification, [9] 294 and 569 of DBD were SCD and ECD, respectively, and 111 and 187 of cDCD were SCD and ECD, respectively.

Main baseline donor/recipient clinical, demographic, and immunological characteristics are depicted in Table 1. The majority of donors and recipients were male (54.7% and 65.5%, respectively), with a similar mean age (61.8 ± 14.4 and 60 ± 12.5 years, respectively). Among transplant recipients, there was a high prevalence of hypertension (89.1%) and diabetes, and previous cardiovascular events were present in 28.1% and 20.1%, respectively. Most patients were first kidney transplants (86%) and very few displayed pretransplant DSA (6.03%). The median dialysis vintage time was of 25 months [range 13.1–47.7].

Recipients of cDCD were similar to recipients of DBD regarding age, gender, pre-KT sensitization, main comorbidities, or baseline kidney histopathological characteristics. While by definition there were differences on main variables defining SCD and ECD, these differences were not significant when comparing ECD-cDCD with ECD-DBD and SCD-cDCD to SCD-DBD. Notably, CIT was lower in cDCD than in DBD (12.8 ± 6.81 h and 17.1 ± 5.67 respectively, $P < 0.001$), and warm ischemia time in cDCD was shorter in SCD as compared with ECD (15.0 [12.0–19.8] and 20.0 [14.0–24.0] minutes respectively, $P = 0.04$).

Kidney graft survival outcomes

Main transplant outcomes using standard quality donor-risk classification

General graft loss rate was 4.51 per 1000 recipients-month (95% CI 3.85–5.23). It was worse in cDCD (6.6 per 1000 recipients-month (95% CI 4.93–8.59) as compared with DBD donors (3.94 per 1000 recipients-month (95% CI 3.25–4.71) (log rank $P = 0.024$). Notably, this finding fundamentally accounted for the differences between ECD and SCD groups (log rank $P < 0.0001$) (Fig. 2a). Among DBD-SCD, graft loss was 1.84 per 1000 recipients-month (95% CI 1.12–2.79) whereas 5.18 per 1000 recipients-month (95% CI 4.19–6.31) within DBD-ECD. Similarly, graft loss in cDCD-SCD was 2.9 per 1000 recipients-month (95% CI 1.39–5.15) but 9.48 per 1000 recipients-month (95% CI 6.83–12.68) among cDCD-ECD.

82 (7%) kidney transplants were lost, 50 (60.98%) occurring during the first 6 months after transplantation. 30 (36.6%) were related to vascular complications, 26 (52%) reached suboptimal graft function and progressively failed, and 4 (4.8%) were due to biopsy-proven acute rejection (BPAR), with no differences between donor types ($P = 0.105$). There were 90 (7.7%) deaths in the entire

Table 1. Clinical characteristics of KT recipients and donors according to the classical donor definitions.

Main variables	All (n = 1161)	cDCD (n = 298) SCD (111, 37.2%)	cDCD (n = 298) ECD (187, 62.8%)	DBD (n = 863) SCD (294, 34.1%)	DBD (n = 863) ECD (569, 65.9%)	P
Donor						
Age (years, mean, range)	61.8 ± 14.4	45.5 ± 10.3	70 ± 8.93	49.5 ± 9.05	69.3 ± 7.27	<0.001
(median, range)	63 [53–73]	52.3 [45.8–56]	69 [64.2–74.5]	48 [40.6–54]	71 [63–77]	<0.001
Gender (female, n, %)	526 (45.3)	127 (43.2)	290 (51.0)	39 (35.1)	70 (37.4)	0.001
BMI (kg/m^2, mean ± SD)	27.2 ± 4.75	26.6 ± 5.29	27.3 ± 4.73	27.7 ± 5.18	27.3 ± 3.42	0.144
Hypertension (n, %)	600 (51.7)	48 (16.3)	403 (70.8)	31 (28.2)	118 (63.1)	<0.001
Diabetes (n, %)	199 (17.1)	19 (6.46)	140 (24.6)	4 (3.60)	36 (19.3)	<0.001
Serum creatinine (mg/dl, median, IQR)	0.80 [0.60–1.02]	0.83 [0.63–1.18]	0.80 [0.63–1.03]	0.79 [0.50–0.95]	0.72 [0.52–0.93]	<0.001
Remuzzi score >5 (n, %)	174 (29.9)	2 (3.64)	119 (34.6)	21 (31.3)	32 (27.6)	<0.001
Cold ischaemia time (h, mean ± SD)	16.0 ± 6.27	11.6 ± 7.02	13.5 ± 6.61	16.1 ± 5.59	17.7 ± 5.63	<0.001
Warm ischaemia time (min, median, IQR)	18.0 [13.0; 23.0]	15.0 [12.0; 19.8]	20.0 [14.0; 24.0]	–	–	0.045
Recipient						
Age (years, mean ± SD)	60.0 ± 12.5	48.2 ± 11.3	65.8 ± 9.36	51.7 ± 9.2	65.8 ± 7.54	<0.001
(median, range)	62.2 [51.9–70]	52.4 [47.5–58]	67 [61–71]	48 [40.6–54]	67.6 [60.9–72]	<0.001
Gender (female, n, %)	400 (34.5)	87 (29.6)	211 (37.1)	48 (43.2)	54 (28.9)	0.011
BMI (Kg/m^2, mean ± SD)	26.6 ± 4.57	26.1 ± 5.04	26.7 ± 4.29	26.1 ± 4.58	27.5 ± 4.52	0.009
Cause of ESRD (n, %)						<0.001
Glomerular	240 (28.9)	71 (31.6)	100 (24.8)	30 (35.7)	39 (32.8)	
PKD	146 (17.6)	41 (18.2)	73 (18.1)	20 (23.8)	12 (10.1)	
Diabetes	172 (20.7)	21 (9.33)	102 (25.3)	17 (20.2)	32 (26.9)	
Vascular	126 (15.2)	31 (13.8)	79 (19.6)	5 (5.95)	11 (9.24)	
CTIN/CPN	93 (11.2)	36 (16.0)	34 (8.44)	8 (9.52)	15 (12.6)	
Other	54 (6.50)	25 (11.1)	15 (3.72)	4 (4.76)	10 (8.40)	
Comorbidities (n, %)						
Hypertension	1034 (89.1)	249 (84.7)	515 (90.5)	97 (87.4)	173 (92.5)	0.022
Diabetes	326 (28.1)	42 (14.3)	190 (33.4)	22 (19.8)	72 (38.5)	<0.001
CV event	233 (20.1)	28 (9.52)	138 (24.3)	16 (14.4)	51 (27.3)	<0.001
Type of dialysis (n, %)						0.001
Preemptive	56 (4.83)	16 (5.44)	27 (4.75)	7 (6.31)	6 (3.23)	
Hemodialysis	907 (78.2)	213 (72.4)	463 (81.4)	74 (66.7)	157 (84.4)	
Peritoneal	197 (17)	65 (22.1)	79 (13.9)	30 (27.0)	23 (12.4)	
Dialysis vintage (months, median, IQR)	25.0 [13.1–47.7]	27.0 [14.2–48]	24.0 [12–45.8]	21.9 [11.6–40]	33.0 [18.1–58.5]	<0.001
Induction IS (n, %)						
Basiliximab	687 (59.4)	185 (63.1)	389 (68.4)	39 (35.1)	74 (40.4)	
ATG	447 (38.7)	92 (31.4)	174 (30.6)	72 (64.9)	109 (59.6)	
None	22 (1.90)	16 (5.46)	6 (1.05)	0	0	

Table 1. Continued.

Main variables	All (n = 1161)	cDCD (n = 298)		DBD (n = 863)		P
		SCD (111, 37.2%)	ECD (187, 62.8%)	SCD (294, 34.1%)	ECD (569, 65.9%)	
First KT (n, %)	998 (86)	244 (83)	487 (85.6)	101 (91)	166 (89.2)	0.101
Number of HLA mismatch (total (mean ± SD))	4.14 ± 1.14	4.04 ± 1.17	4.16 ± 1.12	4.16 ± 1.09	4.24 ± 1.14	<0.001
DSA pre-KT (n, %)	70 (6.03)	21 (7.14)	33 (5.80)	6 (5.41)	10 (5.35)	0.819

ATG, antithymocyte globulin; BMI, Body Mass Index; cDCD, donor after controlled cardiac death; CPN, chronic pyelonephritis; CTIN, chronic tubulointerstitial nephritis; CV, cardiovascular; DBD, donor Brain Death; DSA, donor-Specific Antibodies; ECD, expanded Criteria Donor; ESRD, end-Stage Renal Disease; HLA, human leukocyte antigen; IS, immunosuppression; KT, kidney Transplantation; PKD, polycystic kidney disease; SCD, standard Cardiac Donor; SD, standard deviation.

CV event: Cardiovascular event included: ischemic heart disease, peripheral arterial disease, stroke, or revascularization procedure.

P-value comparing cDCD-ECD vs. cDCD-SCD vs. DBD-ECD vs. DBD-SCD.

cohort. Patient death was mainly due to cardiovascular-related fatal events (n = 21, 30.4%), infections (n = 26, 37.7%), and malignancies (n = 7, 10.1%), without differences between the distinct donor-type groups (P = 0.735).

Refining risk-stratification variables predicting graft loss

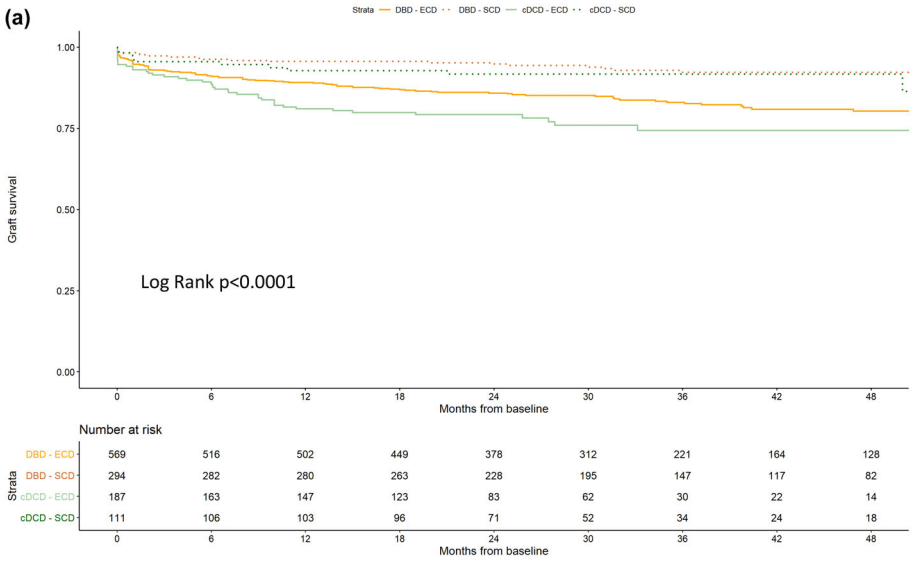
In order to identify additional relevant variables influencing kidney transplant outcomes, we used a bootstrapping method to sample the development cohort, with a number of clinical, demographic, and immunological donor and recipient variables not restricted to the standard donor quality criteria (ECD and SCD) or the type of donor transplant (DBD or cDCD) (Table S1). As depicted in Table 2, besides the standard quality donor classification of ECD, also older recipient age, dialysis vintage, a poor donor/recipient HLA class II mismatch, long CIT, and recipients with previous cardiovascular (CV) events were independent correlates of graft loss. Notably, besides individual variables, the analysis of interaction between distinct variables showed that the combination of a diabetic donor with cDCD was a strong independent correlate of graft loss (Fig. 2b). No interaction was observed when combining ECD with cDCD KT in the model. The internal validation of this model showed a good calibration and fair discrimination capacity (C-Index 0.715, 95%CI 0.675–0.755) (Figure S1).

The refined risk-prediction model outperforms the Kidney Donor Risk Index (KDRI)

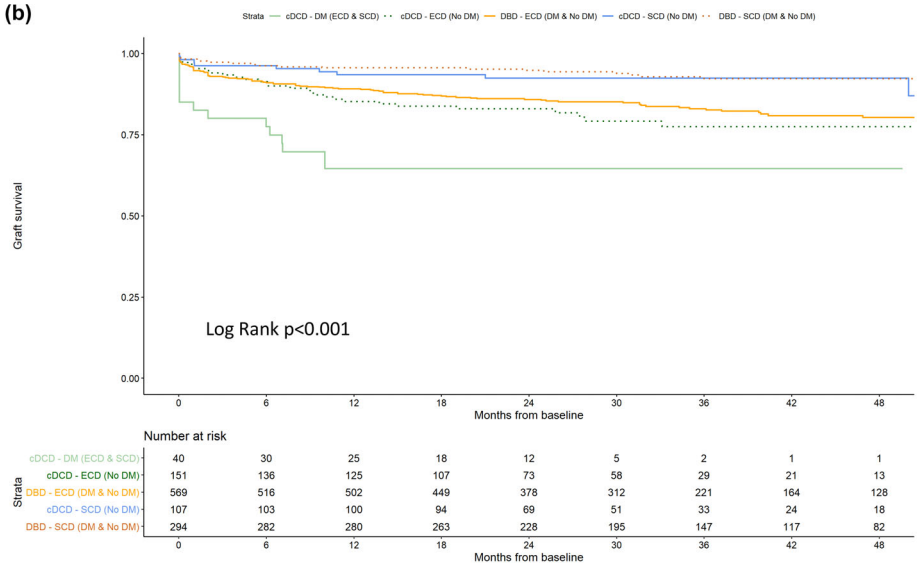
We next compared this new model using data of graft loss not censored for death (which it only included 10 additional events) with the KDRI [12] (including a great proportion of variables of our model such as age, race, history of hypertension or diabetes, last serum creatinine, cerebrovascular cause of death, height, weight, cDCD donors, hepatitis C virus status, HLA-B and DR mismatch, CIT, and double or *en bloc* transplants, but does not take into account recipient factors). As illustrated in Figure S2a, a relatively low correlation between the two models was observed (r = 0.479). As compared with our model, a worse predictive capacity was observed when using the KDRI (C-index 0.623, 95%CI 0.58–0.666) (Figure S2b,c).

External validation of the risk-prediction model in the EKITE cohort

Despite that patients from both transplant cohorts belonged to the same time period, there were some



Abbreviations: cDCD: controlled donor after cardiac death; DBD: Donor after Brain Death; ECD: Expanded Criteria Donor; SCD: Standard Criteria Donor.



Abbreviations: *cDCD: controlled donor after cardiac death; DBD: Donor after Brain Death; DM: Diabetes; ECD: Expanded Criteria Donor; SCD: Standard Criteria Donor.*

Figure 2 (a) Survival curves for the cox-proportional regression model of graft survival after renal transplantation in recipients from cDCD or DBD, stratified according to classical definition of ECD or SCD. Log Ranks between groups were as follows: cDCD-ECD vs. DBD-SCD: $P < 0.001$; cDCD-ECD vs. cDCD-SCD: $P = 0.01$; DBD-ECD vs. cDCD-ECD: $P = 0.122$ and DBD-ECD vs. DBD-SCD: $P < 0.001$. (b) Survival curves for the cox-proportional regression model of graft survival after renal transplantation in recipients from cDCD or DBD donors, stratified according to ECD, SCD, and donor diabetes. Log Ranks between groups were as follows: cDCD-DM vs. cDCD-ECD: $P = 0.1$; cDCD-DM vs. cDBD-ECD: $P = 0.001$; cDCD-DM vs. cDBD-SCD: $P < 0.001$ and cDCD-DM vs. cDCD-SCD; $P < 0.001$.

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Table 2. Cox-proportional regression model of graft loss after bootstrapping variable selection.

Main variables	Hazard Ratio	95% CI	*P*
Donor type cDCD	1.00	0.59–1.68	0.993
ECD	1.68	1.04–2.71	0.032
Donor DM	0.93	0.59–1.46	0.994
Recipient age	1.32	1.05–1.66	0.018
Recipient time dialysis	1.25	1.08–1.45	0.003
Recipient CV event	2.08	1.50–2.90	<0.001
HLA DR MM (2 vs. 0–1)	1.28	0.87–1.86	0.206
Cold ischemia time	1.19	1.01–1.41	0.036
cDCD + Donor diabetes	2.56	1.19–5.54	0.017
cDCD + HLA DR MM (2 vs. 0–1)	1.96	1.00–3.85	0.049
Recipient time dialysis + Recipient CV event	1.34	1.07–1.69	0.011
cDCD + ECD	0.44	0.36–2.02	0.722

Variables were chosen by bootstrap method from all this list: ECD, SCD, DBD, donor gender, donor age, donor hypertension, donor Hepatitis C Virus, donor body mass index, cold ischemia time, baseline kidney allograft histopathological lesions, recipient gender, donor/recipient HLA missmatches, recipient hypertension, diabetes or previous cardiovascular events, recipient number of transplantation, preformed DSA, type of induction immunosuppression, and recipient type of dialysis.

cDCD, controlled donor after cardiac death; CI, confidence interval; CV, cardiovascular event; ECD, Expanded Criteria Donor; HLA, human leukocyte antigens; MM, mismatch; DSA, donor-specific antibodies.

differences between the two groups (Table S2). The number of cDCD transplants were significantly higher within the development cohort (25.7% vs. 12.3%, respectively), donor and recipient age were older in our cohort as compared with EKITE (61.8 ± 14.4 vs. 56 ± 17.2 and 60 ± 12.5 vs. 55 ± 14.3 years old, respectively), and donor DM were more frequent in our study population than in EKITE (17.1% vs. 9.02%, respectively). Conversely, a higher proportion of recipients with previous CV events was present within the EKITE cohort as compared with our study population (39.4% vs. 20.1%, respectively). As illustrated in Figure S3, the impact of our risk-stratification model, using only pretransplant risk factors, in the EKITE cohort showed a clinically useful predictive accuracy (C-index 0.697 (95% CI 0.632–0.741).

Patient survival outcomes

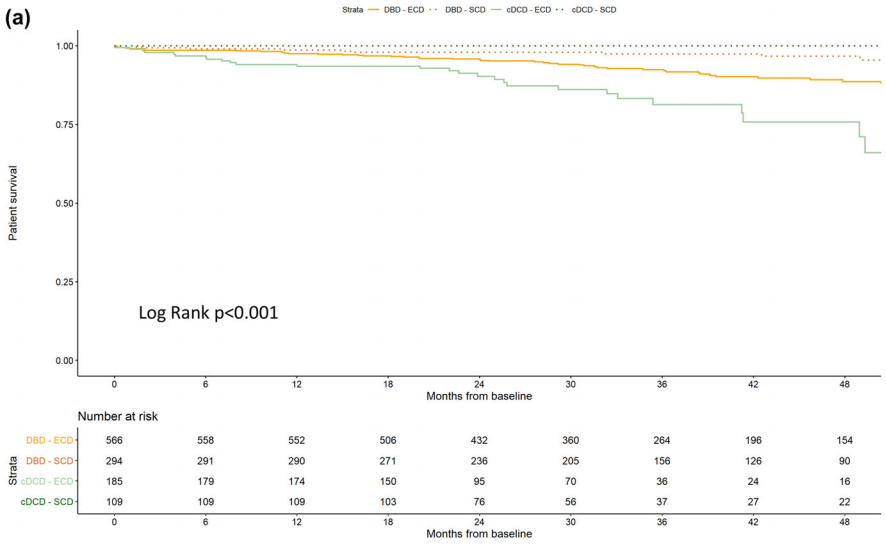
The mortality rate in our study cohort was 2.03 per 1000 recipients-month (95% CI 1.62–2.5). Likewise, to graft survival, while patient survival rates of cDCD transplant were worse (3.08 per 1000 recipients-month [95% CI 2.03–4.41] as compared with DBD (1.97 per 1000 recipients-month [95% CI 1.51–2.50]), and this difference was fundamentally impacted by the quality of organ donor (ECD or SCD). The highest mortality rates were observed among the cDCD-ECD group (5.31 per 1000 recipients-month (95% CI 3.5–7.61) compared with all the other donor types (Log Rank $P < 0.001$) (Fig. 3a).

When different variables other than standard donor organ quality (ECD, SCD) or type of kidney transplant (cDCD or DBD) selected by bootstrapping were also analyzed in adjusted regression models estimating the risk of patient death, we observed that cDCD, recipient age, recipient gender, dialysis vintage, and recipients with previous CV events significantly increased the hazard of mortality (Table 3). Notably, transplant recipients with previous CV events showed a significant high risk of death when transplanted with a cDCD donor (Fig. 3b).

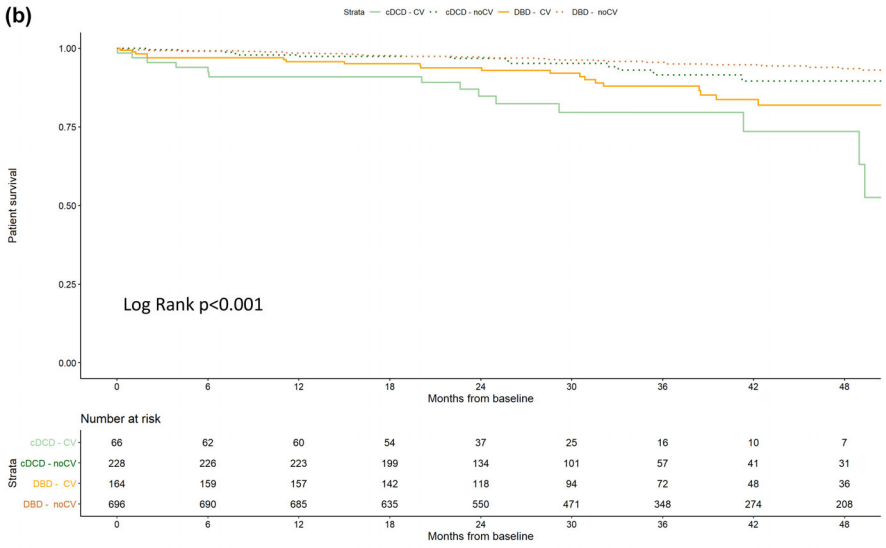
We subsequently evaluated the performance of these variables in the external European EKITE transplant cohort, which showed good calibration and discrimination capacity (C-index 0.733, 95% CI 0.64–0.82) (Figure S4).

Benefit/risk assessment of undergoing KT according to the risk-prediction model

Using data extracted from the National Catalan Renal Registry Data, we assessed the benefit/risk of being transplanted as compared with remaining on the waiting list when taking into account our risk-prediction model. As depicted in Table S3, recipient gender and BMI were similar between KT patients and patients waitlisted. Conversely, while KT patients were significantly older than patients on the waiting list, the KT



Abbreviations*: cDCD: controlled donor after cardiac death; DBD: Donor after Brain Death; DM: Diabetes; ECD: Expanded Criteria Donor; SCD: Standard Criteria Donor.*



Abbreviations*: cDCD: controlled donor after cardiac death; DBD: Donor after Brain Death; DM: Diabetes; ECD: Expanded Criteria Donor; SCD: Standard Criteria Donor; CV: previous cardiovascular event*

Figure 3 (a) Survival curves for the cox-proportional regression model of patient survival after renal transplantation in recipients from cardiac-death or brain-death donors, stratified according to classical definition of expanded or standard criteria donor. Log Ranks between groups were as follows: cDCD-ECD vs. DBD-SCD: $P < 0.001$; cDCD-ECD vs. cDCD-SCD; $P < 0.001$; DBD-ECD vs. cDCD-SCD: $P = 0.016$ and DBD-ECD vs. DBD-SCD; $P = 0.015$. (b) Survival curves for the cox-proportional regression model of patient survival after renal transplantation in recipients from cDCD or DBD, stratified according to recipient previous cardiovascular (CV) event. Log Ranks between groups were as follows: cDCD-CV vs. cDCD-noCV: $P < 0.001$; cDCD-CV vs. cDBD-CV; $P = 0.07$; cDCD-CV vs. DBD-noCV; $P < 0.001$ and DBD-CV vs. DBD-noCV: $P = 0.008$.

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Table 3. Cox-proportional regression model of patient death after bootstrapping variable selection.

Main variables	Hazard Ratio	95% CI	*P*
Donor type cDCD	1.97	1.23 to 3.14	0.005
Recipient age	2.68	1.95 to 3.67	<0.001
Recipient CV event	1.91	1.24 to 2.94	0.003
Recipient sex (male)	1.62	1 to 2.62	0.051
Recipient dialysis vintage	1.16	0.98 to 1.38	0.088

cDCD, controlled donor after cardiac death; CI, confidence interval; CV, cardiovascular event.

Variables were chosen by bootstrap method from all this list: ECD, SCD, DBD, donor gender, donor age, donor diabetes, donor hypertension, donor Hepatitis C Virus, donor body mass index, cold ischemia time, recipient gender, HLA mismatches A or B or DR, recipient hypertension, recipient diabetes, recipient number of transplantation, recipient time dialysis, donor-specific antibodies, type of induction, cold ischemia time, primary nonfunctioning graft, recipient type of dialysis, and delayed graft function.

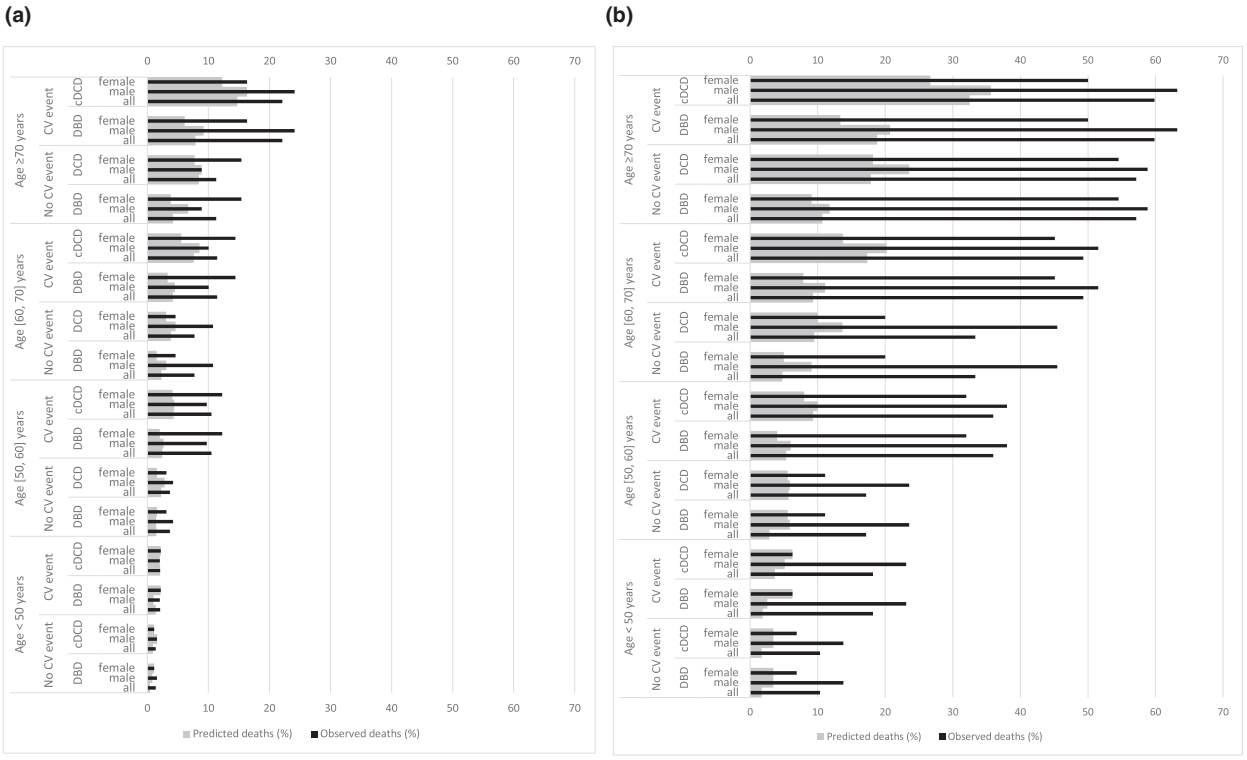
population were significantly less diabetic and had experienced less CV events as compared with waitlisted KT patients.

In order to analyze the benefit/risk of undergoing KT according to the developed risk-stratification model, we stratified the analysis in four different scenarios according to each individual risk factor: recipient age (<50, 50–60, 60–70, ≥70 years old), recipient CV event, recipient gender, and type of transplant (cDCD or DBD). Observed and expected mortality rates were assessed in all contemporaneous waitlisted patients according to the risk-stratification model at 1 and 3 years. We performed a pair-matched analysis stratifying by main variables (recipient age, recipient CV event, recipient DM, and hypertension) that led to similar outcomes than the crude analysis using the logistic regression model including all patients (data not shown). As illustrated in Fig. 4a,b, undergoing KT was shown to be associated with a lower mortality risk as compared with not being transplanted and remaining on the waiting list at 1 and 3 years within all risk-stratification groups. Nonetheless, the risk of mortality in the highest risk-stratification group remained very high even if patients were transplanted (Tables S4 and S5).

Discussion

In this study, we describe that by assessing a number of specific donor-related variables together with recipient risk factors prior to transplantation more precisely discriminates between different transplant and patient outcomes, especially when expanded cDCD KT are to be undertaken. Furthermore, we also show that despite undergoing KT provides better patient survival expectancy as compared with remaining waitlisted, even in the worst risk-prediction scenario, high mortality rates are also predicted when KT is performed under the worst risk-prediction stratification.

While initial thoughts argued against the use of ECD kidneys for cDCD kidney transplantation, [3] a number of subsequent studies subsequently showed noninferior outcomes when comparing cDCD between ECD and SCD [13–16]. Therefore, a significant expansion of this strategy has been spread worldwide over the last decade, representing up to almost 30% of the total deceased donor transplants [17,18]. While these studies showed similar outcomes between them, they all however reinforced the need for shorter CIT and optimal HLA matching [5,19–21]. In line with this observation, in our study, while cDCD KT showed significantly lower CIT than DBD transplants, illustrating the implementation of this policy in our country, this variable was still revealed as an independent predictor of poor graft outcome in our model. Nevertheless, recent studies have challenged this previous data by showing a negative impact of cDCD KT within more senior population. Using data from the Dutch Organ Transplantation Registry, Peters-Sengers [7] reported that elderly recipients of elderly cDCD transplants (>65 years) displayed significantly lower 5-year patient survival rates as compared with receiving an elderly DBD transplant (50.9% vs. 55%, respectively). Notably, they also showed a higher mortality rate of these high-risk population as compared with similarly old waitlisted patients. While "old-for-old" policies of DBD KT have been now issued for years and showed better patient outcomes as compared with remaining on the waiting list, even in very senior donors (>75 years), [16,22] these data suggest that with the addition of warm ischemia time, kidneys



* Detailed point estimates for the predicted probability are presented in Supplemental Table 4.

* Detailed point estimates for the predicted probability are presented in Supplemental Table 5.

Figure 4 (a) Observed and predicted death rates of contemporary waitlisted kidney transplant candidates using the prediction mortality model in the development study population at 1 year. (b) Observed and predicted death rates of contemporary waitlisted kidney transplant candidates using the prediction mortality model in the development study population at 3 years.

from older donors tolerate much worse the related ischemia-reperfusion injury [3,23].

Importantly, we show that besides donor age and the standard ECD classification for risk-stratification, the use of diabetic cDCD in recipients with previous CV events allows for better risk-statification, entailing a significant deleterous impact on graft outcomes. Our model outperfomed the prediction-risk for graft loss of the KDRI, which exclusively includes donor-related variables but not those from the recipient. Main causes of graft loss were found to be related to vascular-related problems (26%), most likely owing to suboptimal quality of graft vessels and to the achievement of a suboptimal graft function (52%), which is difficult to interpret but that may relate to subtle donor-derived graft lesions, disparity in metabolic demand between suboptimal donors and recipients, among other causes. Furthermore, an optimal performance of this model was also observed when implemented in a contemporary European cohort, although it slighly overestimated the risk due to the significantly younger and less expanded donor and recipient transplant population undergoing cDCD KT within the EKITE cohort as compared with ours.

We did no find any added value of baseline histological lesions. This finding is in line with previous reports illustrating the limitation of baseline histological assessment predicting graft outcomes owing to technical limitations, sample processing, and biopsy interpretation [24,25]. Likewise, controversial results have been reported about the impact of donor acute kidney injury, especially among cDCD kidney transplants [26,27]. In our study, although we did not have the information on donor acute kidney injury just prior donation, we did not find any association of last donor kidney graft function and transplant outcomes either, which most likely reflects its poor biological information about graft parenchyma preservation.

Finally, our model predicted high mortality rates within the high-risk transplant group, which were above 15% and 25% at 1 and 3 years. The most frequent causes of death were due to CV events or infectious complications, which highlights how relevant is to individualize immunosuppression, especially in these high-risk populations. Although such mortality rates were lower than those observed in the same group of high-risk patients remaning waitlisted, it provides a

clear call for caution if KT is to be undertaken in this high-risk group.

Our study has some limitations. The retrospective nature of the study and the relatively short follow-up are important drawbacks. However, the large and consecutive contemporarneous cohort of KT representing the actual picture of the donor and recipient patient profile of this last decade, with a balanced number of ECD and SCD patients and the high-quality granular data evaluated, significantly counterbalance these constraints. Notably, the validation of our findings in a large, external contemporaneous kidney transplant cohort further supports the value our findings.

In summary, our study shows that with a more accurate pretransplant stratification of both donor and recipient risk factors besides age and classical risk classifications, a better transplant and patient prediction of outcomes may be delineated. While we confirm that DBD transplants and most cDCD transplants offer a significant survival benefit compared with remaining waitlisted, however, the selected donor−recipient combination is of utmost importance. While shortening CIT, improving HLA matching and preemptively listing remain as key factors for better outcomes, allocating highly expanded cDCD kidneys to less expanded transplant recipients while assigning expanded DBD organs to more expanded recipients would probably contribute to better outcomes and maximize the use of the current donor organ pool. Altogether, our data provide a note of caution about allocating severely expanded kidney allografts to similarly expanded recipients, particularly if cDCD kidney transplantation is to be undertaken.

Authorship

NM: designed the study, collected the data, analyzed the data, interpreted the data, drafted the article and revised the article critically; NT: collected the data; NP: analyzed the data, interpreted the data; MC: revised the article critically; FD: revised the article critically; LG: revised the article critically; RE: collected the data; SC: collected the data; EM: collected the data; AB: collected the data; GV: collected the data; IBT: collected the data; IR: collected the data; AM: collected the data; CF: collected the data; BB: collected the data; LR: collected the data; MF: collected the data; JMC: revised the article critically; JC: collected the data; MG: revised the article critically; MN: revised the article critically; AA: revised the article critically; FM: designed the study, collected the data, analyzed the data and revised the article critically; OB: designed the study, analyzed the data, interpreted the data, drafted the article and revised the article critically.

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Conflict of interest

The authors have no conflicts of interest to declare.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

SUPPORTING INFORMATION

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

Table S1. Bootstrapping to sample the development cohort with replacement 2000 times.

Table S2. Clinical characteristics of transplant recipients and donors of the EKITE validation cohort.

Table S3. Clinical characteristics of transplant recipients compared to patients in the waiting list for kidney transplant.

Table S4. Observed deaths of waitlisted patients at 1 year compared with the expected deaths if these patients had been transplanted using the developed mortality model.

Table S5. Observed deaths of waitlisted patients at 3 years compared with the expected deaths if these patients had been transplanted using the developed mortality model.

Figure S1. Internal validation of the risk-stratification model of graft loss.

Figure S2. Comparison between KDRI with the risk-stratification model of graft loss

Figure S3. Validation of the risk-stratification model of graft loss in EKITE European cohort.

Figure S4. Validation of the risk-stratification model for patient death in EKITE European cohort.

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