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META-ANALYSIS

Comparison of survival outcomes between Expanded Criteria Donor and Standard Criteria Donor kidney transplant recipients: a systematic review and meta-analysis

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SUMMARY

In 2002, the United Network for Organ Sharing proposed increasing the pool of donor kidneys to include Expanded Criteria Donor (ECD). Outside the USA, the ECD definition remains the one used without questioning whether such a graft allocation criterion is valid worldwide. We performed a meta-analysis to quantify the differences between ECD and Standard Criteria Donor (SCD) transplants. We paid particular attention to select studies in which the methodology was appropriate and we took into consideration the geographical area. Thirty-two publications were included. Only five studies, all from the USA, reported confounder-adjusted hazard ratios comparing the survival outcomes between ECD and SCD kidney transplant recipients. These five studies confirmed that ECD recipients seemed to have poorer prognosis. From 29 studies reporting appropriate survival curves, we estimated the 5-year pooled nonadjusted survivals for ECD and SCD recipients. The relative differences between the two groups were lower in Europe than in North America, particularly for death-censored graft failure. It is of primary importance to propose appropriate studies for external validation of the ECD criteria in non-US kidney transplant recipients.

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Key words
Expanded Criteria Donor, kidney transplantation, meta-analysis, survival analysis

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Introduction

Renal transplantation is confronted with a donor organ shortage. In 2002, the American United Network for Organ Sharing (UNOS) proposed to increase the pool of donor kidneys to include Expanded Criteria Donor (ECD), for whom the relative risk of graft failure (return to dialysis or patient death) was estimated to be 1.7-fold higher than kidney transplant recipients from Standard Criteria Donor (SCD) [1]. An ECD is defined

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as a brain-dead donor older than 60 years, or between 50 and 59 years old with at least two of the following criteria: serum creatinine >1.5 mg/dl, Cerebrovascular Accident (CVA) as cause of death, or history of High Blood Pressure (HBP) [2,3]. The ECD definition has been established based on the Organ Procurement Transplantation Network (OPTN) database, which collects data from all transplants in the USA. In 2009, Rao *et al.* [4] proposed a new risk quantification score based on the same OPTN database, the Kidney Donor Risk Index (KDRI), that combines 10 donor variables to express the quality of the donor kidneys relative to other donors.

The KDRI score was implemented in the US allocation system in 2013. Outside the USA, the UNOS ECD definition remains the one used, without questioning whether such a graft allocation criterion, established on the basis of US data, is valid worldwide. Indeed, both the characteristics of recipients and health organizations may differ between countries.

In 2008, Pascual *et al.* [5] performed a systematic review and concluded that ECD recipients had worse long-term survival than SCD recipients. However, their conclusions were drawn from a descriptive evaluation of 160 studies, mainly observational, and therefore possibly subject to confounding bias because of differences in characteristics between ECD and SCD recipients. In addition, the analysis was not stratified according to countries or continents and no meta-analysis was performed.

Therefore, we aimed to conduct the first meta-analysis on this subject. The primary objective was to accurately quantify the differences between ECD and SCD transplants in terms of patient-graft survival, patient survival, and death-censored graft survival. The secondary objective was to estimate the three corresponding survival curves for both ECD and SCD kidney recipients. We paid particular attention to select studies in which the methodology was appropriate and we took into consideration the geographical area.

Methods

Survival outcome definitions

Patient-graft survival was defined based on the time from transplantation to the first event between return to dialysis and patient death with a functional graft. Patient survival was defined based on the time from transplantation to patient death with a functional graft by censoring return to dialysis. Death-censored graft survival was defined based on the time from transplantation to return to dialysis by censoring death with a functional graft.

Eligibility criteria

To be eligible, studies had to report results related to at least one survival outcome, using survival regression models comparing ECD kidney recipients and SCD kidney recipients after adjustment on confounding factors and/or description of long-term outcomes for ECD kidney transplant recipients.

Noninclusion criteria were: (i) studies that included ECD kidney recipients with a definition different from the UNOS definition, or one not clearly expressed; (ii) studies that included only kidneys from SCD, from children donors, dual kidney transplants, multiorgan transplants, nonheart beating donors or from living donors; (iii) studies with nonoriginal statistics (review articles, reports of registries); (iv) overlapping studies with the same patients; and (v) studies for which the number of patients was not reported.

For the analysis specifically related to the estimation of pooled adjusted Hazard Ratio (HR) (primary objective), we excluded studies with (vi) no confounder-adjusted HR; or (vii) confounder-adjusted HR on at least one characteristic of the ECD definition (over adjustment bias).

For the analysis specifically related to the estimation of pooled nonadjusted survival curves (secondary objective), we excluded studies with (viii) no survival curve reported; or (ix) the number of at-risk ECD kidney recipients over follow-up times not available or not estimable from data.

Search strategy

Medline, Embase, Cochrane Database of Systematic Reviews and Clinical Trials, Web of Science, Google Scholar, Open Grey, Base, and the website of the French Society of Nephrology were searched from inception to May 2013, and included studies published in any language. The reference or citation lists of all selected publications were investigated to flag additional studies. The search equation used is listed in Data S1.

Study selection and data collection

Study eligibility was determined independently by teams composed of a nephrologist and a statistician. Two teams first selected papers based on titles and abstracts. Four teams subsequently screened full texts. Intra-team

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disagreements were solved by consensus, and were assisted by a third person from another team if needed.

Data collection was performed independently by each reader, using a standardized data collection form: general study characteristics, donors, recipients, transplantation and survival data. Risks of bias were also evaluated.

Statistical analyses

For the primary objective, the confounder-adjusted HRs were combined using the DerSimonian and Laird random-effects method [6] and the R META package [7]. For the secondary objective, the pooled survival curves were estimated by using a distribution-free approach assuming random effects recently proposed by Combescure *et al.* [8] and implemented in the R METASURV package [8]. The 95% Confidence Intervals (95%CIs) of the pooled survivals were obtained by a bootstrap procedure.

Pictures of the published survival curves were digitalized and the survival probabilities were extracted every 3 months post-transplantation. Corresponding numbers of at-risk patients were collected when available, or estimated using Hoyle's method [9], Parmar's method [10] or simulated to obtain similar confidence intervals of survival or *P*-values compared with the ones reported in the text. The I^2 statistic was used to quantify the impact of the heterogeneity in the published survival curves [11]. In this case, a statistical test was performed to explore the potential association of continent and survival [8]. This heterogeneity analysis was conducted for continents with at least three studies and for a follow-up with at least two studies in each continent.

Because the number of retained studies to combine confounder-adjusted HRs was very small, we only explored the geographical area as a potential heterogeneity factor in pooled nonadjusted survival analysis. By definition, nonadjusted survival curves present multiple biases. Therefore, our aim was not to estimate the differences between ECD and SCD outcomes, but only to determine if the relative differences between ECD and SCD kidney recipients within each geographical area were heterogeneous between geographical areas. For this purpose, the Relative Risk (RR) of failure at 5 years post-transplantation was calculated using the corresponding pooled nonadjusted survival probabilities. The 95% CI was obtained by bootstrapping.

All analyses were performed using the software R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and followed the PRISMA recommendations for systematic review and meta-analyses [12].

Results

Description of the retained studies

A flowchart of the selected studies is presented in Fig. 1. The search strategy identified 2336 publications. After removing duplicates and irrelevant reports based on titles and abstracts, we examined 263 full-text reports. A total of 135 publications were excluded because the ECD definition was incorrect or lacking, and 82 because of statistical inadequacies in the survival analysis. Thirty-two publications were finally included in this study [13–44]. The corresponding main characteristics are summarized in Table 1.

Seventeen studies (53%) included North American recipients (15 from the USA) and 10 studies (31%) included European recipients. Half of the studies were multicentric. Twenty-eight publications (88%) were based on observational data collected in registries or cohorts, the other four studies being clinical trials [20,38,41,43]. Importantly, only three studies were international [15,22,41].

Characteristics of donors, recipients, and transplantations are detailed in Table 2. Among the 32 publications, 25 (78%) also included SCD kidney recipients [13–17,19–30,32,33,36–39,42,44]. Transplantation periods ranged from 1990 to 2010. Most of the recipients were transplanted after 2000, earlier transplants being *a posteriori* reclassified as ECD/SCD. The information related to the Donation after Circulatory Death (DCD) was not specified in 19 publications (59%) [13,14,17,20–22,24,25,28,30–33,35–37,40,43,44]. Seventeen publications described baseline clinical characteristics for both the ECD and SCD groups.

Obviously, ECD transplants were by definition older than SCD (mean age 61.9 vs. 37.2 years). But the difference in terms of recipient age was lower (55.3 vs. 47.4 years). Induction therapy also differed between the two groups, with a lower proportion of depleting treatment in the ECD group (55.5% vs. 62.3%). The percentage of male donors was lower for ECD transplants (48.2% vs. 58.8%). In contrast, other characteristics were similar between ECD and SCD recipients, e.g., diabetes history (approximately 20%) or Cold Ischemia Time (CIT approximately 18 h). One can notice no evidence for differences in the characteristics of ECD kidney recipients between the geographical areas (Table S2).

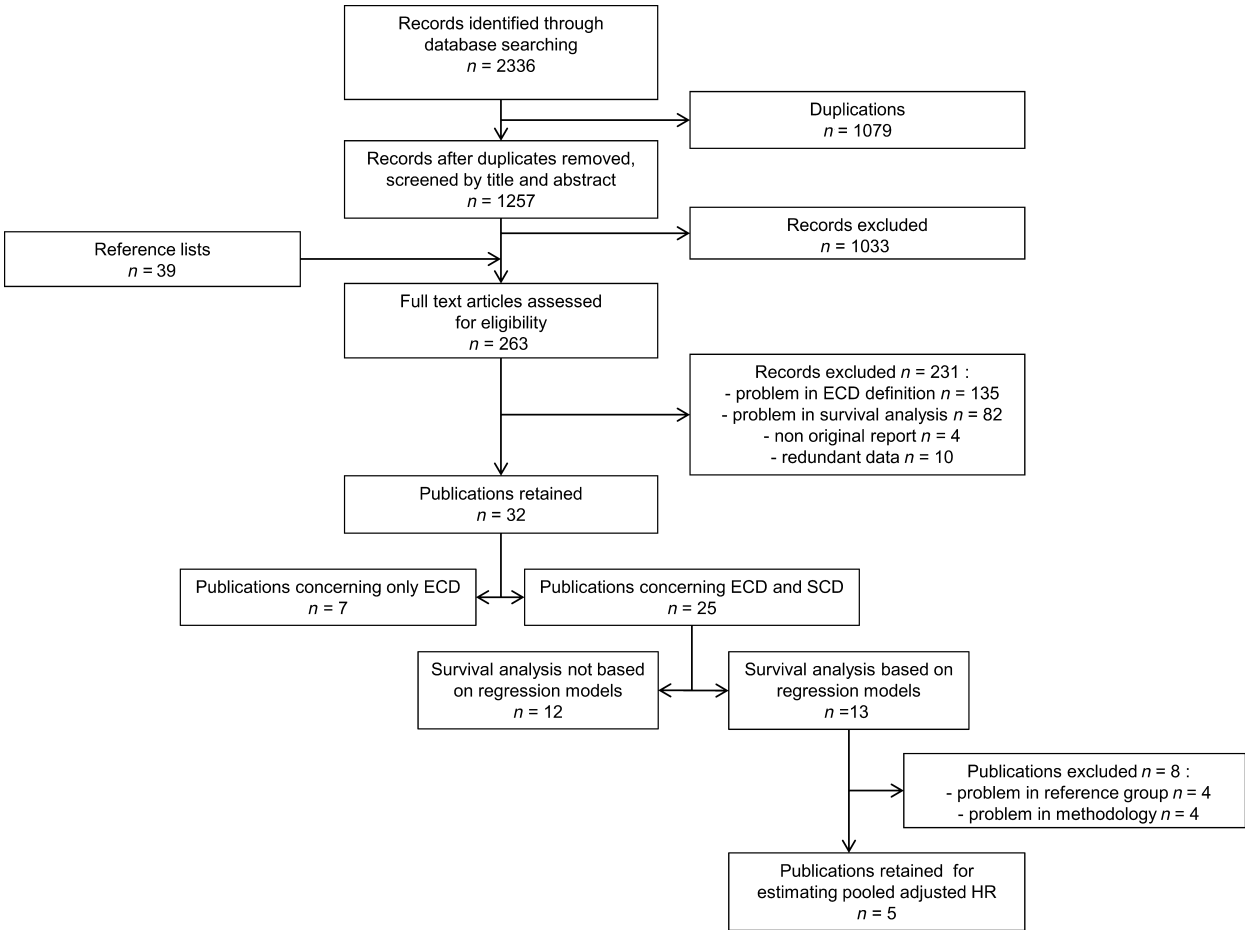

Figure 1 Flowchart for selection of publications reporting survival outcomes of kidney transplant recipients from Expanded Criteria Donor (ECD) and Standard Criteria Donor (SCD).

Comparison of survival between ECD and SCD kidney recipients

Among the 32 publications, 13 (40%) used a survival model to compare the effect of ECD and SCD status on graft and/or patient outcomes. Nevertheless, eight publications were excluded because of methodological issues: HR adjusted on donor age [39], or without any specification of adjustment factors [27,28], no adjustment [30], or a reference group different from SCD recipients [15,21,22,32]. Finally, five publications were retained for this analysis [24,25,29,33,37], and all were based on US recipients. Among these, one article studied the association between donor Apolipoprotein L1 (APOL) genotypes and time to return to dialysis [24], whilst the others focused on ECD outcomes.

Potential biases were noted in three studies: selection bias in Sung *et al.* [29] by studying ECD-listed recipients (who were likely to be older, diabetic, and sensitized), reporting bias in Mezrich *et al.* [33] by not reporting nonsignificant HR, and analytical bias in Woodside *et al.* [37] by not exhaustively reporting the adjustment factors list used for the regression analysis.

Patient-graft survival: two publications

Mezrich *et al.* [33] studied 201 ECD recipients versus 358 SCD recipients. Analyses were stratified on recipient age. Adjustment factors were: recipient ethnicity, DCD status, Human Leukocyte Antigen (HLA) matching, Delayed Graft Function (DGF), recipient diabetes, induction treatment, Body Mass Index (BMI) > 30 kg/m^2, CIT, and Panel Reactive Antibody (PRA). There was an increased risk of graft failure and patient death for ECD kidney recipients (not significant for recipients between 40 and 59 years). The HR calculated for this first study was 1.49 (95%CI [0.98; 2.27]).

Sung *et al.* [29] studied 12 687 kidney recipients (4175 ECD vs. 8512 SCD) from the Scientific Registry of Transplant Recipients (SRTR). Adjustment factors

Table 1. Characteristics of the 32 studies reporting survival outcomes of ECD and SCD transplant recipients.

Author	Country Inclusion period	Sample size		Survival results	Death-censored graft survival at 5 yrs (or last year available)*		Patient survival at 5 yrs (or last year available)*		Patient-graft survival at 5 yrs (or last year available)*	
		ECD	SCD		ECD	SCD	ECD	SCD	ECD	SCD
Anil-Kumar *et al.* (2006)	USA 2002–2005	55	55	Curve	–	–	81% (3 yrs)	100% (3 yrs)	63% (3 yrs)	86% (3 yrs)
Carrier *et al.* (2012)	Canada 2003–2009	456	919	Curve	–	–	89%	91%	–	–
Cecka *et al.* (2004)	USA 1991–2003	5943	33 118	Curve	–	–	69%	83%	52%	69%
Carroll *et al.* (2008)	Australia 1989–2004	55	530	Curve	71%	87%	–	–	–	–
Collins *et al.* (2009)	Australia, New Zealand 1991–2004	781	3248	Curve	74%	88%	88%	92%	65%	81%
Diet *et al.* (2010)	France 1998–2004	656	1465	Curve	84%	88%	–	–	–	–
Fraser *et al.* (2010)	United Kingdom 1995–2005	234	819	Curve	79%	81%	–	–	–	–
Gill *et al.* (2008)	USA 1996–2005	4551	12 197	Curve	67% (4 yrs)	82% (4 yrs)	67% (4 yrs)	76% (4 yrs)	57% (4 yrs)	71% (4 yrs)
Gill *et al.* (2008)	USA 2000–2005	7686	6044	Curve	69% (4 yrs)	77% (4 yrs)	–	–	59% (4 yrs)	68% (4 yrs)
Hofer *et al.* (2013)	Austria 1999–2003	174	454	Curve	58%	77%	72%	85%	–	–
Hosgood *et al.* (2013)	United Kingdom 2008–2012	65	NA	Curve	98% (1 yr)	–	96% (1 yr)	–	–	–
Kayler *et al.* (2011)	USA 1995–2009	14 230	NA	Curve	–	–	–	–	58%	–
Kim *et al.* (2013)	Korea 2006–2010	26	117	Curve	93% (3 yrs)	94% (3 yrs)	–	–	–	–
Lai *et al.* (2009)	Italia 2004–2007	46	NA	Curve	–	–	94% (3 yrs)	–	–	–
Lim *et al.* (2013)	Australia, New Zealand 1997–2009	916	3200	Curve	71%	82%	85%	89%	–	–
Lucarelli *et al.* (2010)	Italia 2000–2008	179	NA	Curve	–	–	91%	–	–	–

Table 1. Continued.

Author	Country Inclusion period	Sample size		Survival results	Death-censored graft survival at 5 yrs (or last year available)*		Patient survival at 5 yrs (or last year available)*		Patient-graft survival at 5 yrs (or last year available)*	
		ECD	SCD		ECD	SCD	ECD	SCD	ECD	SCD
Martinez *et al.* (2010)	Spain 1999–2006	180	NA	Curve	87%	–	–	–	–	–
Matsuoka *et al.* (2006)	USA 2000–2003	4618	NA	Curve	–	–	–	–	67% (3 yrs)	–
Merion *et al.* (2005)	USA 1995–2004	7790	41 052	Curve	76%	–	–	–	–	–
Mezrich *et al.* (2012)	USA 2000–2005	201	358	Curve/ Adjusted HR	79%	–	69%	79%	56%	70%
Molnar *et al.* (2012)	USA 1998–2006	22 515	122 955	Adjusted HR	–	–	–	–	–	–
Moers *et al.* (2012)	Netherlands, Germany, Belgium/ 2005–2006	672	NA	Curve	89% (3 yrs)	–	–	–	–	–
Nardo *et al.* (2011)	Italia 2001–2007	167	229	Curve	–	–	93%	96%	84%	83%
Praehauser *et al.* (2013)	Switzerland 1999–2010	30	104	Curve	–	–	–	–	67%	87%
Reeves-Daniel *et al.* (2011)	USA 1998–2009	27	109	Adjusted HR	–	–	–	–	–	–
Saidi *et al.* (2007)	USA 1998–2005	44	163	Curve	–	–	83% (5 yrs)	88% (4 yrs)	–	–
Salifu *et al.* (2009)	USA 1996–2003	106	194	Curve	–	–	82%	83%	64%	72%
Sellers *et al.* (2004)	USA 1999–2001	45	157	Curve	90%	94%	85%	91%	80%	88%
Shaheen *et al.* (2012)	Saudi Arabia 2009–2010	61	219	Curve	–	–	–	–	92% (2.25 yrs)	88% (2.25 yrs)
Smail *et al.* (2013)	Canada 1990–2006	243	280	Curve	78%	87%	83%	87%	–	–
Sung *et al.* (2007)	USA 1999–2005	4175	8512	Adjusted curve/ Adjusted HR	–	–	–	–	–	–
Woodside *et al.* (2012)	USA 2002–2010	7916	5917	Curve/ Adjusted HR	–	–	74%	80%	–	–

ECD, Expanded Criteria Donor; SCD, Standard Criteria Donor; HR, Hazard Ratio; yrs, years. *from published survival curves digitalized

were: recipient age, gender, ethnicity, peak PRA, diabetes as cause of end-stage renal disease, ABO blood type, previous transplant, time on the waiting list, height, weight, CIT, HLA matching, ABO compatibility, and shared transplant. There was a significantly lower patient-graft survival in ECD kidney recipients (HR = 1.77, 95%CI [1.33; 2.36]).

By merging both studies, the pooled confounder-adjusted HR was 1.68 (95%CI [1.32; 2.12]).

Patient survival: two publications

Mezrich *et al.* [33] used the same adjustment factors as those for patient-graft survival analysis. For recipients older than 60 years, they estimated a higher risk of death for ECD recipients (n = 96) compared with SCD recipients (n = 93) with an HR at 1.97 (95%CI [0.99; 3.91]). This result was not significant for recipients between 40 and 59 years of age ($P > 0.05$, HR not reported).

Woodside *et al.* [37] studied 13 833 kidney recipients (7916 ECD vs. 5917 SCD) from the SRTR. Adjustment factors were: recipient age, gender, ethnicity, and history of diabetes. They also concluded a significant increased risk of death for ECD (HR = 1.25, 95%CI [1.12; 1.40]).

We did not merge these two studies because the HR reported in Mezrich *et al.* only included recipients older than 60 years, while Woodside *et al.* reported the HR for all recipients.

Death-censored graft survival: two publications

Reeves-Daniel *et al.* [24] studied 136 kidney recipients (27 ECD vs. 109 SCD). Adjustment factors were: recipient age, gender, CIT, HLA matching, PRA, APOL gene variant, and the proportion of African ancestry in donors.

Table 2. Donor, recipient, and transplant characteristics for the studies reporting survival outcomes of Expanded Criteria Donor (ECD) kidney recipients (n = 32) or both ECD and Standard Criteria Donor (SCD) kidney recipients (n = 25).

	ECD (n = 32)					SCD (n = 25)				
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Donors										
Sample size	28	2548	5741	26	28 461	21	5099	11 114	48	41 052
Mean age (years)	20	61.9	3.1	53.7	66.0	15	37.2	5.5	29.6	54.0
Male gender (%)	17	48.2	8.4	29.8	63.3	12	58.8	8.4	40.6	75.2
Mean serum creatinine (mg/dl)	12	1.1	0.2	0.8	1.5	10	1.0	0.2	0.8	1.4
History of HBP (%)	11	59.2	12.5	27.6	70.2	8	10.7	5.1	3.6	17.1
Cause of death: anoxia (%)	6	5.1	2.3	2.9	8.3	5	11.8	7.0	4.0	22.9
Cause of death: CVA (%)	15	82.3	4.0	76.3	89.2	11	42.5	11.1	18.8	56.1
Cause of death: trauma (%)	6	10.6	5.1	4.9	19.7	6	32.2	18.5	9.6	52.8
Cause of death: other (%)	8	7.9	7.7	0.0	23.1	7	24.5	21.1	3.5	55.1
Recipients										
Sample size	32	2652	4965	26	22 515	25	9698	25 712	55	122 955
Mean age (years)	22	55.3	5.0	47.1	66.5	16	47.4	7.3	33.0	62.2
Mean BMI (kg/m^2)	2	26.8	0.1	26.8	26.9	1	29.0	NA	NA	NA
PRA at transplantation (%)	2	8.6	5.4	4.7	12.4	2	9.4	2.3	7.8	11.0
Historic PRA (%)	3	9.1	5.0	3.3	12.0	2	11.1	7.9	5.5	17.6
Male gender (%)	17	60.1	7.2	35.6	65.8	15	59.8	6.3	39.6	66.1
History of diabetes (%)	6	21.1	7.5	12.1	31.4	6	17.4	7.0	11.2	30.5
History of HBP (%)	4	76.2	15.0	64.2	96.5	4	70.0	22.6	47.9	97.5
History of CVE (%)	2	15.2	1.7	14.0	16.4	2	13.2	0.2	13.1	13.4
Transplantation										
Depleting induction (%)	9	55.5	44.7	0.0	100.0	8	62.3	42.3	0.0	100.0
CIT (hours)	19	17.8	4.5	3.6	24.1	14	17.8	4.9	3.9	20.7
HLA mismatch	10	3.4	0.8	1.9	4.5	8	3.2	0.8	1.9	3.6

n, number of studies reporting a description of the characteristics; NA, not appropriate; BMI, Body Mass Index; CIT, Cold Ischemia Time; CVA, Cerebrovascular Accident; CVE, Cardiovascular Event; HBP, High Blood Pressure; HLA, Human Leukocyte Antigen; PRA, Panel Reactive Antibody.

Death-censored graft survival tended to be worse in ECD recipients (HR = 1.45, 95%CI [0.48; 4.35]).

Molnar *et al.* [25] studied 145 470 adult kidney recipients (22 515 ECD vs. 122 955 SCD) from the SRTR, and stratified the analysis by recipient age. Adjustment factors were: recipient age, gender, ethnicity, history of diabetes, dialysis vintage, serum creatinine, serum albumin, BMI, coronary artery disease, chronic obstructive pulmonary disease, HBP, peptic ulcer, peripheral vascular disease, and cerebrovascular disease. Regardless of the age category, graft survival was significantly worse in ECD kidney recipients. The mean HR for this study (regardless of the strata) was calculated at 1.82 (95% CI [1.60; 2.07]).

By merging both studies, the pooled confounder-adjusted HR was 1.81 (95%CI [1.60; 2.06]).

Pooled nonadjusted survival curves for ECD and SCD kidney recipients

Nonadjusted survival curves were correctly reported in 29 publications for ECD kidney recipients [13–23,26–28,30–44] and in 21 publications for SCD kidney recipients [13–16,19–23,26–28,30,32,33,36–39,42,44]. Pooled nonadjusted survival is presented in Fig. 2 and Table 3. Figures S3–S8 display the pooled nonadjusted survival by geographical area. Figures S9–S11 display the three survivals for ECD and SCD kidney recipients with the details for each study.

Patient-graft survival

The 5-year pooled patient-graft survival probabilities were 59.2% (95% CI [55.3%; 63.0%]) for ECD recipients (n = 13 studies) and 75.1% (95%CI [69.7%; 79.6%]) for SCD recipients (n = 11 studies) (Fig. 2a, Table 3). There was substantial heterogeneity in patient-graft survival between the studies (ECD: I^2 = 70.6; SCD: I^2 = 83.5). The test for comparison of survivals between geographical areas was not performed because there were less than three studies per geographical area outside North America. However, one can notice that the 5-year pooled nonadjusted patient-graft survivals were closer between ECD and SCD kidney recipients in the European studies, with 74.9% (95%CI [47.2%; 81.7%]) for ECD vs. 83.6% (95%CI [71.7%; 85.6%]) for SCD, compared to the North American studies (53.3% (95% CI [49.6%; 56.7%]) for ECD vs. 70.4% (95%CI 65.1%; 74.8% for SCD). The corresponding pooled RRs were estimated at 1.52 (95%CI [0.82; 2.94]) for the European studies, at 1.58 (95%CI [1.32; 1.87]) for the North American studies, and at 1.79 for the Oceanic study.

Patient survival

The 5-year pooled patient survival probabilities were 78.4% (95%CI [72.9%; 83.2%]) in ECD recipients (n = 17 studies) vs. 86.4% (95%CI [82.3%; 89.7%]) in SCD recipients (n = 14 studies) (Fig. 2b, Table 3). There was substantial heterogeneity in patient survival between the studies (ECD: I^2 = 66.3; SCD: I^2 = 85.2). The test for between-strata comparison indicated a significant difference in patient-graft survival between the North American and European studies (ECD: $P < 0.001$; SCD: test not performed). The 5-year pooled patient survivals were closer between ECD and SCD kidney recipients in the European studies (85.3%, 95% CI [71.5%; 91.4%] for ECD vs. 90.3%, 95%CI [74.3%; 93.4%] for SCD) than in the North American studies (73.4%, 95%CI [67.4%; 78.6%] for ECD vs. 83.6%, 95%CI [79.3%; 87.1%]) for SCD). The corresponding pooled RR were estimated at 1.50 (95%CI [0.50; 3.43]) for the European studies, at 1.62 (95%CI [1.18; 2.22]) for the North American ones, and at 1.53 (95%CI [0.87; 2.35]) for the Oceanic ones.

Death-censored graft survival

The 5-year pooled death-censored graft survival probabilities were 75.6% (95%CI [68.9%; 80.7%]) for ECD recipients (n = 16 studies) and 84.6% (95%CI [81.3%; 87.0%]) for SCD recipients (n = 11 studies) (Fig. 2c, Table 3). There was substantial heterogeneity in death-censored graft survival between the studies (ECD: I^2 = 70.5; SCD: I^2 = 76.2). The test for between-strata comparison indicated significant differences in death-censored graft survival between continents (ECD: $P < 0.001$; SCD: $P < 0.001$). The 5-year pooled death-censored graft survivals were similar for ECD and SCD kidney recipients in the European studies (81.1%, 95% CI [70.3%; 87.9%] for ECD vs. 82.5%, 95%CI [72.5%; 87.6%] for SCD). In contrast, in the North American studies, this difference was considerably greater (72.4%, 95%CI [66.0%; 77.4%] for ECD vs. 83.6%, 95%CI [78.3%; 87.4%] for SCD). The corresponding pooled RR were estimated at 1.08 (95%CI [0.58; 1.95]) for the European ones, at 1.69 (95%CI [1.18; 2.34]) for the North American studies, and at 2.14 (95%CI [1.46; 2.80]) for the Oceanic ones.

Discussion

In 2002, Metzger *et al.* [3] accurately defined ECD kidneys from the data of the SRTR in the USA: the risk of

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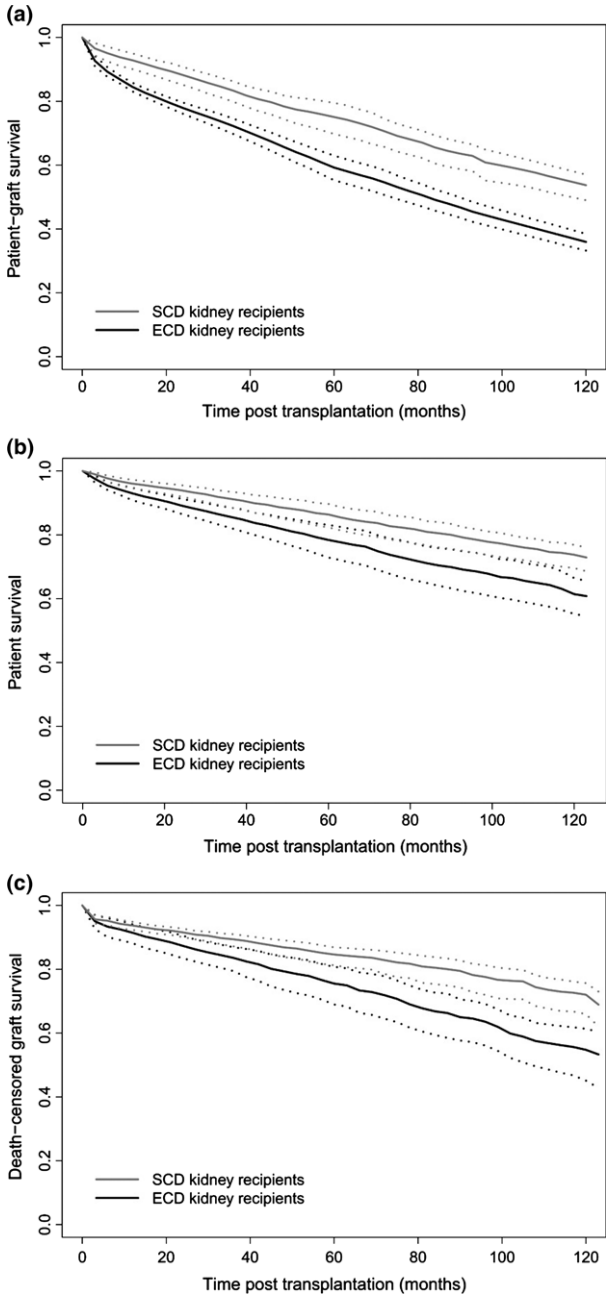

Figure 2 Pooled survival curves for Expanded Criteria Donor (ECD) kidney recipients and Standard Criteria Donor (SCD) kidney recipients. (a) Patient-graft survival (ECD: 13 studies, SCD: 11 studies). (b) Patient survival (ECD: 17 studies, SCD: 14 studies). (c) Death-censored graft survival (ECD: 16 studies, SCD: 11 studies). The dashed lines represent the 95% confidence intervals.

graft failure was >1.7 for ECD kidney recipients compared to SCD recipients (by considering the first event between patient death and return in dialysis). Despite a belief that the literature has already widely demonstrated the relevance of the ECD criteria, we only found two external validation studies [29,33] applying an appropriate methodology (ECD definition, survival definitions, confounder-adjusted results, etc.) and relating to patient-graft survival. By merging both studies, we estimated a pooled confounder-adjusted HR at 1.68 (95% CI [1.32; 2.12]), but this result is highly limited for different reasons. Firstly, the two studies were carried out on US recipients and the study with the highest number of recipients (n = 12 687) was based on the same SRTR registry, the same used to initially define ECD criteria. Secondly, the study based on the smallest sample size (n = 559), proposed by Mezrich *et al.* [33], may underestimate the HR, as the authors overadjusted their results on DGF, a post-transplantation parameter in the pathway between donor characteristics and graft failure [45].

We also performed the meta-analyses of the other two confounder-adjusted HR related to patient survival and death-censored graft survival. For each one, we only found two publications with an appropriate methodology. These studies [24,25,33,37], all from USA, seemed to confirm that survival outcomes were poorer in ECD recipients than in SCD recipients. However, the scale of these three findings is limited by the low number of included studies and the potential biases in three studies [29,33,37]. Indeed, the five publications retained for the analysis were all based on US recipients, and may be all extracted from the same SRTR database. When there was no doubt that studies overlapped, we considered the most recent one as eligible for inclusion in meta-analysis. Otherwise, all studies were eligible. It is therefore possible that we retained some overlapped studies because the SRTR registry was not mentioned in the publication, although this is likely to be the case.

Because of the very low number of studies with confounder-adjusted analysis, we decided to perform a secondary meta-analysis of nonadjusted survival curves to provide additional information on differences between geographical areas. Of course, these nonadjusted results should not be interpreted as comparisons between ECD and SCD outcomes regarding the number of confounding factors. The results only demonstrated the heterogeneity between studies, with outcomes' differences between ECD and SCD kidney recipients lower in Europe than in the USA. Few hypotheses can be formulated including for instance in USA; (i) a higher level of comorbidities in ECD recipients or a lower level in SCD recipients, (ii) a lower use of hypothermic machine perfusions before transplantation from ECD, or (iii) a more exhaustive old-to-old and young-to-young graft allocation policy. Our meta-analysis on aggregated data with little reported information in the characteristics of ECD and SCD kidney recipients did

Table 3. Pooled nonadjusted 5-year survival probabilities for Expanded Criteria Donor (ECD) kidney recipients and Standard Criteria Donor (SCD) kidney recipients according to geographical area of studies.

	Geographical area	Donor	*n*	References	Pooled nonadjusted 5-year survival [95%CI]		Pooled nonadjusted risk ratio of event at 5 years [95%CI]	
Patient-graft survival	All areas	ECD	13		59.2	[55.3; 63.0]		
		SCD	11		75.1	[69.7; 79.6]		
	North America	ECD	9	[16,18,20,21,30,32–34,38]	53.3	[49.6; 56.7]	1.58	[1.32; 1.87]
		SCD	7	[16,20,21,30,32,33,38]	70.4	[65.1; 74.8]	1	
	Europe	ECD	2	[28,36]	74.9	[47.2; 81.7]	1.52	[0.82; 2.94]
		SCD	2	[28,36]	83.6	[71.7; 85.6]	1	
	Oceania	ECD	1	[15]	65.4		1.79	
		SCD	1	[15]	80.6		1	
	Asia	ECD	1	[44]	*			
		SCD	1	[44]	*			
Patient survival	All areas	ECD	17		78.4	[72.9; 83.2]		
		SCD	14		86.4	[82.3; 89.7]		
	North America	ECD	10	[14,16,20,21,23,30,33,37–39]	73.4	[67.4; 78.6]	1.62	[1.18; 2.22]
		SCD	10	[14,16,20,21,23,30,33,37–39]	83.6	[79.3; 87.1]	1	
	Europe	ECD	5	[27,35,36,40,43]	85.3	[71.5; 91.4]	1.50	[0.50; 3.43]
		SCD	2	[27,36]	90.3	[74.3; 93.4]	1	
	Oceania	ECD	2	[15,22]	86.5	[78.5; 87.8]	1.53	[0.87; 2.35]
		SCD	2	[15,22]	91.2	[83.2; 92.1]	1	
Death-censored graft survival	All areas	ECD	16		75.6	[68.9; 80.7]		
		SCD	11		84.6	[81.3; 87.0]		
	North America	ECD	6	[14,17,21,30,32,33]	72.4	[66.0; 77.4]	1.69	[1.18; 2.34]
		SCD	4	[14,21,30,32]	83.6	[78.3; 87.4]	1	
	Europe	ECD	6	[19,26,27,31,41,43]	81.1	[70.3; 87.9]	1.08	[0.58; 1.95]
		SCD	3	[19,26,27]	82.5	[72.5; 87.6]	1	
	Oceania	ECD	3	[13,15,22]	70.8	[62.0; 74.8]	2.14	[1.46; 2.80]
		SCD	3	[13,15,22]	86.3	[79.9; 87.8]	1	
	Asia	ECD	1	[42]	†			
		SCD	1	[42]	†			

n, number of studies.

*Two years of follow-up.

†Three years of follow-up.

not allow us to test such a hypothesis. A limit to this secondary analysis is that pooled nonadjusted survivals may have been underestimated because the statistical method applies a correction when no events are observed in a time interval [8]. This was the case for many of the studies. However, this should not have changed the difference between ECD and SCD recipients because the same correction is equally applied to both groups.

In 2008, Pascual *et al.* [5] concluded a beneficial use of ECD criteria, especially for old recipients who would most likely not survive long waiting periods. Our meta-analysis presents the advantage of displaying quantitative results and of performing the selection of studies by their statistical quality. Indeed, our study highlights the low methodological level of many publications. We excluded 50% of full-text publications for which the ECD definition was not clearly expressed or different from the initial one. We also excluded more than 30% of full-text publications for default of survival definitions, inappropriate statistical analyses (censored data not taken into account, no confounder-adjusted results, etc.), or important elements not reported (sample sizes, adjustment factors, etc.). We hope that these alarming observations can convince researchers in kidney transplantation epidemiology to be more vigilant in the methodology used, the accurate and full reporting of methods and results [46]. For instance, while subject

characteristics are often unbalanced between exposure groups in such observational studies, only 17 publications (68%) among the 25 studies with both ECD and SCD groups proposed a description of the corresponding baseline characteristics.

Although the use of ECD kidneys is a common practice over the last decade, this indicator also has important limitations in terms of medical decision making. In particular, this binary definition does not take into consideration the continuous increase in the risk of graft failure when a donor combines risk factors [3]. Therefore, several scoring systems have been proposed to evaluate the quality of deceased donor kidneys, based on clinical, pathological, or combined parameters. Since 1999, an allocation policy entitled Eurotransplant Senior Program was proposed in Europe to organize transplantation from deceased kidney donors older than 65 years to recipients older than 65 years [47,48]. Besides clinical parameters, donor biopsy findings were also actively discussed [49,50], but with many limitations: heterogeneous definition of vascular lesions, lack of validation in independent cohorts, and difficulties in obtaining preimplantation biopsies. None of these scores are used in clinical practice.

Recently, an allocation policy was approved by the OPTN in the USA, stratifying deceased donors using the KDRI or Kidney Donor Profile Index (KDPI) [4,51]. This scoring system is based on 10 donor factors (without the need of a kidney biopsy): donor age, height, weight, ethnicity, history of HBP and diabetes, cause of death, serum creatinine level, hepatitis C status, and DCD status. KDPI is a continuous score, an advantage compared with the strictly binary ECD indicator. The KDRI/KDPI system was implemented in the US graft allocation system in 2013, but it has the same limitation as the ECD system: the absence of external validation, explaining why we did not study the KDRI/KDPI system in our meta-analysis. Nevertheless, we hope that our results related to the ECD classification will convince the international community to propose methodologically adequate epidemiological studies for external validations of the KDRI/KDPI before its application in practice worldwide.

Conclusion

The ECD classification has been defined for kidney transplant recipients from USA. Despite its use in clinical practice all over the world, our meta-analysis shows that only few studies appropriately compared long-term outcomes of ECD and SCD recipients. Moreover, all of them were from USA. The absence of adequate validation studies outside the USA is even more worrying as we also showed important heterogeneity between geographical areas in terms of patient and/or graft survival. The current use of the ECD criteria definition for graft allocation outside the USA may represent a major public issue, which could be avoided for other recently proposed classification rules, in particular the KDRI/KDPI system.

Authorship

A-HQ and FG: designed and performed the study, collected and analyzed data, and wrote the manuscript. YF and MG: collected data and contributed important reagents. CC: analyzed data. ED, DL, ML and L-MP: collected data.

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Conflicts of interest

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Search equation.

Table S2. Donor, recipient, and transplant characteristics for the studies reporting survival outcomes of ECD kidney recipients (n = 32) according to geographical area.

Figure S3. Overall patient-graft survival for ECD kidney recipients according to geographical area.

Figure S4. Overall patient-graft survival for SCD kidney recipients according to geographical area.

Figure S5. Overall patient survival for ECD kidney recipients according to geographical area.

Figure S6. Overall patient survival for SCD kidney recipients according to geographical area.

Figure S7. Overall death-censored graft survival for ECD kidney recipients according to geographical area.

Figure S8. Overall death-censored graft survival for SCD kidney recipients according to geographical area.

Figure S9. Overall patient-graft survival for ECD and SCD kidney recipients.

Figure S10. Overall patient survival for ECD and SCD kidney recipients.

Figure S11. Overall death-censored graft survival for ECD and SCD kidney recipients.

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