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

Anne-Hélène Querard, Yohann Foucher, Christophe Combescure, Etienne Dantan, David Larmet, Marine Lorent, Lise-Marie Pouteau, Magali Giral, Florence Gillaizeau

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

Anne-Hélène Querard[1,2,3], MD, Yohann Foucher[2,3] PhD, Christophe Combescure[4] PhD, Etienne Dantan[2] PhD, David Larmet[3] MD, Marine Lorent[2] MSc, Lise-Marie Pouteau[3] MD, Magali Giral[2,3,5] PhD and Florence Gillaizeau[2,3] PhD

[1]Nephrology, Dialysis, Transplantation, Centre Hospitalier Départemental de Vendée, La Roche sur Yon, France

[2]EA 4275 SPHERE - bioStatistics, Pharmacoepidemiology and Human sciEnces REsearch, Nantes University, France

[3]Institute for Transplantation, Urology and Nephrology ITUN, CHU Nantes, RTRS « Centaure », Inserm U1064, Nantes University, France

[4]CRC & Division of Clinical Epidemiology, Department of Health and Community Medicine, University of Geneva & University Hospitals of Geneva, Geneva, Switzerland

[5] LabEx Transplantex Nantes, Centre d'Investigation Clinique Biothérapie, Nantes France

Correspondence: Doctor Anne-Hélène QUERARD

Nephrology, Dialysis, Transplantation

1 Bd Stéphane Moreau, 85 000 La Roche sur Yon, France

Phone: + 33-2 51 44 61 63, Fax: + 33-2 51 44 63 02

Email: anne-helene.querard@chd-vendee.fr

Running title: ECD versus SCD survival outcomes: a meta-analysis

CONFLICT OF INTEREST

The authors of this manuscript have no conflict of interest to disclose as described by the Transplant International review.

AUTHORSHIP

Anne-Hélène Querard designed and performed study, collected and analyzed data, and wrote the manuscript.

Yohann Foucher collected data and contributed important reagents.

Christophe Combescure analyzed data.

Etienne Dantan collected data.

David Larmet collected data.

Marine Lorent collected data.

Lise-Marie Pouteau collected data.

Magali Giral collected data and contributed important reagents.

Florence Gillaizeau designed and performed the study, collected and analyzed data, and wrote the manuscript.

KEYWORDS

Kidney transplantation, Expanded Criteria Donor, meta-analysis, survival analysis.

ABBREVIATIONS

APOL	APO Lipoprotein L1
BMI	Body Mass Index
CI	Confidence Interval
CIT	Cold Ischemia Time
CVA	Cerebrovascular Accident
CVE	Cardiovascular Event
DCD	Donation after Circulatory Death
DGF	Delayed Graft Function
ECD	Expanded Criteria Donor
HBP	High Blood Pressure
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
KDRI	Kidney Donor Risk Index
KDPI	Kidney Donor Profile Index
OPTN	Organ Procurement Transplantation Network
PRA	Panel Reactive Antibody
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RR	Relative Risk
SCD	Standard Criteria Donor
SRTR	Scientific Registry of Transplant Recipients
UNOS	United Network for Organ Sharing
U.S.A.	United States of America

ABSTRACT

Introduction: In 2002, the United Network for Organ Sharing proposed increasing the pool of donor kidneys to include Expanded Criteria Donors (ECD). Outside the U.S.A., the ECD definition remains the one used without questioning whether such a graft allocation criteria is worldwide valid.

Study design: 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.

Results: Thirty-two publications were included. Only 5 studies, all from the U.S.A., reported confounder-adjusted hazard ratios comparing the survival outcomes between ECD and SCD kidney transplant recipients. These 5 studies confirmed that ECD recipients seemed to have poorer prognosis. From 29 studies reporting appropriate survival curves, we estimated the 5-year pooled non-adjusted 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.

Conclusion: It is of primary importance to propose appropriate studies for external validation of the ECD criteria in non-US kidney transplant recipients.

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 Donors (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 Donors (SCD) (1). An ECD is defined 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 greater than 1.5 mg/dL, Cerebro Vascular 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 U.S.A. In 2009, Rao (4) proposed a new risk quantification score based on the same OPTN database, the Kidney Donor Risk Index (KDRI), that combines ten 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 U.S.A., the UNOS ECD definition remains the one used, without questioning whether such a graft allocation criteria, established on US data, is valid worldwide. Indeed, both the characteristics of recipients and health organizations may differ between countries.

In 2008, Pascual et al. performed a systematic review (5) 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 due to 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.

Non-inclusion 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, multi-organ transplants, non-heart beating donors or from living donors; (iii) studies with non-original 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 non-adjusted 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 supplemental information S1.

Study selection and data collection

Study eligibility was determined independently by teams composed of a nephrologist and a statistician. Two teams firstly selected papers based on titles and abstracts. Four teams subsequently screened full texts. Intra-team 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 HR 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%CI) 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 three 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 to 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 confounders-adjusted HR was very small, we only explored the geographical area as a potential heterogeneity factor in pooled non-adjusted survival analysis. By definition, non-adjusted 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 five years post-transplantation was calculated using the corresponding pooled non-adjusted survival probabilities. The 95% CI was obtained by bootstrapping.

All analyses were performed using the software R (version 3.0.1) and followed the PRISMA recommendations for systematic review and meta-analyses (12).

RESULTS

Description of the retained studies

A flow-chart of the selected studies is presented in Figure 1. The search strategy identified 2336 publications. After removing duplicates and irrelevant reports based on titles and abstracts, we examined 263 full text reports. 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 U.S.A.) and 10 studies (31%) included European recipients. Half of the studies were multicentric. 28 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 versus 37.2 years). But the difference in terms of recipient age was lower (55.3 versus 47.4 years). Induction therapy also differed between the two groups with a lower proportion of depleting treatment in the ECD group (55.5% versus 62.3%). The percentage of male donors was lower for ECD transplants (48.2% versus 58.8%). In contrast, other characteristics were similar

between ECD and SCD recipients, e.g. diabetes history (~ 30%) or Cold Ischemia Time (CIT ~ 21 hours). One can notice no evidence for differences in the characteristics of ECD kidney recipients between the geographical areas (Supplemental Table S2).

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 due to 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, 5 publications were retained for this analysis (24,25,29,33,37), and all were based on US recipients. Among these, 1 article studied the association between donor APO Lipoprotein 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 (that were likely to be older, diabetic, and sensitized), reporting bias in Mezrich et al. (33) by not reporting non-significant HR, and analytical bias in Woodside et al. (37) by not exhaustively reporting the adjustment factors list used for the regression analysis.

(i) Patient-graft survival: 2 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 (4,175 ECD versus 8,512 SCD) from the Scientific Registry of Transplant Recipients (SRTR). Adjustment factors 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]).

(ii) Patient survival: 2 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 to 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 (7,916 ECD versus 5,917 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.

(iii) Death-censored graft survival: 2 publications.

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

Non-adjusted 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 non-adjusted survival is presented in Figure 2 and Table 3. Supplemental figures S2 to S7 display the pooled non-adjusted survival by geographical area. Supplemental figures S8 to S10 display the three survivals for ECD and SCD kidney recipients with the details for each study.

(i) 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) (Figure 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 non adjusted 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 versus 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 versus 70.4% (95%CI [65.7% ; 75.4%]) for SCD). The corresponding pooled RR 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.

(ii) Patient survival.

The 5-year pooled patient survival probabilities were 78.4% (95%CI [72.9% ; 83.2%]) in ECD recipients (n=17 studies) versus 86.4 % (95%CI [82.3% ; 89.7%]) in SCD recipients (n=14 studies) (Figure 3B, 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 versus 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 versus 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.

(iii) 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) (Figure 3C, 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 versus 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 versus 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 U.S.A.: the risk of graft failure was greater than 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 since the authors over-adjusted 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 U.S.A., 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 non-adjusted survival curves to provide additional information on differences between geographical areas. Of course, these non-adjusted 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 U.S.A. Few hypotheses can be formulated including for instance in U.S.A; 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 not allow us testing such hypothesis. A limit to this secondary analysis is that pooled non-adjusted 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. concluded a beneficial use of ECD criteria, especially for old recipients who would most likely not survive long waiting periods (5). 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 (47). 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 has also 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 (48,49). Beside clinical parameters, donor biopsy findings were also actively discussed (50,51), 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 U.S.A., stratifying deceased donors using the Kidney Donor Risk Index (KDRI) or Kidney Donor Profile Index (KDPI) (4,52). 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 to 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 epidemiologic studies for external validations of the KDRI/KDPI before its application in practiced worldwide.

CONCLUSION

The ECD classification has been defined on kidney transplant recipients from U.S.A.. 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 U.S.A. The absence of adequate validation studies outside the U.S.A. is even more worrying since 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 U.S.A. may represent a major public issue, which could be avoided for other recently proposed classification rules, in particular the KDRI/KDPI system.

ACKNOWLEDGMENTS

The authors are exclusively responsible for the preparation, writing and viewpoints expressed in the manuscript. We would like to thank Nico Midy, trainee, for his help in digitalizing the pictures of the published survival curves and extracting the corresponding survival data. We would like to thank Adrian Chess for the English manuscript proofreading.

SUPPLEMENTARY INFORMATION

Supplementary information is available at Transplant International's website.

REFERENCES

1. Rosengard BR, Feng S, Alfrey EJ, Zaroff JG, Emond JC, Henry ML, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. Am J Transplant. 2002;2(8):701‑11.
2. Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation. 2002;74(9):1281‑6.
3. Metzger RA, Delmonico FL, Feng S, Port FK, Wynn JJ, Merion RM. Expanded criteria donors for kidney transplantation. Am J Transplant. 2003;3 Suppl 4:114‑25.
4. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation. 2009;88(2):231‑6.
5. Pascual J, Zamora J, Pirsch JD. A systematic review of kidney transplantation from expanded criteria donors. Am J Kidney Dis. 2008;52(3):553‑86.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177‑88.
7. R Development Core Team . R: A Language and Environment for Statistical Computing [Internet]. Computing RF for S, éditeur. Vienna, Austria; 2010. Disponible sur: http://www.R-project.org/
8. Combescure C, Foucher Y, Jackson D. Meta-analysis of single-arm survival studies: a distribution-free approach for estimating summary survival curves with random effects. Stat Med. 2014;33(15):2521‑37.
9. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol. 2011;11:139.
10. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17(24):2815‑34.
11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539‑58.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097.
13. Carroll RP, Macgregor L, Walker RG. The improvement in survival of expanded criteria donor kidneys with transplantation era. Clin Transplant. 2008;22(3):324‑32.
14. Smail N, Tchervenkov J, Paraskevas S, Baran D, Mucsi I, Hassanain M, et al. Impact of early graft function on 10-year graft survival in recipients of kidneys from standard- or expanded-criteria donors. Transplantation. 2013;96(2):176‑81.
15. Collins MG, Chang SH, Russ GR, McDonald SP. Outcomes of transplantation using kidneys from donors meeting expanded criteria in Australia and New Zealand, 1991 to 2005. Transplantation. 2009;87(8):1201‑9.
16. Cecka JM. The OPTN/UNOS renal transplant registry. Clin Transpl. 2004;1‑16.
17. Merion RM, Ashby VB, Wolfe RA, Distant DA, Hulbert-Shearon TE, Metzger RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. JAMA. 2005;294(21):2726‑33.
18. Kayler LK, Magliocca J, Zendejas I, Srinivas TR, Schold JD. Impact of cold ischemia time on graft survival among ECD transplant recipients: a paired kidney analysis. Am J Transplant. 2011;11(12):2647‑56.

19. Fraser SM, Rajasundaram R, Aldouri A, Farid S, Morris-Stiff G, Baker R, et al. Acceptable outcome after kidney transplantation using « expanded criteria donor » grafts. Transplantation. 2010;89(1):88‑96.
20. Salifu MO, Norin AJ, O'Mahony C, Sumrani N, Apel A, Ikram M, et al. Long-term outcomes of dual kidney transplantation-a single center experience. Clin Transplant. 2009;23(3):400‑6.
21. Gill J, Bunnapradist S, Danovitch GM, Gjertson D, Gill JS, Cecka M. Outcomes of kidney transplantation from older living donors to older recipients. Am J Kidney Dis. 2008;52(3):541‑52.
22. Lim WH, Clayton P, Wong G, Campbell SB, Cohney S, Russ GR, et al. Outcomes of kidney transplantation from older living donors. Transplantation. 2013;95(1):106‑13.
23. Saidi RF, Elias N, Kawai T, Hertl M, Farrell M-L, Goes N, et al. Outcome of kidney transplantation using expanded criteria donors and donation after cardiac death kidneys: realities and costs. Am J Transplant. 2007;7(12):2769‑74.
24. Reeves-Daniel AM, DePalma JA, Bleyer AJ, Rocco MV, Murea M, Adams PL, et al. The APOL1 gene and allograft survival after kidney transplantation. Am J Transplant. 2011;11(5):1025‑30.
25. Molnar MZ, Streja E, Kovesdy CP, Shah A, Huang E, Bunnapradist S, et al. Age and the associations of living donor and expanded criteria donor kidneys with kidney transplant outcomes. Am J Kidney Dis. 2012;59(6):841‑8.
26. Diet C, Audard V, Roudot-Thoraval F, Matignon M, Lang P, Grimbert P. Immunological risk in recipients of kidney transplants from extended criteria donors. Nephrol Dial Transplant. 2010;25(8):2745‑53.
27. Hofer J, Regele H, Böhmig GA, Gutjahr G, Kikić Z, Mühlbacher F, et al. Pre-implant biopsy predicts outcome of single-kidney transplantation independent of clinical donor variables. Transplantation. 2014;97(4):426‑32.
28. Praehauser C, Hirt-Minkowski P, Saydam Bakar K, Amico P, Vogler E, Schaub S, et al. Risk factors and outcome of expanded-criteria donor kidney transplants in patients with low immunological risk. Swiss Med Wkly. 2013;143:w13883.
29. Sung RS, Guidinger MK, Leichtman AB, Lake C, Metzger RA, Port FK, et al. Impact of the expanded criteria donor allocation system on candidates for and recipients of expanded criteria donor kidneys. Transplantation. 2007;84(9):1138‑44.
30. Sellers MT, Velidedeoglu E, Bloom RD, Grossman RA, Markmann JW, Naji A, et al. Expanded-criteria donor kidneys: a single-center clinical and short-term financial analysis--cause for concern in retransplantation. Transplantation. 2004;78(11):1670‑5.
31. Martínez Esteban D, Jironda Gallegos C, Cabello Diaz M, Frias P, López Jiménez V, Gutierrez de la Fuente C, et al. Creatinine clearance and proteinuria as early markers of kidney graft survival. Transplant Proc. 2010;42(8):2880‑2.
32. Gill J, Cho YW, Danovitch GM, Wilkinson A, Lipshutz G, Pham P-T, et al. Outcomes of dual adult kidney transplants in the United States: an analysis of the OPTN/UNOS database. Transplantation. 2008;85(1):62‑8.
33. Mezrich JD, Pirsch JD, Fernandez LA, Foley DP, Bellingham JM, Odorico JS, et al. Differential outcomes of expanded-criteria donor renal allografts according to recipient age. Clin J Am Soc Nephrol. 2012;7(7):1163‑71.
34. Matsuoka L, Shah T, Aswad S, Bunnapradist S, Cho Y, Mendez RG, et al. Pulsatile perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation. Am J Transplant. 2006;6(6):1473‑8.

35. Lucarelli G, Bettocchi C, Battaglia M, Impedovo SV, Vavallo A, Grandaliano G, et al. Extended criteria donor kidney transplantation: comparative outcome analysis between single versus double kidney transplantation at 5 years. Transplant Proc. 2010;42(4):1104‑7.
36. Nardo B, Bertelli R, Cavallari G, Capocasale E, Cappelli G, Mazzoni MP, et al. Analysis of 80 dual-kidney transplantations: a multicenter experience. Transplant Proc. 2011;43(5):1559‑65.
37. Woodside KJ, Merion RM, Leichtman AB, de los Santos R, Arrington CJ, Rao PS, et al. Utilization of kidneys with similar kidney donor risk index values from standard versus expanded criteria donors. Am J Transplant. 2012;12(8):2106‑14.
38. Anil Kumar MS, Khan SM, Jaglan S, Heifets M, Moritz MJ, Saeed MI, et al. Successful transplantation of kidneys from deceased donors with acute renal failure: Three-year results. Transplantation. 2006;82(12):1640‑5.
39. Carrier M, Lizé JF, Québec-Transplant Programs. Impact of expanded criteria donors on outcomes of recipients after kidney transplantation. Transplant Proc. 2012;44(7):2227‑30.
40. Lai Q, Pretagostini R, Poli L, Melandro F, Ferretti S, Della Pietra F, et al. Delayed graft function decreases early and intermediate graft outcomes after expanded criteria donor kidney transplants. Transplant Proc. 2009;41(4):1145‑8.
41. Moers C, Pirenne J, Paul A, Ploeg RJ, Machine Preservation Trial Study Group. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med. 2012;366(8):770‑1.
42. Kim SM, Ahn S, Min SI, Park D, Park T, Min SK, et al. Cold ischemic time is critical in outcomes of expanded criteria donor renal transplantation. Clin Transplant. 2013;27(1):132‑9.
43. Nicholson ML, Hosgood SA. Renal transplantation after ex vivo normothermic perfusion: the first clinical study. Am J Transplant. 2013;13(5):1246‑52.
44. Shaheen FA, Attar B, Hejaili F, Binsalih S, Al Sayyari A. Comparison of expanded criteria kidneys with 2-tier standard criteria kidneys: role of delayed graft function in short-term graft outcome. Exp Clin Transplant. 2012;10(1):18‑23.
45. Debout A, Foucher Y, Trébern-Launay K, Legendre C, Kreis H, Mourad G, et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. Kidney Int. 2015;87(2):343‑9.
46. Gill JS, Tonelli M. Penny wise, pound foolish? Coverage limits on immunosuppression after kidney transplantation. N Engl J Med. 16 févr 2012;366(7):586‑9.
47. Vickers AJ. Basic introduction to research: how not to do research. J Soc Integr Oncol. 2008;6(2):82‑5.
48. Mayer G, Persijn GG. Eurotransplant kidney allocation system (ETKAS): rationale and implementation. Nephrol Dial Transplant. 2006;21(1):2‑3.
49. Boesmueller C, Biebl M, Scheidl S, Oellinger R, Margreiter C, Pratschke J, et al. Long-term outcome in kidney transplant recipients over 70 years in the Eurotransplant Senior Kidney Transplant Program: a single center experience. Transplantation. 2011;92(2):210‑6.
50. Remuzzi G, Cravedi P, Perna A, Dimitrov BD, Turturro M, Locatelli G, et al. Long-term outcome of renal transplantation from older donors. N Engl J Med. 2006;354(4):343‑52.
51. Philosophe B, Malat GE, Soundararajan S, Barth RN, Manitpisikul W, Wilson NS, et al. Validation of the Maryland Aggregate Pathology Index (MAPI), a pre-implantation scoring system that predicts graft outcome. Clin Transplant. 2014;28(8):897‑905.
52. Israni AK, Salkowski N, Gustafson S, Snyder JJ, Friedewald JJ, Formica RN, et al. New national allocation policy for deceased donor kidneys in the United States and possible effect on patient outcomes. J Am Soc Nephrol. 2014;25(8):1842‑8.

TITLES AND LEGENDS

Figure 1. Flow-chart for selection of publications reporting survival outcomes of kidney transplant recipients from ECD and SCD.

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

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

Figure 2. Pooled survival curves for ECD kidney recipients and 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.

Table 3. Pooled non-adjusted 5-year survival probabilities for ECD kidney recipients and SCD kidney recipients according to geographical study area

DESCRIPTION OF SUPPLEMENTARY INFORMATION

Supplementary information is available at Transplant International's website.

Supplemental information S1: Search equation

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

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

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

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

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

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

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

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

Supplemental figure S10. Overall patient survival for ECD and SCD kidney recipients.

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

FIGURES AND TABLES

Figure 1. Flow-chart for selection of publications reporting survival outcomes of kidney transplant recipients from ECD and SCD.

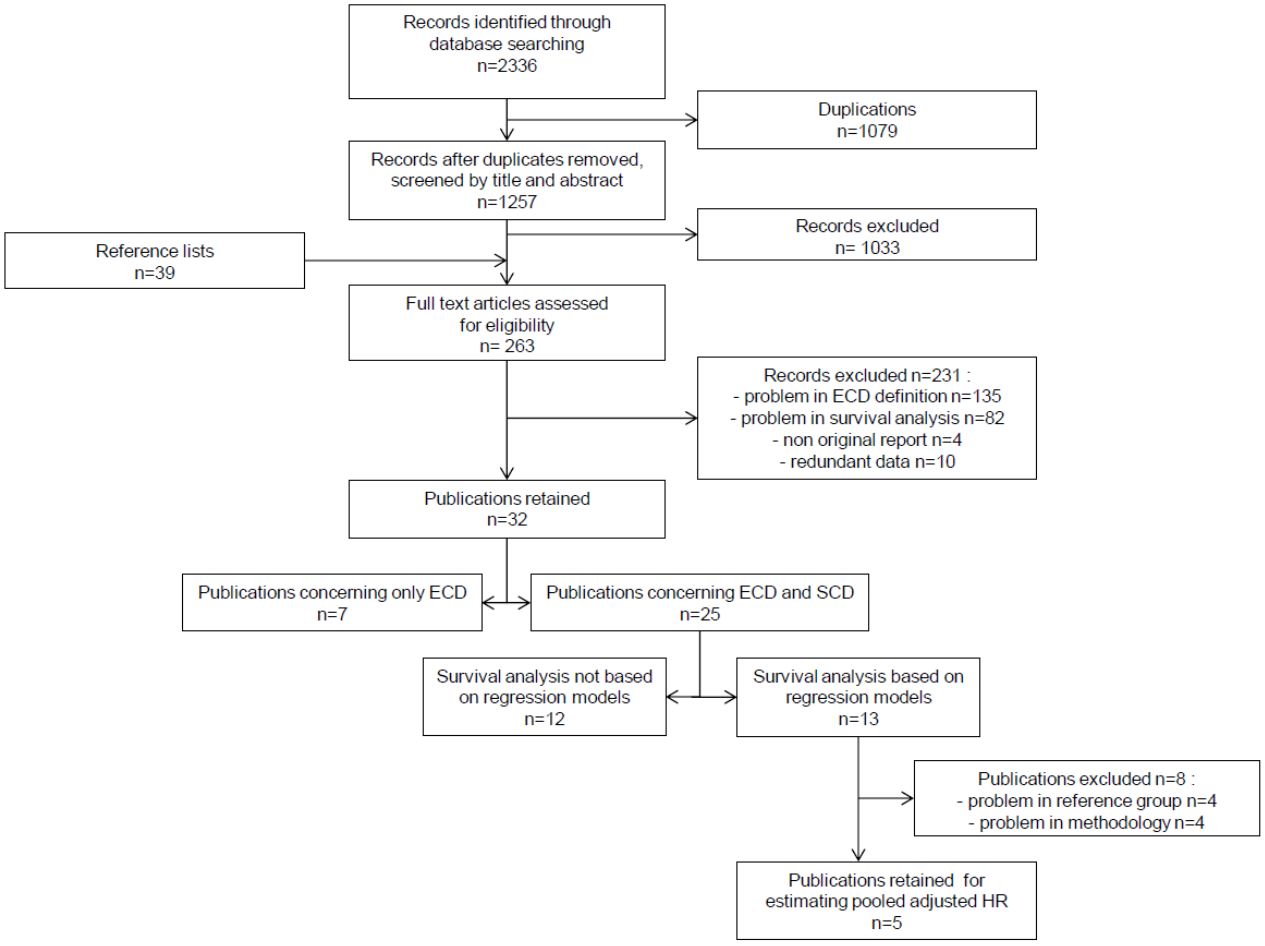

Table 1. Characteristics of the 32 studies reporting survival outcomes of ECD and SCD transplant recipients.

Author	Country Inclusion period	Sample size ECD	 SCD	Survival results	Death-censored graft survival at five years (or last year available)* ECD	 SCD	Patient survival at five years (or last year available)* ECD	 SCD	Patient-graft survival at five years (or last year available)* ECD	 SCD
Anil-Kumar et al, (2006)	U.S.A. 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)	U.S.A. 1991-2003	5,943	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	3,248	Curve	74%	88%	88%	92%	65%	81%
Diet et al, (2010)	France 1998-2004	656	1,465	Curve	84%	88%	-	-	-	-
Fraser et al, (2010)	United Kingdom 1995-2005	234	819	Curve	79%	81%	-	-	-	-
Gill et al, (2008)	U.S.A. 1996-2005	4,551	12,197	Curve	67% (4 yrs)	82% (4 yrs)	67% (4 yrs)	76% (4 yrs)	57% (4 yrs)	71% (4 yrs)
Hosgood et al, (2013)	United Kingdom 2008-2012	65	NA	Curve	98% (1 yr)	-	96% (1 yr)	-	-	-
Kayler et al, (2011)	U.S.A. 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)	-	-	-
Lucarelli et al, (2010)	Italia 2000-2008	179	NA	Curve	-	-	91%	-	-	-
Martinez et al, (2010)	Spain 1999-2006	180	NA	Curve	87%	-	-	-	-	-
Matsuoka et al, (2006)	U.S.A. 2000-2003	4,618	NA	Curve	-	-	-	-	67% (3 yrs)	-
Merion et al, (2005)	U.S.A. 1995-2004	7,790	41,052	Curve	76%	-	-	-	-	-
Mezrich et al, (2012)	U.S.A. 2000-2005	201	358	Curve/ Adjusted HR	79%	-	69%	79%	56%	70%

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

Author	Country Inclusion period	Sample size ECD	 SCD	Survival results	Death-Censored Graft survival at five years (or last year available)* ECD	 SCD	Patient survival at five years (or last year available)* ECD	 SCD	Patient-Graft survival at five years (or last year available)* ECD	 SCD
Molnar et al, (2012)	U.S.A. 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%
Reeves-Daniel et al, (2011)	U.S.A. 1998-2009	27	109	Adjusted HR	-	-	-	-	-	-
Saidi et al, (2007)	U.S.A. 1998-2005	44	163	Curve	-	-	83% (5 yrs)	88% (4 yrs)	-	-
Salifu et al, (2009)	U.S.A. 1996-2003	106	194	Curve	-	-	82%	83%	64%	72%
Sellers et al, (2004)	U.S.A. 1999-2001	45	157	Curve	90%	94%	85%	91%	80%	88%
Shaheen et al, (2012)	Saoudi Arabia 2009-2010	61	219	Curve	-	-	-	-	92% (2.25 yrs)	88% (2.25 yrs)
Woodside et al, (2012)	U.S.A. 2002-2010	7,916	5,917	Curve/ Adjusted HR	-	-	74%	80%	-	-
Lim et al, (2013)	Australia, New Zealand 1997-2009	916	3,200	Curve	71%	82%	85%	89%	-	-
Sung et al, (2007)	U.S.A. 1999-2005	4,175	8,512	Adjusted curve/ Adjusted HR	-	-	-	-	-	-
Gillet al, (2008)	U.S.A. 2000-2005	7,686	6,044	Curve	69% (4 yrs)	77% (4 yrs)	-	-	59% (4 yrs)	68% (4 yrs)
Smail et al, (2013)	Canada 1990-2006	243	280	Curve	78%	87%	83%	87%	-	-
Praehauser et al, (2013)	Switzerland 1999-2010	30	104	Curve	-	-	-	-	67%	87%
Hofer et al, (2013)	Austria 1999-2003	174	454	Curve	58%	77%	72%	85%	-	-

ECD Expanded Criteria Donor, SCD Standard Criteria Donor, HR Hazard Ratio, yrs years

Table 2. Donor, recipient, and transplant characteristics for the studies reporting survival outcomes of ECD kidney recipients (n=32) or both ECD and 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	2,548	5,741	26	28,461	21	5,099	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	2,652	4,965	26	22,515	25	9,698	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.

Figure 2. Pooled survival curves for ECD/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.

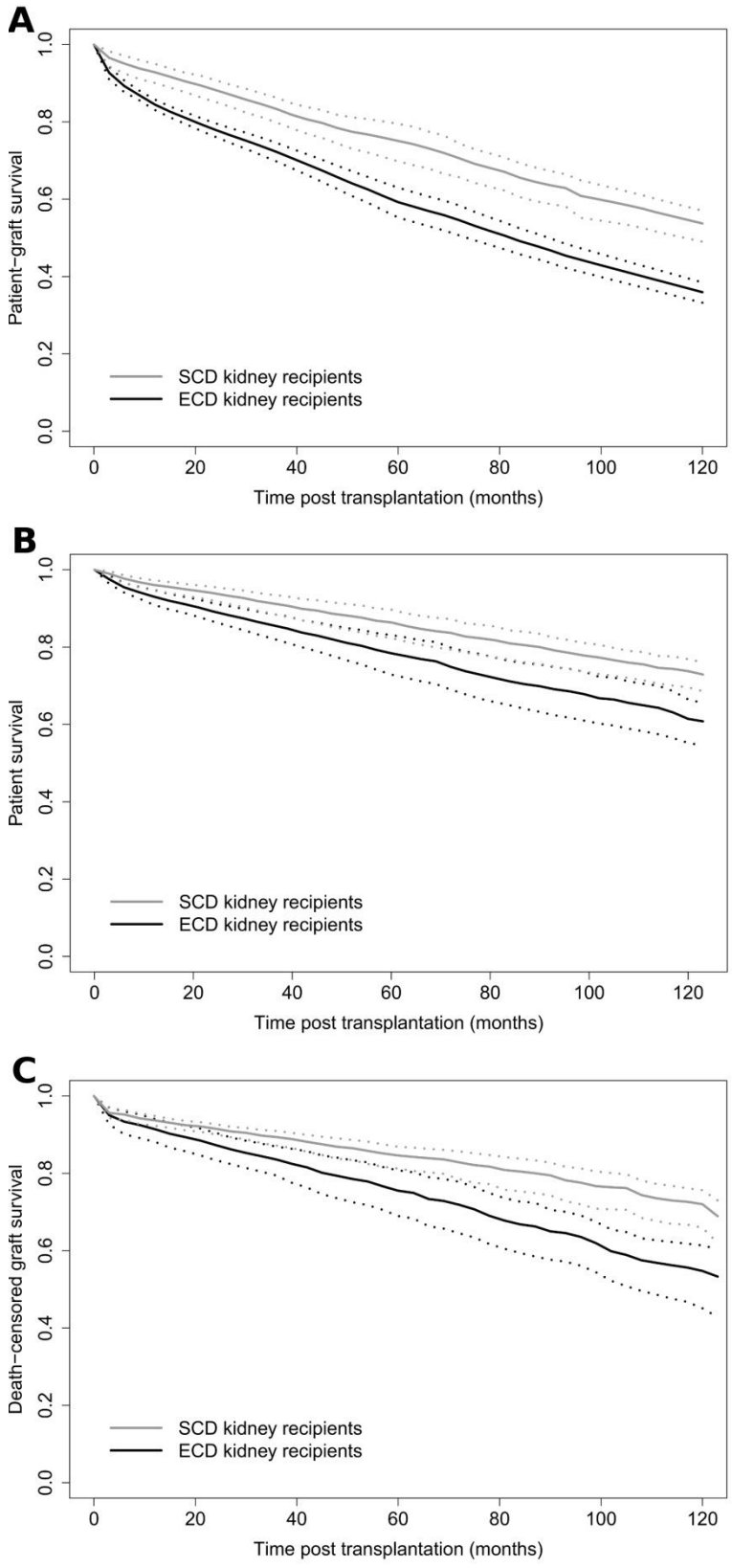

Table 3. Pooled non-adjusted 5-year survival probabilities for ECD kidney recipients and SCD kidney recipients according to geographical area of studies.

	Geographical area	Donor	n	Reference	Pooled non-adjusted 5-year survival [95%CI]		Pooled non-adjusted 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)(14)(13)7	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
* 2 years of follow-up
† 3 years of follow-up