Propensity score-based comparison of the graft failure risk between kidney transplant recipients of standard and expanded criteria donor grafts: Toward increasing the pool of marginal donors

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Abbreviations: ECD: Expanded Criteria Donor; SCD: Standard Criteria Donor; BMI: Body Mass Index; HBP: High Blood Pressure; HLA: Human Leukocyte Antigen; 95% CI: 95% Confidence Interval; HR: Hazard Ratio; DSA: Donor Specific Antibody; CIT: Cold Ischemia Time; SD: Standard Deviation; ATT: Average Treatment effect on the Treated; CVA: CerebroVascular Accident; DIVAT: Données Informatisées et VAlidées en Transplantation; IPW: Inverse Probability Weighted

Abstract

From a prospective and multicentric French cohort, we proposed an external validation study for the Expanded Criteria Donor (ECD), based on 4833 kidney recipients transplanted for the first time between 2000 and 2014. We estimated the subject-specific effect from a multivariable Cox model. We confirmed a 1.75-fold (95%CI from 1.53 to 2.00, p<0.0001) increase in graft failure risk if a given patient received an ECD graft compared to a graft from a donor with standard criteria (SCD). Complementarily, we estimated the population-average effect using propensity scores. We estimated a 1.34-fold (95%CI from 1.09 to 1.64, p=0.0049) increase in graft failure risk among ECD patients receiving an ECD graft compared to receiving a SCD graft. With a 10 years' follow-up, it corresponded to a decrease of 8 months of the mean time to graft failure due to ECD transplantation (95%CI from 2 months to 14 months). The population-average relative risk due to ECD transplantation and the corresponding absolute effect seems finally not so high. Regarding the increase of quality of life in transplantation, our study constitutes an argument to extend the definition of marginality by considering more grafts at high risk and therefore to enlarge the pool of kidney grafts.

Introduction

Kidney transplantation is recognized as the best treatment for end-stage renal disease in terms of morbidity, mortality and quality of life (1). Its development and expansion is limited on one hand by donor organ shortfalls, resulting in the search for new donors, and on the other hand by optimizing the use of available grafts. Due to an ageing population, waiting lists are increasing, further exacerbating the need to increase successful transplants by extending the pool of available kidneys (2). One possibility is to consider marginal grafts for kidney transplantation as they may deliver sufficient 'renal function' to improve patient wellbeing.

In 2002, the Expanded Criteria Donor (ECD) was proposed in the United States (3). The ECD is defined as a donor older than 60 years, or one aged between 50 and 59 years with at least two other comorbidities: serum creatinine higher than 1.5 mg/dL, a history of high blood pressure or a cerebro-vascular accident as the cause of donor death. The ECD classification was proposed in order to obtain a subject-specific relative risk of graft failure equal to 1.7 compared to the Standard Criteria Donor (SCD). More precisely, such a subject-specific effect can be interpreted as follows: on average, the graft failure risk for a given patient is multiplied by 1.7 if she/he received an ECD graft instead of a SCD graft.

We recently confirmed this subject-specific effect in a meta-analysis (4) based on 5 studies (5–9), where we also demonstrated the lack of external validation studies for this criteria. Indeed, no European study was selected in this meta-analysis. However, Aubert et al. (10) recently confirmed these results in France. More recently, Ma et al. (11) described that this effect seemed more important among younger recipients, while it could not be significantly shown for older recipients. In kidney transplantation, it is well known that ECD grafts are preferentially attributed to older recipients resulting in a possible shift of the recipient age distributions between ECD and SCD recipients. A consequence may be the difficulty to interpret the ECD transplantation effect among young recipients. Nevertheless, no report in the literature has examined this positivity assumption that requires that one can observe both ECD and SCD recipients at every combination of the values of the observed confounders (12). From a French prospective and observational cohort of kidney recipients, we proposed an external validation study of the subject-specific effect of ECD transplantation. Beyond this scope, thanks to the recent developments in propensity score-based analyses and more generally in causal inference, the main objective of our study was to propose an alternative

and complementary estimation by providing the absolute effect of ECD transplant organs on graft failure risk. More precisely, we compared for the first time the observed graft survival in ECD recipients and the expected graft survival if all ECD recipients had received SCD grafts. In order to ensure the robustness of this propensity score-based analysis, we paid special attention to the respect of the assumptions necessary to achieve causality.

Materials and methods

Study Population

All data were extracted from the French, multicentric, observational and prospective DIVAT cohort of transplanted patients (www.divat.fr, CNIL final agreement, decision DR-2025-087 (N°914184) the 15th February 2015). A total of 5048 patients met the following inclusion criteria: adult recipients of a single kidney, transplanted for the first time between January 2000 and December 2014, from heart beating deceased donor, and ABO-compatible. We used the ECD definition as proposed by Port al. (3). We did not include 215 patients since they had missing data on at least one variable involved in the ECD definition. Finally, 4833 patients constituted the studied population.

Data collected

Recipient pre-transplantation variables included: age, gender, Body Mass Index (BMI), initial nephropathy (relapsing disease or not), histories of either High Blood Pressure (HBP), diabetes, dyslipidemia, cardiovascular diseases, neoplasia, urological disease, dialysis technique before transplantation, time spent on dialysis and CytoMegaloVirus serology. Immunization against class I or class II Anti-Human Leukocyte Antigen (HLA) was scored positive if at least one Donor Specific Antibody (DSA) was identified by Luminex® Single Antigen Bead technology within the 6 months pre-transplantation, unless if at least one DSA was not identified but later determined by Luminex® screening or other technology (ELISA or CDC). Transplantation parameters were Cold Ischemia Time (CIT), HLA A-B-DR incompatibilities and type of induction treatment (depleting vs. non-depleting).

Statistical analyses

Patient characteristics were expressed as mean, standard deviation (SD), first and third quartile for continuous variables, or as count and percentage for categorical variables. Comparisons regarding the ECD and SCD status were performed using Student's t-tests, or Chi-square tests for quantitative or categorical variables, respectively. For each variable, standardized differences between ECD and SCD recipients were calculated on the original sample. The median event-free follow-up time was obtained by the reverse Kaplan-Meier method (13).

Similarly to the initial study (3), the main judgment criteria was the time from the transplantation (baseline) to graft failure which was defined as a return-to-dialysis or a death with a functioning graft. To estimate the subject-specific relative risk of graft failure related to the ECD, we used a multivariable Cox proportional hazards model (14). In addition, we estimated the population-average effect of ECD (15,16) in a propensity score-based analysis by using the Inverse Probability Weighted (IPW) estimator (17,18) with the robust variance estimator (19). More precisely, we estimated the Average Treatment effect on Treated (ATT) effect (20–22), i.e. the patient-graft survival of ECD recipients in a counterfactual world in which these recipients would have instead received SCD graft. Logistic regression was used to compute propensity scores. Positivity assumption was graphically evaluated (Web Supplementary Figure S1). Standardized differences on the pseudo-population were all lower than 10%, illustrating that the propensity score-based analysis allows to straighten up the initial covariates' imbalance between ECD and SCD recipients. Adjusted survival curves were estimated by using the weighted Kaplan-Meier estimator (23,24). The corresponding restricted mean survival times were also estimated (25).

Concerning the subject-specific estimation, a pool of variables initially selected on univariable survival analysis ($p<0.20$) as presented in Web Supplementary Table S1 was reduced to a lower number by a descending selection procedure ($p<0.05$) in a multivariable Cox model. Then, each significant remaining variable was removed if it did not affect the estimation of the hazard ratio associated with ECD transplantation of more than 10%, in order to appraise the efficient confounding variables. Concerning the population-average estimation, we first selected variables only associated with graft failure in univariable survival analysis ($p<0.20$). Second, this pool of selected variables was included in a multivariable logistic regression and,

then, reduced to a lower number by a descending selection procedure ($p<0.05$), allowing to retain the efficient confounding variables and to limit the imprecision in the estimation (26). The final retained variables were used to estimate the propensity score used to define ATT weights. Log-linearity assumption was graphically verified. Log-minus-log survival curves allowed graphical assessment of the proportional hazards assumption.

We additionally studied the time from the transplantation to the death-censored graft failure and the time from the transplantation to the patient death with graft function (returns in dialysis were right censored). Note that we only reported relative risks by using a cause-specific approach to deal with competing events, i.e. death with functioning graft and return in dialysis. Indeed, one can expect an important competition in the ECD population because of the age of recipients. We did not report the absolute effects, which would have been based on the cumulative incidence functions, for instance by using the Aalen-Johansen estimator (27). However, to our knowledge, no one has developed this estimator in an Inverse Probability of Treatment Weighting framework.

Additionally, we investigated the level of marginality within the ECD recipient cohort. We therefore performed a subgroup analysis by comparing the risk between recipients of ECD grafts from donors older than 75 years versus recipients of ECD graft from younger donors.

All analyses were performed using R software version 3.0.2 (28). The IPW-based analyses were performed using the 0.4 version of the *IPWsurvival* package (www.labcom-risca.com).

Results

Description of kidney transplant recipients at baseline

Among the 4833 studied patients, 2105 (44%) received an ECD graft and 2728 (56%) received an SCD graft. We observed a larger proportion of patients receiving an ECD graft compared to the 15% of ECD transplantation in the initial work of Port et al. (3), confirming that marginal grafts are increasingly used. We observed 25% of patients with a donor aged between 50 and 59 years, 35% of patients had a donor older than 60 years, while 5% of patients had received a graft from a donor older than 75 years. The maximum donor age was 89 years. Moreover, 14% of donors presented a serum creatinine higher than 1.5 mg/dL and 31% of donors had history of high blood pressure. Fifty-seven percent of donors died from cerebro-vascular accident, 28% died from trauma (including 12% of public road accident), 12% died from anoxia,

and 3% died from others causes (intoxication, meningitides, tumor, etc.). Demographic characteristics of recipients are summarized in Table 1. When comparing ECD and SCD recipients, significant differences were expected, notably concerning recipient age since grafts were matched on age where possible. As also illustrated in Web Supplementary Figure S2, ECD kidneys are preferentially proposed to older recipients with a mean recipient age estimated at 61 years for ECD and 45 years for SCD ($p<0.0001$). As might be expected, ECD recipients presented significantly more comorbidity histories than SCD recipients: notably concerning diabetes (20% for ECD vs. 10% for SCD, $p<0.0001$), dyslipidemia (37% for ECD vs. 24% for SCD, $p<0.0001$) and cardiovascular diseases (38% for ECD vs. 26% for SCD, $p<0.0001$).

Description of the follow-up

792 patients returned to dialysis and 488 patients died with a functioning graft. The causes of the recipient death were not collected. The cumulative follow-up covered 22406 patient-years. The median follow-up time was 5.22 years. The patient-graft survival probability at 3, 6 and 10 years post-transplantation were 85% (95% CI from 84% to 86%), 73% (95% CI from 72% to 75%) and 58% (95% CI from 56% to 60%), respectively. Patient-graft survival curves for ECD and SCD kidney recipients are presented in Web Supplementary Figure S3.

Subject-specific effect on patient and graft survival

Table 2 presents results for the multivariable Cox model. The subject-specific relative risk related to ECD versus SCD was estimated at 1.75 (95%CI from 1.53 to 2.00, $p<0.0001$). In other words, we confirmed a 1.75-fold increase in the risk of graft failure if a given patient received an ECD graft compared to a graft from a SCD donor. This estimation should be interpreted independently of recipient age. Nevertheless, regarding the important shift of the recipient age distributions in the ECD and SCD groups (Web Supplementary Figure S2), this effect should not be interpreted for young recipients, since they do not have an equal chance to receive ECD or SCD graft.

Population-average effect on patient and graft survival

The recipient age was the only significant variable retained in the final logistic regression used to estimate the propensity score. This variable also appeared significantly associated with the

patient-graft survival (Web Supplementary Table S1). The Table 3 presents the distribution of the characteristics of the pseudo-population obtained by propensity score weighting. In this pseudo-population, where the characteristics at baseline between ECD and SCD were balanced and comparable with the observed characteristics of the ECD recipients (fifth column of the Table 1), we estimated a population-average relative risk of graft failure between the ECD and SCD groups at 1.34 (95%CI from 1.09 to 1.64, p=0.0049). In other words, we estimated a 1.34-fold decrease in risk of graft failure between patients who had received an ECD and the same patients if they received instead an SCD graft. The corresponding patient-graft adjusted survival curves are presented in Figure 1. The ECD curve represents the estimated patient-graft survival probability for ECD recipients of an ECD kidney while the SCD curve represents the estimated patient-graft survival probability for ECD patients in the hypothetical situation of receiving a SCD kidney. The survival rates at 3, 6 and 10 years post-transplantation were respectively 77%, 62% and 40% for ECD recipients and 82%, 68% and 53% for the comparable group of SCD recipients. Therefore, at 10 years post-transplantation, the absolute risk excess due to ECD transplantation was 13% (95%CI from 2% to 24%). This means that, if 100 patients followed-up to 10 years had received an SCD instead of an ECD graft, 13 graft failures would have been prevented. The corresponding number needed to treat was about 8 (95%CI from 4 to 45). This means that we have to transplant 8 patients with an SCD graft instead of an ECD graft in order to prevent one graft failure at 10 years post-transplantation. For a cohort with a 10 years' follow-up, the mean time to graft failure were respectively 6.63 years for ECD recipients (95%CI from 6.44 years to 6.83 years) and would have been 7.31 years (95%CI from 6.85 years to 7.75 years) if they had received an SCD graft. It therefore corresponded to a decrease of 8 months due to ECD transplantation (95%CI from 2 months to 14 months).

Cause-specific risk of graft failure and cause-specific risk of death with functioning graft

As presented in Web Supplementary Table S2, we estimated a 1.84-fold increase in the population-average risk of death-censored graft failure between ECD and SCD recipients (95%CI from 1.33 to 2.55). This population-average relative risk was 0.97 for the risk of death with graft function (95%CI from 0.73 to 1.30).

ECD grafts from donors older than 75 years versus ECD grafts from younger donors

We estimated a non-significant population-average relative risk of graft failure between patients with an ECD graft from donors older than 75 years versus recipients with an ECD graft from younger donors (HR=1.19, 95%CI from 0.90 to 1.58). At 5 years post-transplantation, the graft survival was 46% (95%CI from 28% to 64%) in the recipients of older donors versus 60% (95%CI from 45% to 75%) in the recipients of younger donors. We therefore estimated an absolute risk increase due to donor age at 14% (95% CI from -10% to 38%). This non-significant difference was also observed for the risk of death with graft function (HR=0.98, 95%CI from 0.64 to 1.51), and for the risk of death censored graft failure (HR=1.39, 95%CI from 0.97 to 1.99). These estimates are also summarized in Web supplementary Table S2.

Discussion

From the French multicentric DIVAT cohort, we confirmed that the subject-specific relative risk of graft failure between ECD and SCD is close to the one obtained in the initial study: HR=1.75 (95%CI from 1.53 to 2.00) versus 1.70 (95%CI not available). Nevertheless, to our knowledge, no study has estimated the population-average effect of ECD transplantation. Namely, what would the decrease in patient-graft survival be if patients received ECD kidneys instead of SCD? Alternatively, what would the results have been for a clinical trial among the potential ECD recipients with a randomization into the ECD and SCD groups? Although randomized trials are the gold standard study design for estimating a population-average effect, such a design is not conceivable here, since ethically the graft allocation could not be randomized. Our study proposes an interesting solution using a suitable methodology providing population-average effects. We estimated a 1.34-fold increase in graft failure risk between the ECD recipients and a comparable group of patients receiving SCD grafts (95%CI from 1.09 to 1.64). This relative risk may possibly not be explained by a difference in the risk of death with a functioning graft (HR=0.97, 95%CI from 0.73 to 1.30). Our propensity score-based approach presents a major interest since it also provides confounder-adjusted absolute effects. At 10 years post-transplantation, the decrease in the mean time to graft failure due to ECD transplantation was estimated at 8 months (95%CI from 2 months to 14 months). We also described a difference of 13% in terms of patient and graft survival at 10 years post-

transplantation (95%CI from 2% to 24%), corresponding to a number needed to treat at 8 patients (95%CI from 4 to 45).

The population-average effects of ECD transplantation may appear not so high in our population. The absolute risk difference between marginal donor transplantation and non-marginal donor transplantation could be authorized to be higher and this may constitute an argument in favor of extending the definition of marginality criteria. To better discuss this possibility, we have further compared the recipients of a graft older than 75 years compared to patients receiving a younger ECD graft. The risk excess may be considered as low with a population-average relative risk of graft failure estimated at 1.19 (95%CI from 0.90 to 1.58) while the confounder-adjusted patient and graft survival at 5 years post-transplantation was 46% (95%CI from 28% to 64%) in the oldest group versus 60% (95%CI from 45% to 75%) in the youngest group. These results definitively encourage to increase the pool of marginal donors by considering higher risk grafts. One could for instance allow older donors. Nevertheless, to more precisely address the possible increase of the donor pool, future studies should consider patient survival if the sample of ECD recipients had received no graft, i.e. the population-average of ECD versus dialysis.

Several limitations may be highlighted from our observational study. First, we could not exclude the potential bias induced by non-observed confounders. Second, we did not include patients with missing data concerning variables used in the ECD definition. It concerns 215 patients, i.e. less than 5% of the whole sample. Third, even if the ECD status has the advantage of simplicity as a binary criteria defined from only four donor characteristics, an important limit of our work is not to study a graduating scale of donor marginality. In 2014, the American Organ Procurement and Transplantation Network (OPTN) proposed the Kidney Donor Risk Index (KDRI) (29), a continuous score of donor marginality, with few external validations (30). As a perspective of our work, future studies should externally validate the KDRI by studying both subject-specific and population-average effects. Finally, we believe that the most important limit of the ECD definition is to be only based on donor characteristics. This limit is also true for other scoring systems of graft quality, such as the Deceased Donor Score (31), the Donor Risk Score (32), the Maryland Aggregate Pathology Index (33), or the KDRI (29). None of these scoring systems takes into account the interactions between donors and

recipients characteristics. But, the kidney graft marginalization should not be determined as an absolute criteria but should depend on the recipients' features.

In conclusion, even if our study confirmed the subject-specific relative risk related to ECD versus SCD, the population-average effects of ECD transplantation seemed not so important. Using a propensity score-based analysis, we proposed an alternative estimation of ECD transplantation at a population level, not better than the traditional multivariate modeling giving subject-specific estimation, but allowing a complementary interpretation. This study reinforces the idea of further increasing the pool of marginal kidneys. This perspective has probably to integrate both the donor and recipient characteristics for better identify recipients who will benefit of being transplanting by such highly marginal grafts.

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Disclosure

The Authors declare that there is no conflict of interest.

References

1. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. oct 2011;11(10):2093-109.

2. Hart A, Smith JM, Skeans MA, Gustafson SK, Stewart DE, Cherikh WS, et al. OPTN/SRTR 2015 Annual Data Report: Kidney. Am J Transplant. 1 janv 2017;17:21-116.

3. 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.

4. Querard A-H, Foucher Y, Combescure C, Dantan E, Larmet D, Lorent M, et al. Comparison of survival outcomes between Expanded Criteria Donor and Standard Criteria Donor kidney transplant recipients: a systematic review and meta-analysis. Transpl Int Off J Eur Soc Organ Transplant. avr 2016;29(4):403-15.

5. 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 Off J Natl Kidney Found. juin 2012;59(6):841-8.

6. 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. 15 nov 2007;84(9):1138-44.

7. 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 Off J Am Soc Transplant Am Soc Transpl Surg. mai 2011;11(5):1025-30.

8. 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 CJASN. juill 2012;7(7):1163-71.

9. 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 Off J Am Soc Transplant Am Soc Transpl Surg. août 2012;12(8):2106-14.

10. Aubert O, Kamar N, Vernerey D, Viglietti D, Martinez F, Duong-Van-Huyen J-P, et al. Long term outcomes of transplantation using kidneys from expanded criteria donors: prospective, population based cohort study. BMJ. 31 juill 2015;351:h3557.

11. Ma MKM, Lim WH, Craig JC, Russ GR, Chapman JR, Wong G. Mortality among Younger and Older Recipients of Kidney Transplants from Expanded Criteria Donors Compared with Standard Criteria Donors. Clin J Am Soc Nephrol CJASN. 7 janv 2016;11(1):128-36.

12. Westreich D, Cole SR. Invited Commentary: Positivity in Practice. Am J Epidemiol. 1 janv 2010;171(6):674-7.

13. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. août 1996;17(4):343-6.

14. Cox D. Regression models and life-tables. J R Stat Soc Ser B. 1972;34:187-229.

15. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc. 1984;79(387):516–524.

16. Gayat E, Resche-Rigon M, Mary J-Y, Porcher R. Propensity score applied to survival data analysis through proportional hazards models: a Monte Carlo study. Pharm Stat. mai 2012;11(3):222-9.

17. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed. 2004;75(1):45-9.

18. Binder DA. Fitting Cox's Proportional Hazards Models from Survey Data. Biometrika. 1992;79(1):139-47.

19. Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. J Am Stat Assoc. 1 déc 1989;84(408):1074-8.

20. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 30 mars 2014;33(7):1242-58.

21. Pirracchio R, Carone M, Rigon MR, Caruana E, Mebazaa A, Chevret S. Propensity score estimators for the average treatment effect and the average treatment effect on the treated may yield very different estimates. Stat Methods Med Res. oct 2016;25(5):1938-54.

22. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 30 déc 2016;35(30):5642-55.

23. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Stat Med. 30 oct 2005;24(20):3089-110.

24. Le Borgne F, Giraudeau B, Querard AH, Giral M, Foucher Y. Comparisons of the performance of different statistical tests for time-to-event analysis with confounding factors: practical illustrations in kidney transplantation. Stat Med. 29 oct 2015;

25. Andersen PK, Perme MP. Pseudo-observations in survival analysis. Stat Methods Med Res. 1 févr 2010;19(1):71-99.

26. Heinze G, Jüni P. An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J. 1 juill 2011;32(14):1704-8.

27. Aalen OO, Johansen S. An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. Scand J Stat. 1 janv 1978;5(3):141-50.

28. 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/

29. 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.

30. Peters-Sengers H, Heemskerk MBA, Geskus RB, Kers J, Homan van der Heide JJ, Berger SP, et al. Validation of the Prognostic Kidney Donor Risk Index (KDRI) Scoring System of Deceased Donors for Renal Transplantation in the Netherlands. Transplantation. 21 juill 2017;

31. Nyberg SL, Matas AJ, Kremers WK, Thostenson JD, Larson TS, Prieto M, et al. Improved scoring system to assess adult donors for cadaver renal transplantation. Am J Transplant. 2003;3(6):715-21.

32. Schold JD, Kaplan B, Baliga RS, Meier-Kriesche H-U. The broad spectrum of quality in deceased donor kidneys. Am J Transplant. 2005;5(4 Pt 1):757-65.

33. 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. août 2014;28(8):897-905.

Figure legends

Table 1: Description of recipient, donor and transplantation characteristics for the sample of kidney transplanted patients (n=4833) according the ECD/SCD transplantation.

Table 2: Multivariable Cox model to study the association of ECD and the risk of graft failure, adjusted on the year of transplantation (n=4833).

Table 3: Description of recipient, donor and transplantation characteristics for the pseudo-population obtained after ATT weighting.

Figure 1: Adjusted patient-graft survival curves estimated by the IPW Kaplan–Meier estimator for ECD kidney recipients (solid line) and SCD kidney recipients (dashed line).

Table 1

	Missing data	Global N=4833	SCD recipients N=2728 (56.4%)	ECD recipients N=2105 (43.6%)	p-value	Standardized difference (%)
Quantitative characteristics : mean ± SD (1^{st} quartile - 3^{rd} quartile)						
Recipient age (years)	0	51.8±13.4 (43 – 62)	44.7±11.9 (36 – 54)	60.9±8.9 (56 – 67)	<0.0001	153.67
Recipient BMI (kg/m²)	40	24.4±4.4 (21.3 – 27.1)	23.9±4.5 (20.8 – 26.4)	25.1±4.2 (22.1 – 27.6)	<0.0001	26.56
Time spent on dialysis (years)	13	3.4±3.2 (1.3 – 4.6)	3.5±3.3 (1.3 – 4.7)	3.2±3.1 (1.2 – 4.4)	0.0052	8.10
CIT (hours)	30	19.9±7.6 (14.4 – 24.0)	20.0±7.9 (14.0 – 24.8)	19.8±7.2 (14.8 – 23.5)	0.2460	3.36
Categorical characteristics : N (%)						
Recipient men	0	2970 (61.5)	1661 (60.9)	1309 (62.2)	0.3737	2.67
History of HBP	0	3644 (75.4)	2022 (74.1)	1622 (77.1)	0.0206	6.84
History of diabetes	0	704 (14.6)	282 (10.3)	422 (20.0)	<0.0001	27.30
History of dyslipidemia	0	1442 (29.8)	655 (24.0)	787 (37.4)	<0.0001	29.31
History of cardiovascular diseases	0	1501 (31.1)	709 (26.0)	792 (37.6)	<0.0001	25.18
History of neoplasia	0	395 (8.2)	138 (5.1)	257 (12.2)	<0.0001	25.67
History of urological disease	0	753 (15.6)	405 (14.8)	348 (16.5)	0.1182	4.64
Dialysis technique	5				0.2131	5.09
Pre-emptive transplantation		378 (7.8)	199 (7.3)	179 (8.5)		
Peritoneal dialysis		324 (8.7)	177 (6.5)	147 (7.0)		
Hemodialysis		4126 (85.5)	2350 (86.2)	1776 (84.5)		
Relapsing initial disease	14	1326 (27.5)	883 (32.5)	443 (21.1)	<0.0001	25.81
Recipient CMV infection	42	2880 (60.1)	1535 (56.7)	1345 (64.5)	<0.0001	15.87
Detectable daily anti-HLA class I	1706	698 (22.3)	374 (21.1)	324 (24.0)	0.0598	6.93
Detectable daily anti-HLA class II	1790	536 (17.6)	280 (16.2)	256 (19.4)	0.0261	8.28
HLA A-B-DR incompatibilities ≥ 5	121	681 (14.5)	367 (13.8)	314 (15.3)	0.1835	4.02
Depleting induction	31	1883 (39.2)	1060 (39.0)	823 (39.5)	0.7875	0.87

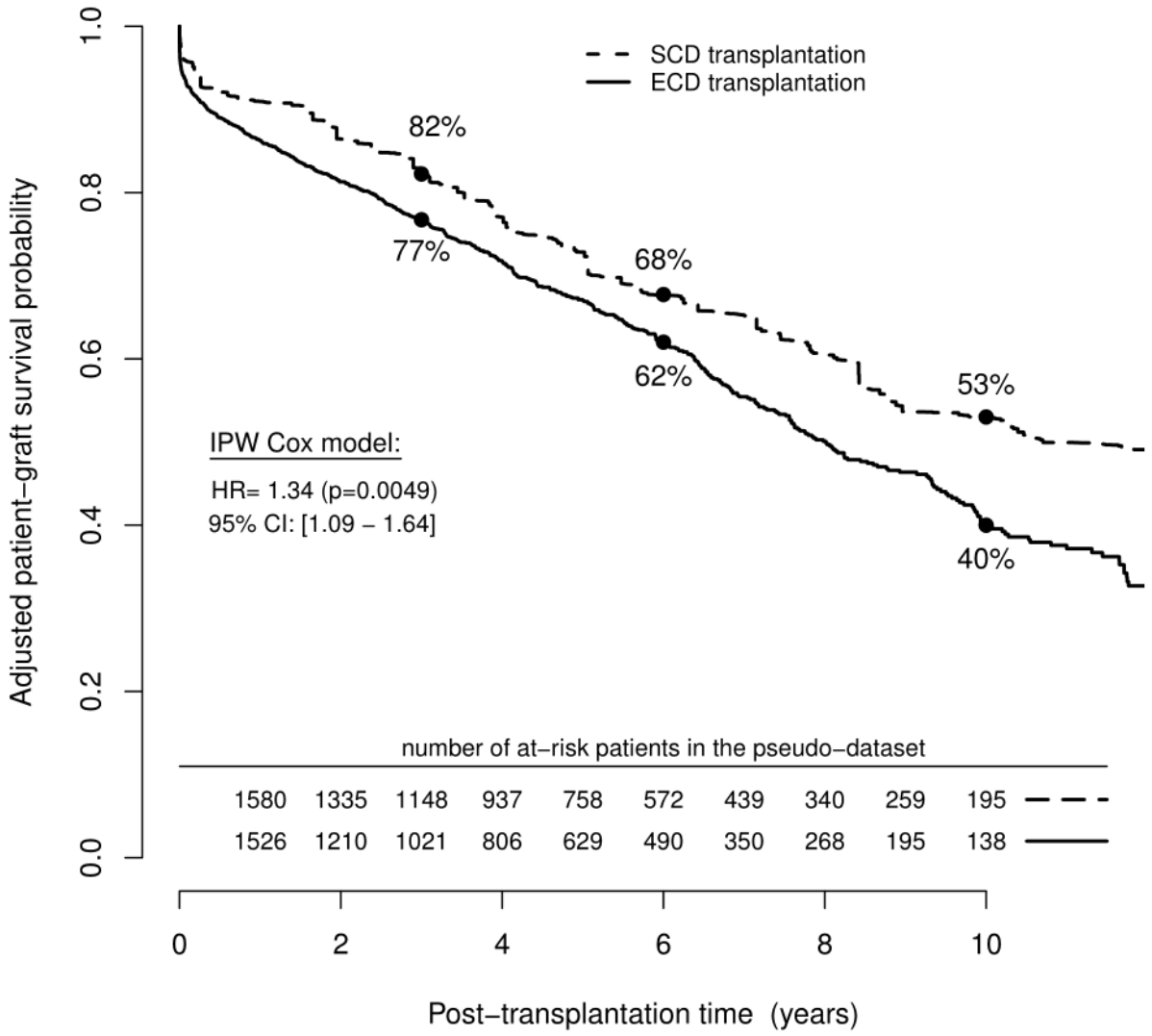
Table 2

	HR	95% CI	p
Marginal donor criteria (ECD vs. SCD)	1.75	1.53 – 2.00	<0.0001
Recipient age (years)	1.02	1.01 – 1.03	<0.0001

Table 3

	SCD recipients in the pseudo-population N=2054 (49.4%)	ECD recipients in the pseudo-population N=2105 (50.6%)	Standardized difference (%)
Quantitative characteristics : mean ± SD			
Recipient age (years)	60.9±9.1	60.9±8.9	0.18
Recipient BMI (kg/m²)	25.1±4.3	25.1±4.2	1.10
Time spent on dialysis (years)	3.6±3.7	3.2±3.1	12.85
CIT (hours)	20.2±8.0	19.8±7.2	5.99
Categorical characteristics : N (%)			
Recipient men	1152 (56.1)	1309 (62.2)	12.42
History of HBP	1570 (76.4)	1622 (77.1)	1.51
History of diabetes	463 (22.5)	422 (20.0)	6.04
History of dyslipidemia	725 (35.3)	787 (37.4)	4.35
History of cardiovascular diseases	824 (40.1)	792 (37.6)	5.12
History of neoplasia	185 (9.0)	257 (12.2)	10.43
History of urological disease	303 (14.7)	348 (16.5)	4.94
Dialysis technique			4.35
Pre-emptive transplantation	156 (7.6)	179 (8.5)	
Peritoneal dialysis	132 (6.4)	147 (7.0)	
Hemodialysis	1767 (86.0)	1776 (84.5)	
Relapsing initial disease	467 (22.7)	443 (21.1)	3.92
Recipient CMV infection	1354 (66.1)	1345 (64.5)	3.49
Detectable daily anti-HLA class I	359 (27.5)	324 (24.0)	8.06
Detectable daily anti-HLA class II	284 (22.3)	256 (19.4)	7.21
HLA A-B-DR incompatibilities ≥ 5	324 (16.1)	314 (15.3)	2.22
Depleting induction	817 (39.9)	823 (39.5)	0.81

Figure 1


SCD transplantation
ECD transplantation
82%
77%
68%
62%
53%
40%
IPW Cox model:
HR= 1.34 (p=0.0049)
95% CI: [1.09 – 1.64]
Adjusted patient–graft survival probability
0.0
0.2
0.4
0.6
0.8
1.0
number of at–risk patients in the pseudo–dataset
1580 1335 1148 937 758 572 439 340 259 195
1526 1210 1021 806 629 490 350 268 195 138
0
2
4
6
8
10
Post–transplantation time (years)

Web supplementary materials

Table S1. Univariable patient-graft survival analyses for each possible confounding variable.

	Hazard Ratio	95% CI	p
Marginal donor criteria (ECD vs. SCD)	2.35	2.11 – 2.63	<0.0001
Recipient age (years)	1.03	1.02 – 1.04	<0.0001
Recipient BMI (kg/m²)			<0.0001
18-29 vs. <18	0.86	0.69 – 1.06	
≥30 vs. <18	1.45	1.13 – 1.86	
Recipient gender (men vs. women)	1.03	0.92 – 1.15	0.6270
History of HBP (positive vs. negative)	0.93	0.81 – 1.06	0.2650
History of diabetes (positive vs. negative)	1.84	1.60 – 2.11	<0.0001
History of dyslipidemia (positive vs. negative)	1.21	1.07 – 1.36	0.0016
History of cardiovascular diseases (positive vs. negative)	1.57	1.41 – 1.76	<0.0001
History of neoplasia (positive vs. negative)	1.44	1.19 – 1.73	0.0002
History of urological disease (positive vs. negative)	1.01	0.87 – 1.18	0.8490
Dialysis technique			0.0152
Peritoneal dialysis vs. pre-emptive transplantation	1.13	0.81 – 1.57	
Hemodialysis vs. pre-emptive transplantation	1.35	1.06 – 1.72	
Recipient initial disease (relapsing vs. not relapsing)	0.88	0.78 – 0.99	0.0387
Recipient CMV infection (positive vs. negative)	1.24	1.10 – 1.39	0.0002
Daily anti-HLA class I (detectable vs. non detectable)	1.35	1.14 – 1.59	0.0005
Daily anti-HLA class II (detectable vs. non detectable)	1.11	0.90 – 1.37	0.3456
CIT (hours)	1.01	1.00 – 1.02	0.0447
Time spent on dialysis (years) (≥3 years vs. < 3 years)	1.13	1.01 – 1.26	0.0360
HLA incompatibilities (≥5 vs. < 5)	1.10	0.94 – 1.28	0.2410
Induction treatment (depleting vs. non depleting)	0.96	0.86 – 1.08	0.4859

Table S2. Population-average effect for patient-graft survival, graft survival with death censored and patient survival with graft function given the comparison of ECD and SCD transplantation and the comparison of ECD recipients of donor older than 75 years and ECD recipients of younger donor.

	Patient-Graft survival			Graft survival (death censored)			Patient survival with graft function		
	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
ECD vs. SCD transplantation									
Population-average effect	1.34	1.09 – 1.64	0.0049	1.84	1.33 – 2.55	0.0002	0.97	0.73 – 1.30	0.8562
Among ECD, Donor age > 75 years vs. 75 ≤ years									
Population-average effect	1.19	0.90 – 1.58	0.2290	1.39	0.97 – 1.99	0.0697	0.98	0.64 – 1.51	0.9366

Figure S1: Distribution of the propensity score according to the ECD/SCD status.

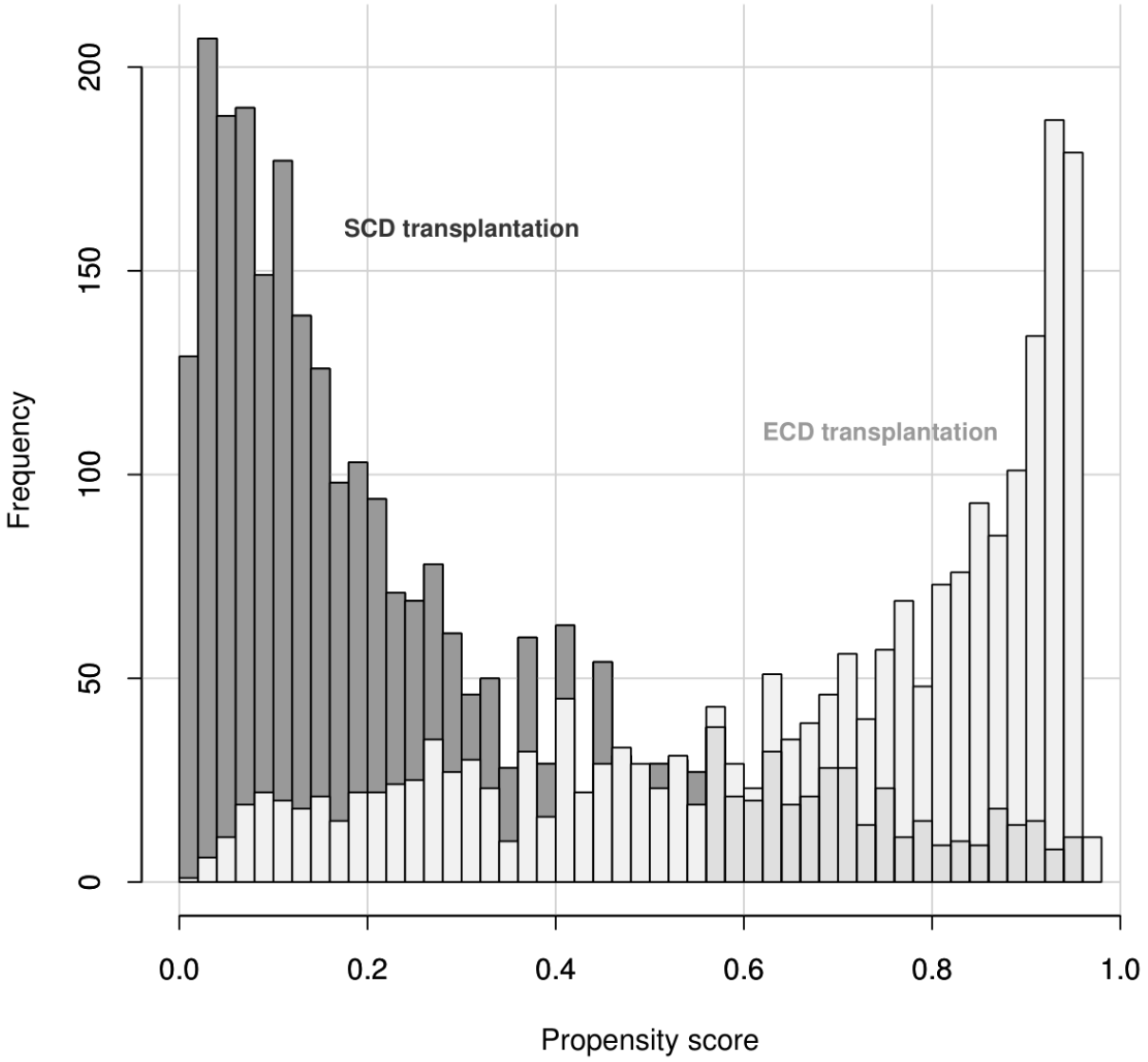


Figure S2: Distribution of the recipient age according to the ECD/SCD transplantation.

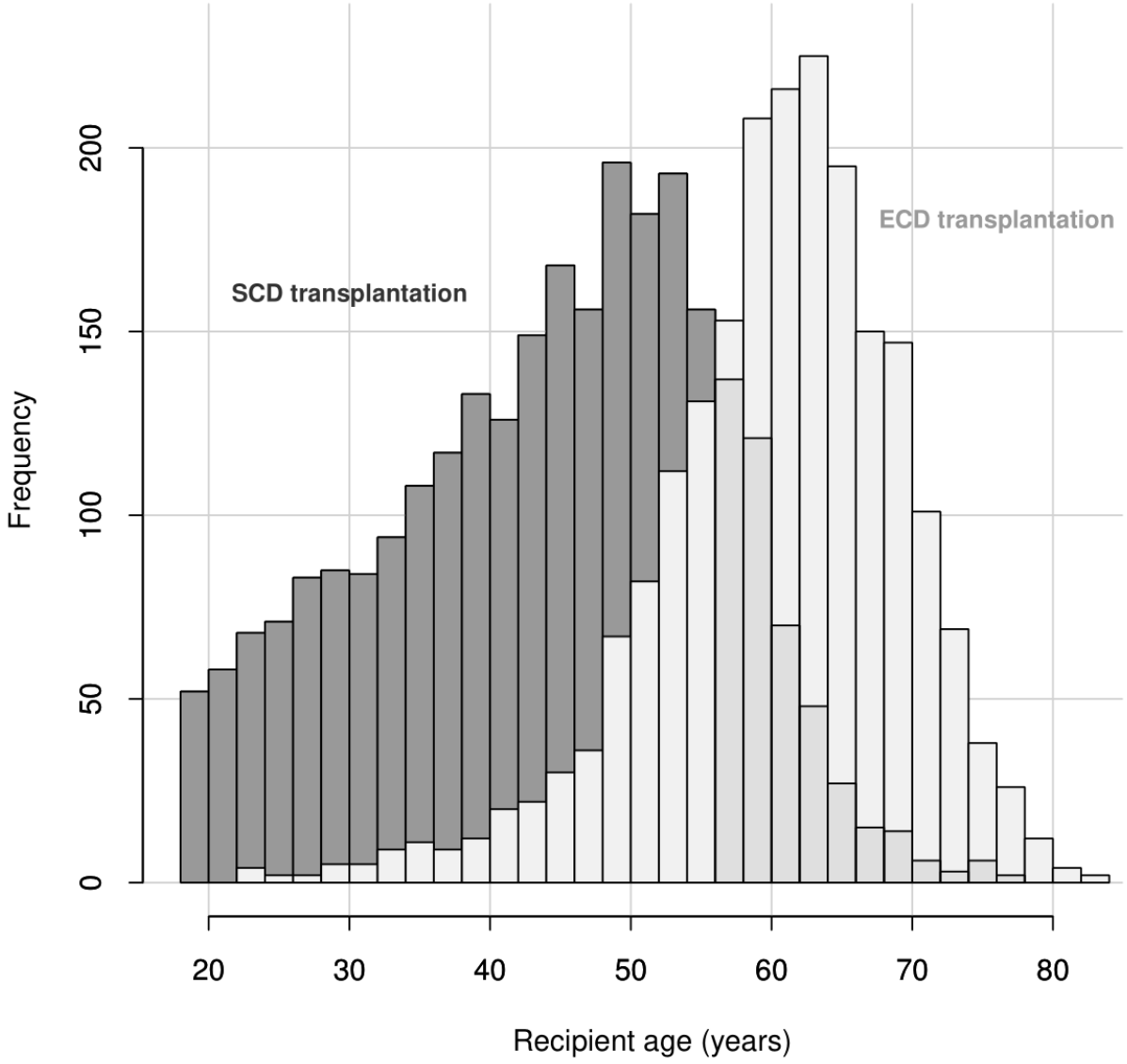


Figure S3: Patient-graft survival curves estimated by the Kaplan–Meier estimator for ECD kidney recipients (solid line) and SCD kidney recipients (dashed line).