ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2018; 23: 775-781
DOI: 10.12659/AOT.909622

Received: 2018.02.24
Accepted: 2018.05.02
Published: 2018.11.06

Association of Kidney Donor Risk Index with the Outcome after Kidney Transplantation in the Eurotransplant Senior Program

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Beate Schamberger
ABCD 2 Dario Lohmann
CDE 3 Daniel Sollinger
ABD 4 Raimund Stein
ADEF 1 Jens Lutz

1 Medical Clinic, Section of Nephrology and Infectious Diseases, Gemeinschaftsklinikum Mittelrhein, Koblenz, Germany
2 Medical Clinic III, Section of Nephrology, University Hospital Frankfurt, Frankfurt, Germany
3 I Medical Clinic, Section of Nephrology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
4 Department of Pediatric Urology, University Medical Center Mannheim, Mannheim, Germany

Corresponding Author: Beate Schamberger, e-mail: beate.schamberger@gk.de
Source of support: Departmental sources

Background: We evaluated the Kidney Donor Risk Index (KDRI) scoring system for kidney transplantation in the Eurotransplant Senior Program (ESP) that allocates kidneys from older donors to older recipients (≥65 years).

Material/Methods: We retrospectively analyzed data of 37 kidney transplant recipients and 36 kidney donors who participated in kidney transplantation program according to the ESP at our center from January 2004 until December 2013.

Results: Mean recipient and donor age was 67.9±2.6 and 70.5±4.0 years respectively. The mean KDRI score was 1.7±0.27. Uncensored graft survival after 1 year and 5 years was 64.2% and 53.7% respectively. Subgroup analysis showed that in kidney transplantation with KDRI >1.83, graft survival was significantly reduced compared to lower KDRI subgroups. KDRI was significantly correlated with serum creatinine level at discharge (r=0.4).

Conclusions: ESP kidneys represent a group of high-risk grafts with high KDRI scores. Higher KDRI scores in ESP kidneys was associated with reduced postoperative short-term and long-term graft outcomes. KDRI might be useful in decision-making for selecting donors for ESP kidney transplantation.

MeSH Keywords: Donor Selection • Kidney Transplantation • Organs at Risk • Patient Outcome Assessment

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/909622

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

The Eurotransplant Senior Program (ESP) was developed in 1999 in response to the growing number of older recipients and older donors, aiming to reduce the waiting time for patients ≥65 years by allocation of organs from donor ≥65 years to such patients [1]. The ESP allocation system is based on regional allocation according to age, blood group, and waiting time but independent of HLA matching, thus, leading to significantly reduced waiting times in patients older than 65 years. Moreover, this system aims to achieve a good primary organ function by a reduction of the cold ischemic time. Short-term results of the ESP have been promising [2,3]. Five-year results of the ESP, however, revealed higher rejection rates and lower patient and graft survival as compared to renal transplantation in older recipients with kidneys from younger donors [4]. On the other hand, it has been shown that kidney transplantation in the elderly improves survival compared to patients of the same age who remain on the waiting list [5–7].

ESP donor kidneys were derived from expanded criteria donors [8] as all donors were ≥65 years old. The Kidney Donor Risk Index (KDRI) has been introduced to improve risk evaluation of deceased donor kidneys using 10 donor characteristics instead of 4 in the expanded criteria donors system [9]. With increasing KDRI, the relative risk of kidney graft failure after transplantation increases. As many older patients on dialysis treatment have a high degree of comorbidity, it is often difficult to decide who would benefit from kidney transplantation in the ESP using marginal kidneys from high-risk donors. The prognostic value of the KDRI in ESP kidney transplantation has not yet been characterized. In this study, we evaluated the outcome of kidney transplantation and potential risk factors, including KDRI, for patient and graft survival in the ESP.

Material and Methods

Study design

There were 225 patients who underwent kidney transplantation at our center from January 2004 until December 2013. Of these patients, 37 patients (16.4%) received a kidney transplant from 36 donors according to the ESP and included in this retrospective study.

Patient und follow-up data were evaluated from medical reports for kidney function [serum creatinine, estimated glomerular filtration rate (eGFR)], primary function, primary non-function, delayed graft function (DGF), graft loss, patient survival, and biopsy proven acute rejection (BPAR). DGF was defined as need for dialysis only during the first week after transplantation. Donor data, including age, gender, smoking, body mass index (BMI), cytomegalovirus (CMV) serology, human leukocyte antigen (HLA) mismatches, cause of brain death, serum creatinine, and comorbidities, were collected from the Eurotransplant donor reports; eGFR was calculated according to the CKD-EPI formula. KDRI was calculated from donor variables using the method described by the Organ Procurement and Transplantation Network (OPTN) [10].

Statistics

Quantitative data are expressed as mean ± standard deviation, median, and minimum-maximum. Patient survival and graft survival were analyzed using the Kaplan-Meier method. Subgroup analysis was performed using the Fisher's exact test and the Log-rank test. Three size-matched KDRI subgroups were defined according to the distribution of the KDRI score [1.16–1.54 (n=12); 1.55–1.82 (n=11), and 1.83–2.26 (n=14)]. Spearman correlation analysis was used to determine the association of KDRI and the outcome parameters. *P*-values <0.05 were considered significant. All analyses were performed using the statistics program IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA).

Results

Recipient and donor characteristics

Mean age of ESP recipients and donors was 67.9±2.6 and 70.5±4.0 years, respectively (Table 1). The body mass index (BMI) was ≥30 kg/m^2 in 6 recipients (16.7%) and 6 donors (16.2%). A history of smoking was present in 8 recipients (21.6%) and 6 donors (16.7%). Mean eGFR of the ESP donors was 73 mL/min/1.73 m^2. Comorbidities such as arterial hypertension and diabetes mellitus were frequent among recipients and donors. Mean KDRI score was 1.70±0.27 (Figure 1).

The HLA mismatches were 4.4±1.2 (Table 1). Mean cold ischemic time was 9 hours 25 minutes ±2 hours 52 minutes. All patients received quadruple immunosuppressive therapy (induction, calcineurin inhibitor, mycophenolate, and steroids). Steroids were administered on a long-term basis to 36 patients (97.3%).

Short-term and long-term outcomes

Primary kidney function was present in 19 patients (51.4%), DGF in 14 patients (37.8%), and primary non-function in 4 patients (10.8%) (Table 2). BPAR was detected in 5 patients (13.5%). The mean serum creatinine was 1.99 mg/dL (mean eGFR 36.4 mL/min/1.73 m^2) at discharge while it was 1.95 mg/dL (mean eGFR 35.6 mL/min/1.73 m^2) after a mean follow-up of 12 months. Serum creatinine and eGFR at discharge were significantly

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Table 1. Donor, recipient and transplantation data.

	Donor (n=36)	Recipient (n=37)
Age (years)	70.5±4.0 (70.0; 65–79)	67.9±2.6 (67.0; 65–76)
Gender (M/F) (%/%)	17/20 (45.9/54.1)	27/10 (73.0/27.0)
BMI [kg/m^2]	26.2±3.1 (26.0; 20.1–31.4)	26.8±4.4 (25.8; 21.0–41.9)
Obesity (%)	6 (16.7)	6 (16.2)
Smoking (%)	6 (16.7)	8 (21.6)
Comorbidities (%)		
Diabetes mellitus	2 (5.4)	8 (21.6)
Arterial hypertension	20 (54.1)	32 (86.5)
HCV	0	
Cause of death due to cerebrovascular event (%)	6 (16.7%)	
eGFR [ml/min./1.73 m^2]	73±19.9 (73; 25.4–104.8)	
KDRI	1.7±0.27 (1.67; 1.16-2.26)	
Time on dialysis (months)		46.0±23.4 (40.0; 10–113)
HLA mismatches		4.4±1.2 (5.0; 2–6)
Cold ischemia time (h: min)		9: 25±2: 52 (9: 15; 4: 00–16: 38)
Immunosuppression		
Steroids (%)		36 (97.3)
Cyclosporin A (%)		25 (67.6)
Tacrolimus (%)		12 (32.4)
Mycophenolat-mofetil (%)		37 (100)
Basiliximab (%)		36 (97.3)
rATG (%)		1 (2.7)

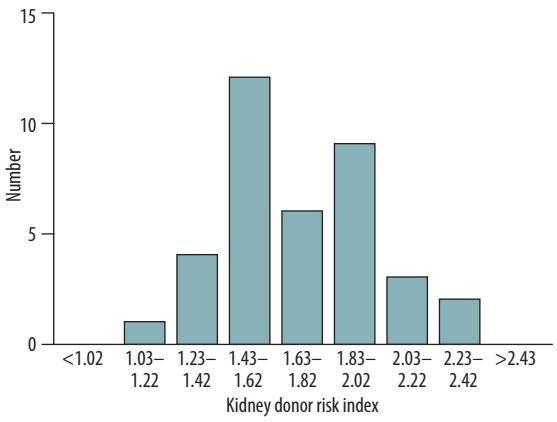

Figure 1. Distribution of Kidney Donor Risk Index in Eurotransplant Senior Program kidneys.

correlated to KDRI (P=0.033 and P=0.039; r=0.4 and r=-0.34, respectively, Figure 2).

Patient survival after 1-year and 5-years was 83.7% and 68.8%, respectively. Main cause of death was sepsis in 6 patients (46%). Smoking/history of smoking of the recipient was significantly associated with poor survival (P<0.001, Figure 3A). Obesity of the recipient (BMI >30 kg/m^2) was also associated with poor survival (one-year survival: 50.0% versus 90.3% for patients with BMI <30 kg/m^2, P=0.002).

In 10 patients (27%) graft loss occurred during the first year after transplantation because of acute rejection (10.8%), infectious complications (10.8%), or for unknown reasons (5.4%). No further graft loss occurred 1 year after transplantation until 5 years after transplantation. Accordingly, death-censored graft survival did not change 1 year and 5 years after

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Table 2. Short and long-term outcome.

Patient survival 1-yr/5-yr	83.7%/68.8%
Cause of death (n [%])	Sepsis (6; 16.2%)
	Lactacidosis (1; 2.7%)
	Intracranial hemorrhage (1; 2.7%)
	Sudden cardiac death (1; 2.7%)
	Acute basilar artery occlusion (1; 2.7%)
	Pulmonary embolism (1; 2.7%)
	Malignancy (1; 2.7%)
	Unknown (1; 2.7%)
Graft survival 1-yr/5-yr	73%/73%
Uncensored graft survival 1-yr/5-yr	64.2%/53.7%
Primary Function	51.4%
Delayed Graft Function	37.8%
Primary Non-Function	10.8%
Acute rejection	13.5%
Borderline changes	10.8%
sCR/eGFR at discharge	1.99 mg/dl (36.4 ml/min/1.73 m^2)
sCR/eGFR after 12 months	1.95 mg/dl (35.6ml/min/1.73 m^2)

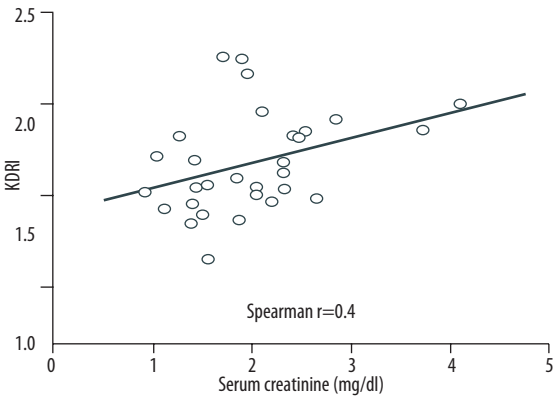

Figure 2. Correlation of Kidney Donor Risk Index (KDRI) and creatinine at discharge. There was a positive correlation of the KDRI with the serum creatinine of the recipients at discharge after kidney transplantation according to the European Senior Program.

transplantation and was 73%. Smoking of the donor was associated with a reduced death-censored graft survival (P=0.01, Figure 3B). Death-censored graft survival did not differ significantly between KDRI subgroups (Figure 3C). Uncensored graft survival was 64.2% after 1 year and 53.7% after 5 years. Death with a functioning graft was the most common reason for graft loss (7 out of 17; 41.2%). Uncensored graft survival differed significantly between KDRI subgroups (P=0.02, Figure 3D). The subgroups did not differ regarding recipient factors like BMI, smoking status, diabetes mellitus, recipient age, time on dialysis, HLA-mismatch, or cold ischemic time.

Discussion

Demographic changes and the increasing shortage of donor organs has resulted in an increase in older recipients and older donors during the past decade in the Eurotransplant region. Between 1991 and 2007, the percentage of recipients older than 65 years rose from 3.6% to 19.7%, whereas the percentage of kidney donors of age more than 55 years increased from 12.5% to 38.5% and donors of more than 64 years of age increased from 2.3% to 18.1% [1]. Based on regional allocations according to age, blood group, and waiting time, but independent of HLA matching, the ESP leads to significantly reduced waiting times and enhances the chance for older patients to receive a renal graft. In 2008, Frei et al. published the outcomes of more than 1400 patients transplanted in the ESP [4] representing the largest published cohort so far. More recent data regarding the outcome of patients in the ESP has been limited to few single center experiences [11–14].

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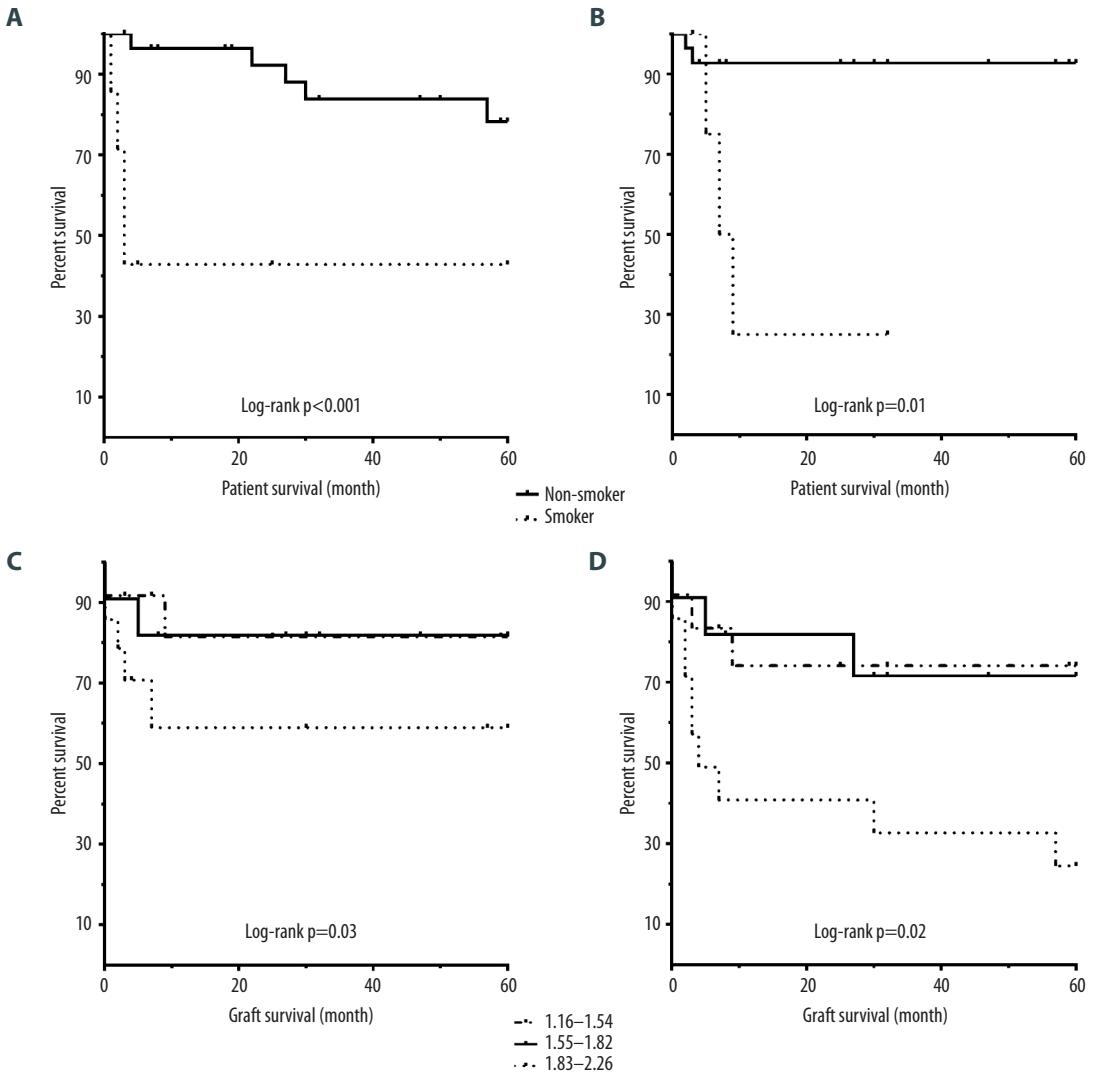

Figure 3. (**A**) Kaplan-Meier plots of patient survival by smoking status of the patients. Patient survival was decreased in smokers versus non-smokers. (**B**) Kaplan-Meier plots of death-censored graft survival by smoking status of the donor. Graft survival was reduced in donors with a history of smoking. (**C**) Kaplan-Meier plots of death-censored graft survival in 3 different Kidney Donor Risk Index (KDRI) subgroups [1.16–1.54 (n=12); 1.55–1.82 (n=11);1.83–2.26 (n=14)] showed a trend towards reduced death-censored graft survival in donors with a KDRI above 1.83. However, death-censored graft survival did not differ significantly between the 3 subgroups. (**D**) Kaplan Meier plots of uncensored graft survival in 3 different KDRI subgroups [1.1–1.54 (n=12); 1.55–1.82 (n=11); 1.83–2.26 (n=14)] showed that uncensored graft survival was reduced in donors with a KDRI above 1.83.

In these studies, patient and graft survival were comparable to our own results. Primary non-function seems to be high in our cohort (10.8%) but has also been observed in other ESP cohorts with similar rates ranging from 7.3% to 10.1% [11–14].

Most deaths in our cohort occurred during the first year after transplantation. The leading cause of death was infectious disease not only during the first year after transplantation but also afterwards. Infectious disease was also a relevant reason for graft loss. It is well established that older patients are at a high risk for infectious diseases [15]. However, other studies in ESP patients did not report an increased risk for infections [12,16]. These differing results might be related to the immunosuppressive regimen. In all of our patients quadruple immunosuppressive therapy was used, which could explain the higher rate of infections, especially during the first year after transplantation. However, infectious diseases themselves are a growing mortality factor, especially with increasing age in patients with

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renal replacement therapies [15]. On the other hand, the risk of acute rejection has to be considered. In our patients, BPAR of 13.5% was quite low compared to other ESP cohorts, which had rates of BPAR ranging up to 37% [11–14]. Still, in our ESP patients, it was a relevant factor accounting for graft loss in 10.8% of the patients in the first year after transplantation. Compared to the standard allocation and to renal transplantation in older recipients with kidneys from younger donors, Frei et al. observed higher rates of acute rejection in the ESP patients and lower patient and graft survival [4]. Acute rejection in older patients has been associated with poorer graft and patient survival [17,18]. This could be related to the increased immunogenicity of kidneys from older donors together with the HLA mismatch and the impaired ability of older kidneys to recover from tissue injury [17]. It is challenging to balance the risk of acute rejection with the risk of severe infection in administrating an appropriate immunosuppressive regimen in ESP patients.

To our knowledge, this is the first study evaluating ESP kidney transplantation and the KDRI. As expected in our ESP cohort donor, KDRI had a rather high variance. With a mean KDRI of 1.7, the estimated risk of graft failure from these donors was higher than in the 93% of kidney donors recovered. Graft outcome after the first year was lower, but similar after 5 years compared to the OPTN data [10] with respect to the mean KDRI. A higher KDRI was associated with inferior short-term kidney function as well as with reduced uncensored graft survival but not with censored graft survival in our analysis. However, death-censored graft survival was associated with the smoking status of the donor. To our knowledge, this is the first study to demonstrate that the smoking status of the donor might influence graft survival in ESP patients. Data on the effect of smoking of the donor on the outcome in deceased-donor kidney transplantation are sparse. Analysis of United States Renal Data System and United Network for Organ Sharing registry data from 38 000 kidney transplantations between 1995 and 1999 revealed a negative impact on graft and patient survival [19]. However, the analysis leading to the development of the KDRI did not demonstrate that smoking of the donor has a significant effect on graft failure [9].

We did not detect any association of KDRI with overall survival as we did with recipient factors such as obesity and smoking. It has been demonstrated in previous studies that smoking of the recipient is associated with an increased risk for graft loss [20], DGF [21], and reduced patient survival; whereas the effect of obesity on patient survival is not clear [22,23].

Limitations of our study were the retrospective design and the small sample size of our cohort. Between KDRI subgroups, we did not observe significant differences regarding recipient factors like age, BMI, smoking, etc. However, further confounding factors could not be ruled out, thus leading to potential bias. Although the KDRI has been established and validated in USA kidney transplantation programs, its prognostic value for kidney transplantation in European countries and the Eurotransplant region is unclear. Recently, validation of the KDRI for kidney transplantation in The Netherlands showed comparable survival probabilities between the Dutch and the USA cohorts [24]. Further results showed that an increase in recipient age decreased the effect of KDRI on graft survival, which has also been shown by others [25]. In another recently published USA study, a survival benefit was observed in recipients older than 60 years of age with high KDPI allografts over 85% compared with patients on the wait list [7]. However, comparison of KDRI subgroups within our ESP cohort revealed significant reduced graft survival with a KDRI score above 1.83. Outcomes of ESP kidney transplantations might be improved by consideration of KDRI. Further studies are needed to test the prognostic value in the setting of an old-for-old kidney transplantation programs.

Conclusions

Evaluation of kidney transplantation in the ESP at our institution showed that in this group of high-risk donors, a high KDRI score was associated with reduced long-term and short-term outcomes. Decisions regarding kidney transplantation of older recipients are often very difficult. Multimorbidity of older recipient makes it challenging to decide who would benefit from kidney transplantation. Also, the donor quality has significant interactions with recipient characteristics. The KDRI might be helpful in ESP kidney transplantation to predict clinical outcomes.

Acknowledgements

This work is part of the thesis of D. Lohmann.

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References:

1. de Fijter JW: An old virtue to improve senior programs. Transpl Int, 2009: 22(3): 259–68
2. Beckurts UT, Stippel D, Pollok M et al: Single-center experience with the "Old for Old" program for renal transplantation. Transplant Proc, 2001: 33(7–8): 3779–80
3. Smits JM, Persijn GG, van Houwelingen HC et al: Evaluation of the Eurotransplant Senior Program. The results of the first year. Am J Transplant, 2002: 2(7): 664–70
4. Frei U, Noeldeke J, Machold-Fabrizii V et al: Prospective age-matching in elderly kidney transplant recipients – a 5-year analysis of the Eurotransplant Senior Program. Am J Transplant, 2008: 8(1): 50–57
5. Oniscu GC, Brown H, Forsythe JL: Impact of cadaveric renal transplantation on survival in patients listed for transplantation. J Am Soc Nephrol, 2005: 16(6): 1859–65
6. Wolfe RA, Ashby VB, Milford EL et al: Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med, 1999: 341(23): 1725–30
7. Jay CL, Washburn K, Dean PG et al: Survival benefit in older patients associated with earlier transplant with high KDPI kidneys. Transplantation, 2017: 101(4): 867–72
8. Port FK, Bragg-Gresham JL, Metzger RA et al: Donor characteristics associated with reduced graft survival: An approach to expanding the pool of kidney donors. Transplantation, 2002: 74(9): 1281–86
9. Rao PS, Schaubel DE, Guidinger MK et al: A comprehensive risk quantification score for deceased donor kidneys: The kidney donor risk index. Transplantation, 2009: 88(2): 231–36
10. Organprocurement and Transplantation Network (OPTN). A Guide to Calculating and Interpreting the Kidney Donor Profile Index (KDPI). 2012. Available from *https://optn.transplant.hrsa.gov/media/1512/guide_to_calculating_interpreting_kdpi.pdf*
11. Bahde R, Vowinkel T, Unser J et al: Prognostic factors for kidney allograft survival in the Eurotransplant Senior Program. Ann Transplant, 2014: 19: 201–9
12. Bentas W, Jones J, Karaoguz A et al: Renal transplantation in the elderly: Surgical complications and outcome with special emphasis on the Eurotransplant Senior Programme. Nephrol Dial Transplant, 2008: 23(6): 2043–51
13. Giessing M, Fuller TF, Friedersdorff F et al: Outcomes of transplanting deceased-donor kidneys between elderly donors and recipients. J Am Soc Nephrol, 2009: 20(1): 37–40
14. Jacobi J, Beckmann S, Heller K et al: Deceased donor kidney transplantation in the Eurotransplant Senior Program (ESP): A single-center experience from 2008 to 2013. Ann Transplant, 2016: 21: 94–104
15. Meier-Kriesche HU, Ojo AO, Hanson JA et al: Exponentially increased risk of infectious death in older renal transplant recipients. Kidney Int, 2001: 59(4): 1539–43
16. Fabrizii V, Kovarik J, Bodingbauer M et al: Long-term patient and graft survival in the eurotransplant senior program: A single-center experience. Transplantation, 2005: 80(5): 582–89
17. de Fijter JW, Mallat MJ, Doxiadis II et al: Increased immunogenicity and cause of graft loss of old donor kidneys. J Am Soc Nephrol, 2001: 12(7): 1538–46
18. Heldal K, Hartmann A, Leivestad T et al: Clinical outcomes in elderly kidney transplant recipients are related to acute rejection episodes rather than pretransplant comorbidity. Transplantation, 2009: 87(7): 1045–51
19. Lin SJ, Koford JK, Baird BC et al: Effect of donors' intravenous drug use, cigarette smoking, and alcohol dependence on kidney transplant outcome. Transplantation, 2005; 80(4): 482–86
20. Hurst FP, Altieri M, Patel PP et al: Effect of smoking on kidney transplant outcomes: Analysis of the United States Renal Data System. Transplantation, 2011: 92(10): 1101–7
21. Gavela Martinez E, Pallardo Mateu LM, Sancho Calabuig A et al: Delayed graft function after renal transplantation: An unresolved problem. Transplant Proc, 2011; 43(6): 2171–73
22. Chang SH, Coates PT, McDonald SP: Effects of body mass index at transplant on outcomes of kidney transplantation. Transplantation, 2007: 84(8): 981–87
23. Ahmadi SF, Zahmatkesh G, Streja E et al: Body mass index and mortality in kidney transplant recipients: A systematic review and meta-analysis. Am J Nephrol, 2014: 40(4): 315–24
24. Peters-Sengers H, Heemskerk MBA, Geskus RB et al: Validation of the Prognostic Kidney Donor Risk Index (KDRI) scoring system of deceased donors for renal transplantation in the Netherlands. Transplantation, 2018: 102(1): 162–70
25. Heaphy EL, Goldfarb DA, Poggio ED et al: The impact of deceased donor kidney risk significantly varies by recipient characteristics. Am J Transplant, 2013; 13(4): 1001–11

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