Original Article

Korean J Transplant 2021;35:86-92
https://doi.org/10.4285/kjt.21.0011

KOREAN JOURNAL OF TRANSPLANTATION

pISSN 2671-8790
eISSN 2671-8804

Development of predictive score for post-transplant survival based on pre-transplant recipient characteristics

Tai Yeon Koo[1,]*, Joongyub Lee[2,]*, Jaeseok Yang[3,4]

[1]Department of Internal Medicine, Seongnam Citizens Medical Center, Seongnam, Korea
[2]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea
[4]Transplantation Center, Seoul National University Hospital, Seoul, Korea

Background: The new kidney allocation system in the United States has introduced longevity matching, which gives priority to allocating the best quality organs to wait-listed candidates with the longest predicted survival for the efficient utilization of organs that are of limited availability. The estimated post-transplant survival (EPTS) score was developed in the United States to risk-stratify all wait-listed patients. However, prognostic indices used in Western countries were derived from data that may be different for Korea and do not necessarily reflect prognostic values for Korean deceased donor kidney transplantation. Prognostic indices for Korean wait-listed candidates therefore need to be developed from Korean data.

Methods: We analyzed 6,731 adult solitary kidney transplant patients for candidate risk prediction using the national data from the Korean Network for Organ Sharing (KONOS) and National Health Insurance Data Sharing Service (NHISS). Cox regression analysis was used to model the risk of patient death.

Results: The Korean EPTS (K-EPTS) score was developed based on four recipient parameters (age, diabetes mellitus, hepatitis C virus, and duration of dialysis) that showed a significant association with post-transplant survival. K-EPTS scores showed good discrimination (C-statistics: 0.690; 95% confidence interval, 0.666–0.715). Moreover, the ability of the K-EPTS score to discriminate patient survival was better than that of the EPTS according to the criteria of the United Network for Organ Sharing (US-EPTS) score (P<0.001).

Conclusions: The K-EPTS score, which was developed based on Korean national data, is expected to contribute to the assessment of recipient prognosis and efficient utilization of deceased donor kidneys.

Keywords: Kidney transplantation; Prognosis; Survival; Transplant recipient

Received May 20, 2021
Revised June 16, 2021
Accepted June 20, 2021

Corresponding author: Jaeseok Yang
Transplantation Center, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-4128
Fax: +82-2-2072-4129
E-mail: jcyjs@snu.ac.kr
*These authors contributed equally to this work.

HIGHLIGHTS

- **Korean estimated post-transplant survival (K-EPTS) score was developed based on four parameters (age, diabetes mellitus, hepatitis C virus, and dialysis duration).**
- **K-EPTS score showed good discrimination (C-statistics: 0.690; 95% confidence interval, 0.666–0.715).**
- **The K-EPTS score could assess recipient prognosis after kidney transplantation in Korea.**
- **The K-EPTS score could contribute to efficient utilization of deceased donor kidneys.**

INTRODUCTION

A balance between equitable distribution and optimal utilization is necessary in organ allocation systems for deceased donor transplantations. A key feature of the new kidney allocation system in the US is the preferential allocation of best quality organs to wait-listed candidates with the longest predictive survival for efficient utilization of limited organ sources [1,2]. Several prognostic indices for deceased donor kidneys, including the kidney donor risk index and the kidney donor profile index (KDPI), have been developed for deceased donor kidney transplantation (DDKT) and are used for their allocation [1,3,4]. Furthermore, the estimated post-transplant survival (EPTS) score was developed in the US to risk-stratify all wait-listed patients [5]. The EPTS score considers patient age, prior organ transplantation, diabetes, and dialysis duration [6]. The EPTS score and KDPI have been introduced to the new kidney allocation system in the United States, and donor kidneys with a KDPI of 20% or less are allocated to the wait-listed candidates with an EPTS score of 20% or less for longevity matching [1,7].

Recently, the DDKT program has been activated in Korea. However, the waiting time in Korea is still much longer than in Western countries, because the increasing rate of end-stage kidney disease patients outnumbers organ donation rates [8-10]. Therefore, efficient and maximal utilization of the limited number of deceased donor organs is a very important issue in Korea. Therefore, adequate prognostic indices for wait-listed recipients as well as donor kidneys must be developed based on Korean data. This is because prognostic indices developed in Western countries, which have different characteristics from those developed Korea, do not necessarily have equivalent prognostic values for Korean DDKT. Herein, we have developed a predictive score for post-DDKT patient survival based on pre-transplant wait-listed candidate characteristics using the Korean nationwide database.

METHODS

This study was approved by the Institutional Review Board (IRB No. E-1906-064-1040) of Seoul National University Hosptial and performed in accordance with the Helsinki Declaration (2000) and the Declaration of Istanbul (2008). The IRB waived the requirement for informed consent because this was a retrospective study.

Study Population

We enrolled a nationwide cohort to develop a predictive model for recipient prognosis. The study used Korean Network for Organ Sharing (KONOS) data for all wait-listed candidates and transplant recipients, supplemented with comorbidity conditions (hypertension, diabetes), mortality information, and information on dialysis patients from the National Health Insurance Data Sharing Service (NHISS). Between January 1, 2010, and December 31, 2018, 7,166 end-stage kidney disease patients underwent DDKT in Korea. Recipients were excluded if they were under 18 years of age (n=95); underwent multi-organ transplantation at the same time as kidney transplantation (n=294); or had

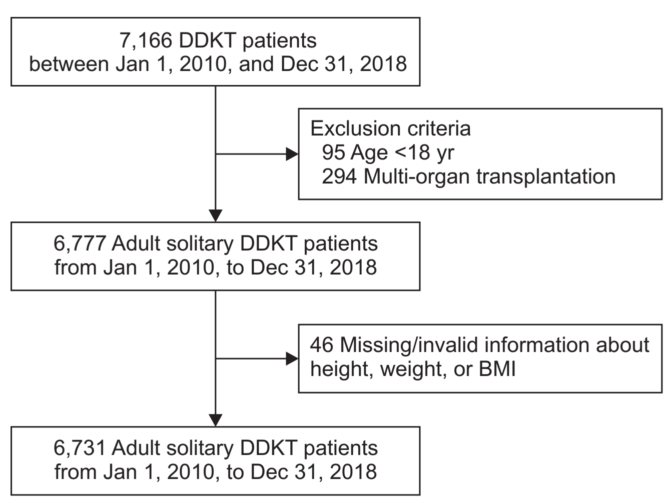

Fig. 1. Study profile. DDKT, deceased donor kidney transplantation; BMI, body mass index.

missing/invalid information about height, weight, or body mass index (n=46) (Fig. 1).

Outcomes

The primary outcome was the patient's death. Data on deaths were obtained from the Ministry of the Interior and Safety and the NHISS. Patient survival after kidney transplantation was calculated using the time from kidney transplantation to death and censoring at the end of the study.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation, and categorical variables are expressed as percentages or frequencies. Mortality was estimated using the Kaplan-Meier method, and comparisons between groups were performed using a log-rank test. Statistical significance was defined as a two-tailed P-value of <0.05. To predict recipient prognosis, a Cox regression model was fitted to estimate the relative rate of mortality independently associated with recipient factors. Recipient factors included age; sex; weight; height; comorbidity conditions such as hypertension or diabetes mellitus; duration of dialysis; presence of hepatitis B virus (HBV) based on HBV surface antigen; and presence of hepatitis C virus (HCV) based on anti-HCV antibody. We determined model discrimination using a concordance (C) statistic to discriminate between subjects with different survival times. The value of C ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination) [11]. The discrimination ability of the Korean estimated post-transplant survival (K-EPTS) score was compared with that of the EPTS according to the criteria of the United Network for Organ Sharing (US-EPTS) score using Uno's concordance test [12]. All analyses were conducted using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. Baseline characteristics of the study population

Recipient parameter	Value (n=6,731)
Age (yr)	49.6±11.1
Female sex	2,507 (37.2)
Prior solid organ transplant	459 (6.8)
Hypertension	6,550 (97.3)
Diabetes	5,412 (80.4)
Mode of dialysis	
Hemodialysis	5,146 (76.5)
Peritoneal dialysis	1,585 (23.5)
Duration of dialysis (yr)	4.0±2.7
HBV positivity	410 (6.1)
HCV positivity	100 (1.5)
Death	542 (8.1)
Graft loss	438 (6.5)

Values are presented as mean±standard deviation or number (%).
HBV, hepatitis B virus; HCV, hepatitis C virus.

RESULTS

Baseline Characteristics of Study Population

The study population included 6,731 adult solitary DDKT recipients. Patients were followed up from the time of transplant until the earliest death, or until they were lost to follow-up, or until the conclusion of the observational period. The baseline characteristics of the patients are shown in Table 1. The mean age of recipients at transplantation was 49.6 years, and the majority of patients were male (62.8%). A history of prior solid organ transplantation was present in 459 patients (6.8%), 5,146 (76.5%) underwent hemodialysis before transplantation, and the mean duration of dialysis before transplantation was 4 years. Diabetes mellitus was present as a comorbidity in 5,412 (80.4%) patients, and 100 (1.5%) patients had HCV. There were 542 (8.1%) deaths and 438 (6.5%) graft losses among the 6,731 recipients in this cohort.

Development of the Recipient Prognosis Prediction Score

All available recipient-related variables potentially associated with mortality were included in the initial model. Our final model included recipient age of 50 years or older, diagnosis of diabetes mellitus as a comorbidity, duration of dialysis, and positive HCV, which were independently associated with mortality. The association between these factors and patient survival time after transplantation was determined by estimating a multivariable Cox proportional hazards regression model (Table 2). Based on this final model (Table 2), the K-EPTS score was developed as follows:

K-EPTS=0.0152×[age−50 (years)]+0.4192×I[diabetes]+0.6746×I[HCV]−0.0678×[dialysis duration (years)]+0.0393×[age−50 years]×I[diabetes]+0.0046×[age−50 (years)]×[dialysis duration (years)], where age and dialysis duration are measured in years and I(A) is set to 1 if condition A is applied to the donor kidney of interest, otherwise it is set to 0.

To determine a candidate's K-EPTS score, the raw

Table 2. Relative mortality risk after DDKT according to recipient-associated factors

Variable	Univariate analysis		Multivariate analysis		
	HR	P-value	HR	95% CI	P-value
Recipients parameter					
Age ≥50 yr	2.922	<0.001	2.773	2.266–3.393	<0.001
Sex (female)	1.749	<0.001			
Weight (kg)	1.017	0.001			
Height (cm)	0.995	0.159			
Hypertension	39.743	0.085			
Diabetes	2.758	<0.001	1.713	1.287–2.279	<0.001
Duration of dialysis (yr)	0.999	0.012	0.953	0.918–0.990	0.013
Prior organ transplantation	1.067	0.110			
HBV	1.799	0.153			
HCV	3.648	0.008	2.004	1.154–3.479	0.014
Positive PRA I	0.949	0.619			
Positive PRA II	0.946	0.707			

DDKT, deceased donor kidney transplantation; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; PRA, panel reactive antibody.

K-EPTS score was calculated and converted to a cumulative percentage using the K-EPTS mapping table (Supplementary Table 1), which was based on all adult wait-listed patients for DDKT on July 31, 2019 (n=19,742). Supplementary Fig. 1 showed that distribution of raw K-EPTS scores in the reference population ranged from −4.23 to 2.64 (median, 0.12). Lower K-EPTS scores were associated with higher expected post-transplant longevity.

Candidate Risk Prediction Model Discrimination and Performance

When the EPTS score according to the criteria of the United Network for Organ Sharing (UNOS) was applied to our cohort, candidates with lower EPTS scores (≤20%) showed better patient survival than those with higher EPTS scores (>20%) (Fig. 2A). Similarly, candidates with K-EPTS scores less than or equal to 20% showed better patient survival than those with K-EPTS scores greater than 20% (Fig. 2B). Next, we determined the discrimination ability of the established EPTS scoring models by calculating the discrimination C statistics. The discrimination C statistic of the K-EPTS score was 0.690 (95% confidence interval, 0.666–0.715) (Table 3), indicating that our prediction score for mortality provided acceptable discrimination. Moreover, the ability of the new K-EPTS score to discriminate post-transplant survival was better than that of the US-EPTS score (P<0.001) (Table 3).

DISCUSSION

In this study, we developed post-transplant prognosis-prediction models based on recipient parameters obtained from Korean nationwide databases (KONOS and NHISS). From these prediction models, we propose a new K-EPTS scoring system to assess the post-transplant prognosis of wait-listed candidates for DDKT.

The new kidney allocation system in the US is basically a longevity matching allocation system, where the best-quality kidneys with the lowest KDPI are allocated to recipients with the lowest EPTS scores, that is, with the longest predicted post-transplant survival [1,2]. However, the US-EPTS scoring system is derived from the Scientific Registry of Transplant Recipients and might not be the best prognostic tool for Korean DDKT, which exhibit different characteristics, such as shorter cold ischemic time and longer waiting time. Therefore, this study developed the K-EPTS score, a prognostic prediction score based on Korean recipient characteristics, obtained from the Korean KONOS and NHISS nationwide databases. The K-EPTS score considers the candidate's age, presence of diabetes mellitus, duration of dialysis, and HCV positivity, which were selected based on their independent and significant association with post-transplant patient survival. The K-EPTS score shares candidate age, diabetes mellitus status, and duration of dialysis with the US-EPTS score, whereas the K-EPTS score includes HCV instead of prior

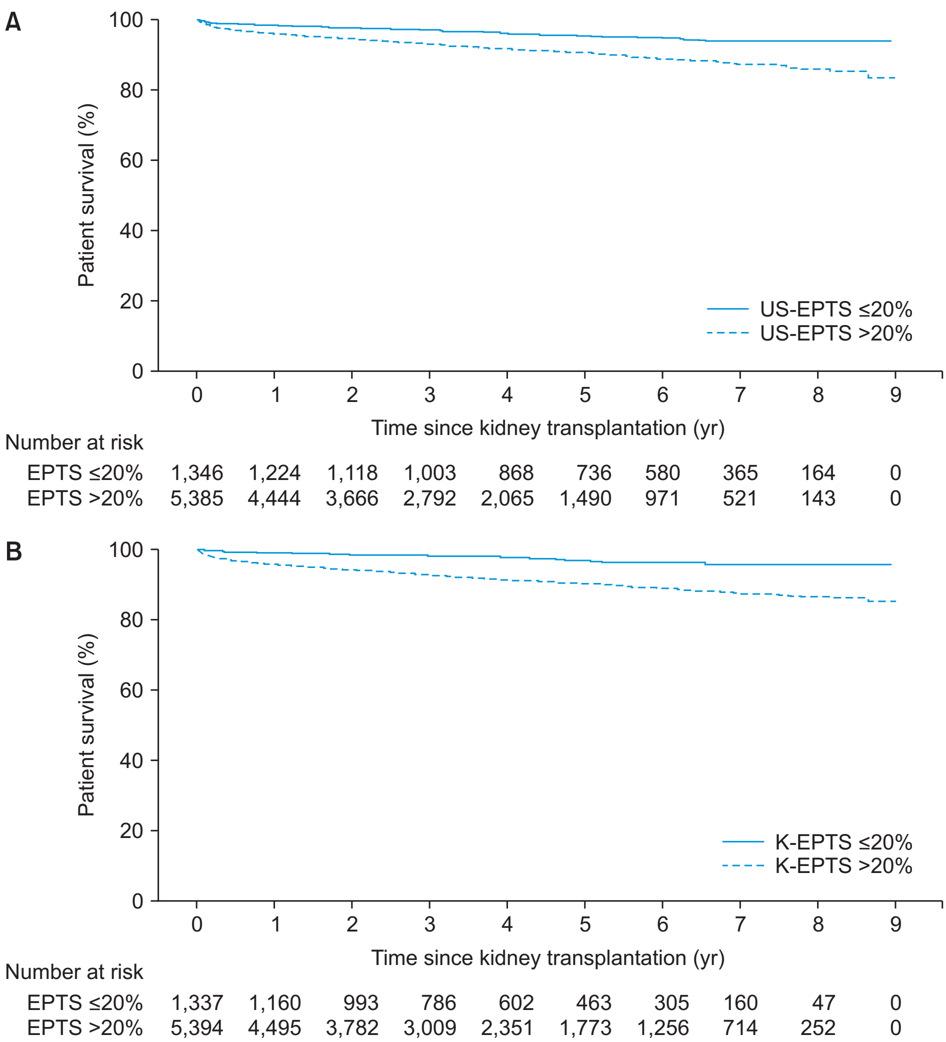

Fig. 2. Patient survival in deceased donor kidney transplantation by US-EPTS or K-EPTS scores. (A) The lower US-EPTS score group (≤20%) showed a significant survival benefit as compared with the higher US-EPTS score group (>20%) (P<0.001). (B) The lower K-EPTS score group (≤20%) showed a significant survival benefit as compared with the higher K-EPTS score group (>20%) (P<0.001). US-EPTS, estimated post-transplant survival according to the criteria of the United Network for Organ Sharing; K-EPTS, Korean estimated post-transplant survival.

Table 3. Discrimination C statistics for K-EPTS and US-EPTS

Model	Discrimination C	95% CI of discrimination C	Differences in Uno's concordance statistics
K-EPTS <20%	0.690	0.666–0.715	Reference
US-EPTS <20%	0.652	0.626–0.679	<0.001

K-EPTS, Korean estimated post-transplant survival; US-EPTS, estimated post-transplant survival according to the criteria of United Network for Organ Sharing; C, concordance; CI, confidence interval.

transplantation, in contrast to the US-EPTS score. The K-EPTS score, derived from Korean data, showed better discrimination ability for post-transplant survival in Korean DDKT than the US-EPTS score.

The discrimination C statistic of the K-EPTS score was 0.690, suggesting that there are additional predictors that may improve the ability to discriminate outcomes. However, we need a balance between simple decision-making from easily obtained predictors, which are available in a real clinical setting, versus better predictive power. In this sense, this 4-parameter-based K-EPTS scoring system is worth implementing for assessing recipient's prognosis and making decisions about the allocation of deceased donor kidneys and acceptance of deceased donor kidney offers.

In the United States, a tool has recently been proposed

https://doi.org/10.4285/kjt.21.0011

to estimate the 5-year and 10-year post-transplant survival rates by combining the KDPI and EPTS score [13]. This tool also provides a calculator to predict survival benefits from DDKT versus waiting. The estimated survival rates and predicted survival benefits derived from this tool could be very helpful for individualized decision-making on kidney offers in clinical practice [13]. Further studies are needed to estimate the survival benefits of DDKT versus waiting according to the K-KDPI and K-EPTS score.

The Korean KDPI system, based on data obtained from Korean nationwide databases, has been officially adopted in the KONOS and will be used for national organ allocation from late 2021. However, there is a need for more discussion, both in society at large and in the transplantation community, about how the K-EPTS score could be incorporated into the national organ allocation system. For efficient utilization of deceased donor organs, good quality organs had better be allocated to wait-listed candidates with better expected post-transplant survival. However, equitable distribution is also an important consideration in the allocation of deceased donor organs that are of limited availability [14]. We therefore need social consensus for an appropriate balance between efficient utilization and equity. We hope that active discussion in our society will lead to social consensus and the development of a new allocation policy, which incorporates the K-EPTS score.

This study has a few limitations. Comorbidity data in our study were obtained from the NHISS, which may have resulted in comorbid conditions being over-reported. Most importantly, our prediction model has not been validated in independent cohorts. Future studies need to validate the K-EPTS score in other cohorts. Nevertheless, this study has important implications for the field of DDKT. The K-EPTS score was developed from Asian nationwide data with different characteristics from Western data, which have been used in most studies [15,16]. Therefore, the development and application of the K-EPTS scoring system for Korea could contribute to the development of new tailored EPTS scoring system in each country based on country-specific data.

In conclusion, the K-EPTS score, based on Korean nationwide data, is expected to contribute to the assessment of recipient prognosis and efficient utilization of deceased donor kidneys.

ACKNOWLEDGMENTS

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding/Support

This study was supported by research grant from the Korean Society for Transplantation (2021-00-01004-012) and the Research Program funded by the Korean Centers for Disease Control and Prevention (2019-E8201-00).

ORCID

Tai Yeon Koo https://orcid.org/0000-0003-2014-7723
Joongyub Lee https://orcid.org/0000-0003-2784-3772
Jaeseok Yang https://orcid.org/0000-0002-5378-7797

Author Contributions

Conceptualization: TYK, JY. Data curation & Formal analysis: JL. Funding acquisition: JY. Methodology: TYK, JY. Writing–original draft: TYK, JY. Writing–review & editing: all authors.

Additional Contributions

We thank Soon Il Kim as the former chairman and Jongwon Ha as the current chairman of the Korean Society for Transplantation, for supporting this study. We also thank National Health Insurance Service for sharing database.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.4285/kjt.21.0011.

REFERENCES

1. United Network for Organ Sharing (UNOS). OPTN policy 3.5: allocation of deceased kidneys [Internet]. Richmond, VA: UNOS; 2021 [cited 2021 Jun 21]. Available from: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf.
2. Organ Procurement and Transplantation Network (OPTN). Proposal to substantially revise the national kidney allocation system [Internet]. Richmond, VA: U.S. Department of Health and Human Services; 2012 [cited 2021 Jun 21]. Available from: http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_311.

pdf.
3. 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;88:231-6.
4. 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;74:1281-6.
5. Molnar MZ, Nguyen DV, Chen Y, Ravel V, Streja E, Krishnan M, et al. Predictive score for posttransplantation outcomes. Transplantation 2017;101:1353-64.
6. Organ Procurement and Transplantation Network (OPTN). A guide to calculating and interpreting the Estimated Post-Transplant Survival (EPTS) score used in the kidney allocation system (KAS) [Internet]. Richmond, VA: U.S. Department of Health and Human Services; 2020 [cited 2021 Jun 21]. Available from: https://optn.transplant.hrsa.gov/media/1511/guide_to_calculating_interpreting_epts.pdf.
7. Friedewald JJ, Samana CJ, Kasiske BL, Israni AK, Stewart D, Cherikh W, et al. The kidney allocation system. Surg Clin North Am 2013;93:1395-406.
8. Min SI, Ahn C, Han DJ, Kim SI, Chung SY, Lee SK, et al. To achieve national self-sufficiency: recent progresses in deceased donation in Korea. Transplantation 2015;99:765-70.
9. Orlandi PF, Huang J, Fukagawa M, Hoy W, Jha V, Oh KH, et al. A collaborative, individual-level analysis compared longitudinal outcomes across the International Network of Chronic Kidney Disease (iNETCKD) cohorts. Kidney Int 2019;96:1217-33.
10. Korean Network for Organ Sharing (KONOS). 2019 Annual data report [Internet]. Seoul: KONOS; 2020 [cited 2021 Jun 21]. Available from: http://konos.go.kr.
11. Pencina MJ, D'Agostino RB Sr. Evaluating discrimination of risk prediction models: the C statistic. JAMA 2015;314:1063-4.
12. Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. Stat Med 2011;30:1105-17.
13. Bae S, Massie AB, Thomas AG, Bahn G, Luo X, Jackson KR, et al. Who can tolerate a marginal kidney? Predicting survival after deceased donor kidney transplant by donor-recipient combination. Am J Transplant 2019;19:425-33.
14. Li B, Cairns JA, Johnson RJ, Watson CJ, Roderick P, Oniscu GC, et al. Equity-efficiency trade-offs associated with alternative approaches to deceased donor kidney allocation: a patient-level simulation. Transplantation 2020;104:795-803.
15. Coca A, Arias-Cabrales C, Valencia AL, Burballa C, Bustamante-Munguira J, Redondo-Pachón D, et al. Validation of a survival benefit estimator tool in a cohort of European kidney transplant recipients. Sci Rep 2020;10:17109.
16. Clayton PA, McDonald SP, Snyder JJ, Salkowski N, Chadban SJ. External validation of the estimated post-transplant survival score for allocation of deceased donor kidneys in the United States. Am J Transplant 2014;14:1922-6.

https://doi.org/10.4285/kjt.21.0011