HHS Public Access

Author manuscript

Transplantation. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Transplantation. 2017 June ; 101(6): 1353–1364. doi:10.1097/TP.0000000000001326.

Predictive Score for Posttransplantation Outcomes

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Abstract

Background—Most current scoring tools to predict allograft and patient survival upon kidney transplantion(Tx) are based on variables collected posttransplantation. We developed a novel score to predict posttransplant outcomes using pretransplant information including routine laboratory data available prior to or at the time of transplantation.

Methods—Linking the 5-year patient data of a large dialysis organization to the SRTR, we identified 15,125 hemodialysis patients who underwent first deceased Tx. Prediction models were developed using Cox models for (a)mortality, (b)allograft loss(death censored) and (c)combined death or transplant failure. The cohort was randomly divided into a two-thirds set(N_d=10,083) for

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Conflict of interest: None.

Disclosures
CPK and KKZ are employees of the Department of Veterans affairs. MK is employees of DaVita. Opinions expressed in this paper are those of the authors' and do not necessarily represent the opinion of the Department of Veterans Affairs. The results of this paper have not been published previously in whole or part. **This work has been presented as oral presentation at ASN Kidney Week 2015.**

model development and a one-third set(N_V=5,042) for validation. Model predictive discrimination was assessed using the index of concordance, or C statistic, which accounts for censoring in time-to-event models(a–c). We used the bootstrap method to assess model overfitting and calibration using the development dataset.

Results—Patients were 50±13 years old and included 39% women, 15% African-Americans and 36% diabetics. For prediction of post-transplant mortality and graft loss, 10 predictors were used (recipients' age, cause and length of ESRD, hemoglobin, albumin, selected comorbidities, race and type of insurance as well as donor age, diabetes status, extended criteria donor kidney(ECD), and number of HLA mismatches). The new model (www.TransplantScore.com) showed the overall best discrimination(C-statistics:0.70(95%CI: 0.67–0.73) for mortality;0.63(95%CI: 0.60–0.66) for graft failure;0.63(95%CI: 0.61–0.66) for combined outcome).

Conclusions—The new prediction tool, using data available prior to the time of transplantation, predicts relevant clinical outcomes and may perform better to predict patients' graft survival than currently used tools.

Introduction

Kidney transplantation is the treatment of choice for patients with end stage renal disease (ESRD).[1] One of the main challenges in transplant medicine is prioritizing the best recipients for a kidney transplant according to criteria which would maximize both patient and kidney allograft survival. Previous studies have identified risk factors of patient mortality and graft failure in kidney transplant recipients, including donor kidney status (living vs. deceased), age and race, as well as recipient age, smoking status, race-ethnicity, malnutrition inflammation score, comorbidities, acute rejection, delayed graft function, circulating angiopoietin, sleep apnea, and posttransplant proteinuria.[2–16] However, a number of these risk factors are measured in the posttransplant period. Studies done by our group have previously identified several pretransplantation risk factors such as lower muscle mass and serum albumin level, higher body mass index and alkaline-phosphotase level, hemodialysis vs. peritoneal dialysis modality, poor glycemic control and higher erythropoietin stimulating agent responsiveness index associated with higher risk of adverse outcomes posttransplant such as delayed graft function, allograft loss or death.[15,17–25] Physicians often have to urgently select a proper candidate for a kidney transplant using available data. Tools which can inform physicians in the decision-making process by predicting the recipient's chance of overall and allograft survival are needed.

Several prediction scores and calculations have been developed in the last decades to assist physicians.[26–41] However, all of these scores are partially based on data obtained after kidney transplantation,[30,38–41] or used data from the last century,[29,34,38] when the practice and transplant outcomes were different or used incorrect methodology[26]. Moreover, most of these studies had defined death censored allograft failure as the primary outcome of interest and only some of them have focused on the outcome of patient/recipient survival.[38–40] To this end, the currently used Estimated PostTransplant Survival (EPTS) score in the United States allocation system was created and is implemented to predict recipients' survival.[36,37]

To our knowledge, no prediction score has been developed to predict both allograft loss and transplant recipient death based only on data available at the time of transplantation in the 21st century. The purpose of the present study was to develop and robustly validate scores predictive of death-censored allograft failure and recipients' death up to 5 years posttransplantation based on variables which are available at the time of transplantation for kidney transplant recipients across the United States in the 21st century.

Materials and Methods

Data Source and Cohort Definition

We linked data of all kidney transplant recipients listed in the Scientific Registry of Transplant Recipients (SRTR) to a list of individuals with end stage renal disease who underwent maintenance hemodialysis treatment from July 2001 to June 2006 in 1 of the outpatient dialysis facilities of a large dialysis organization (DaVita Inc, prior to its acquisition of former Gambro dialysis facilities). The study was approved by the Institutional Review Committees of Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California Irvine Medical Center, University of Washington, University of Tennessee Health Science Center and DaVita Clinical Research. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Clinical and Demographic Measures

The creation of the national DaVita hemodialysis patient cohort has been described previously.[42–46] Demographic data and details of medical history were collected, with information on age, gender, race, type of insurance, marital status, presence of diabetes, height, posthemodialysis dry weight (to calculate averaged body mass index [BMI]) and dialysis vintage. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the day of kidney transplantation. Preexisting comorbid conditions, such as coronary artery disease (CAD), peripheral vascular disease (PAD), were obtained by linking the DaVita database to the Medical Evidence Form 2728 of the United States Renal Data System (USRDS).[47] The transplantation related data, such as donor characteristics, recipients' viral serology, cold ischemic time and HLA mismatches, were collected from SRTR.

Laboratory Measures

Blood samples were drawn using uniform techniques in all of the DaVita dialysis clinics and were transported to a central laboratory in Deland, Florida, typically within 24 hours. All laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly, including serum urea nitrogen, creatinine, albumin, phosphorus and alkaline phosphatase. Hemoglobin was measured at least monthly in essentially all patients and weekly to bi-weekly in most patients. Most blood samples were collected predialysis with the exception of the postdialysis serum urea nitrogen to calculate urea kinetics. The pretransplantation laboratory data from the last quarter before transplantation were used in our calculations.

Statistical Methods

Characteristics of the study cohort, including all predictors, are summarized as means ± standard deviation (SD) or proportions for continuous and categorical variables, respectively. Prediction models were developed for 3 outcomes: (a) mortality, (b) allograft loss (death censored) and (c) a combined outcome of death or allograft loss (a or b), using Cox proportional hazards models. Study follow-up was censored at the end of the study (October 29th, 2007). The cohort (N=15,125) (Figure 1) was divided into a two-thirds training/development set (N_d=10,083) and a one-third test/validation set (N_v=5,042). We used multiple imputation (10 imputations) for continuous missing values (27–28%) in the development dataset of recipients' albumin, alkaline phosphatase, hemoglobin and phosphorus. Missing values (20%) in organ preservation total cold ischemic time were also imputed. Candidate predictors were based on clinical considerations and those used in previous studies.[15,19–25] Final models with reduced number of predictors were obtained using backward-selection based on Akaike's information criterion (AIC) since it has better statistical properties in variable selection compared to p-value based selection[48] and it avoids arbitrary and ineffective selection rules based on p-values. To address potential model overfitting (optimism) and also for model calibration, we estimated a linear shrinkage factor (γ) using the bootstrap method applied to the development dataset. Briefly, for each of the 100 bootstrap datasets, the exact development steps described above (Cox regression with AIC backward selection) were fitted. Then the outcome was regressed on the prognostic score or linear predictor (LP; $X\beta$) in a univariate Cox regression. The LP was calculated using the fitted bootstrap coefficients (β) for each patient in the original development dataset. The process was repeated to obtain 3 shrinkage factors corresponding to the 3 outcomes. The shrinkage factor γ was used to adjust the final Cox prediction models to correct for model overoptimism as further detailed below.[48–51] Furthermore, model calibration was assessed by a group-based goodness-of-fit (GOF) test developed for survival model[52] for each prediction model. Briefly, the population was divided into deciles (groups) of the risk score and the group-based GOF test provides an overall assessment of model calibration as well as for each group. Calibration plot for 5-year survival was also examined for each model.

Model prediction was assessed using internal validation on the one-third validation dataset. Model predictive discrimination was assessed using the index of concordance, or C statistic, which accounts for censoring in time-to-event models (for death, allograft loss or combined event) and is equivalent to the area under the ROC curve for binary outcomes (logistic regression).[50,53] Estimate of C and its 95% confidence interval based on the validation data are provided for the 3 outcomes. The final prediction models for each of the 3 outcomes based on the shrunken prognostic score (PS) can be used to estimate the predicted probabilities of death, allograft loss or combined event at a given time t (year). That is, the shrunken PS, say PS^*, that will be used to predict the outcomes of new/future patients will be $PS^* = \gamma X\beta$, where β is collection of estimated coefficients in the final prediction model. The predicted survival at time t for new a patient can be obtained as $S_0(t)^{\exp(PS^*)}$, where PS^* is the aforementioned calibrated/shrunken prognostic score and $S_0(t)$ is the baseline survival estimate from the final model. Analyses were performed in SAS version 9.3 PROC PHREG and R version 2.12 using libraries RMS and SURVIVAL.

Results

Baseline characteristics of the cohort and patients' outcome

Baseline characteristics of the cohort are shown in Table 1. Briefly, the mean±SD age was 50±13 years (range: 18–86 years), 61% were male, 36% diabetic, 48%, 28% and 15% were White, Hispanic and African American, respectively; and the mean±SD time on dialysis was 3.6±3.1 years. Median follow-up time was 794 days (interquartile range (IQR): 384–1,348 days) for combined outcome. There were 1,492 deaths (9.9%, mortality rate: 35.9; 95% confidence interval (CI): 34.1–37.7/1000 patient-years), and 1,647 graft losses (10.9%, graft loss rate: 41.1; 95%CI: 39.2–43.1/1000 patient-years) during the follow-up period.

Development of the prediction score

We developed 2 prediction scores, 1 including donor variables (main score) and the other with only recipients' variables (score for dialysis patients). From the 19,166 transplant events in the SRTR database identified among the study cohort, we excluded transplants which were not the recipients' first transplant and patients with age<18 years or who received the first kidney transplant before July 1st, 2001 (Figure 1). The final prediction mortality model coefficients are presented in Table 2. Older recipient age, longer time on dialysis, presence of diabetes, coronary artery disease (CAD), peripheral vascular disease (PAD) and older donor age were associated with increased risk of mortality. The final prediction mortality without donor variables model coefficients are presented in Table S1. The final prediction model coefficients for graft loss are presented in Table 3 and for the combined outcome are presented in Table 4. Younger recipient age, Hispanic ethnicity, hypertension and glomerulonephritis as cause of ESRD, shorter time on dialysis, recipient's and donor's diabetes, extended criteria donor kidney (ECD) and number of HLA mismatch were associated with increased risk of death censored allograft loss (Table 3). Similar risk factors were associated with increased risk of the combined outcome (death or allograft loss), as shown in Table 4. The final prediction mortality without donor variables model coefficients for graft loss are presented in Table S2 and for the combined outcome are presented in Table S3. For comparission, hazard ratios using coefficients from the EPTS score prediction model are presented in Table S4 for all outcomes. The performances of our reduced/simplified models were practically the same as the full models (not shown). In addition, we have performed prediction models after leaving out the variables with missing values. The C statistics from models without these laboratory values are similar, as quantified by the C statistics (not shown). Finally, we have also performed prediction models using multiple imputation for missing values. The C statistics from these models are similar, as quantified by the C statistics (not shown).

Internal validation and comparison with other prediction scores

Performance of the prediction score was tested in the validation dataset of 5,042 patients. Our prediction score for mortality discriminated acceptably, with a C statistic of 0.70 (95%CI: 0.67–0.73) for the main model and 0.70 (95%CI: 0.67–0.72) for the model without donor variables (Table 5). The ability of our new score to discriminate mortality outcomes was better than the EPTS score and the score from Kasiske et al[41] and similar to the Cox model based on variables from iChoose Kidney model[26] (Table 5). Our main prediction

score for allograft loss and for the combined outcome had a C statistic of 0.63 (95%CI: 0.60–0.66) for allograft loss and 0.63 (95%CI: 0.61–0.66) for combined outcome (Table 5). The discrimination ability for these 2 outcomes using our new score was similar or slightly better than the EPTS score and iChoose Kidney model[26] and similar to the score from Kasiske et al (Table 5).[41] Figure 2 shows the predicted probability of (Panel A) mortality, (Panel B) graft failure, and (Panel C) combined outcome within 5 years of transplant as a function of risk score. The predicted probabilities at 25th, 50th and 75th percentile of the risk level for mortality are 8.3%, 13.8% and 22.1%, respectively; for graft failure: 9.6% 13.8% and 19.4%; for combined outcome: 19.2%, 25.2% and 33.1%. Model calibration was assessed using the slopes of the prognostic index; slopes of 1.0 represent perfect calibration. Table S5 provides calibration statistics for the group-based goodness-of-fit tests with the observed number of events and expected/predicted events from each model. There was good overall calibration for the main models for mortality, graft failure and combined outcome (all $p>0.05$). However, for graft failure and combined outcome, the fit was poor for higher deciles of the risk score. Not surprisingly, for models without donor variables, the overall goodness-of-fit was not as good and similarly poorer fit prediction was observed for several of the higher deciles of the risk score. Calibration plots for 5-year survival (observed vs predicted survival) are provided in Figure S1, which shows graphically similar results as the group-based GOF tests.

Using scores from our main model, we present the estimated 1 to 5 year predicted outcome event failure probabilities for several distinct, typical patient characteristics in Table 6. In addition, Table 7 compares the 1 to 5 year event probabilities in 4 typical patients for our current main model score with the scores of the EPTS model and the model from Kasiske et al.[41] Results from this table show that, using our score, estimated event probabilities are quite different when patients have many comorbidities (eg, comparing 1A to 2A or 1B to 2B). For example, the predicted 5-year event probabilities for a patient with no comorbidities (1B) compared a patient with all comorbidities present are 21% and 67%, respectively; a greater than 3-fold increased in event failure risk for patients with comorbidities present. The EPTS model, however, does not make this distinction since comorbidities (except for diabetes mellitus) are not included in the model. Similarly, the model from Kasiske et al[41] includes a limited number of patient comorbidities in prediction scores and the estimated probabilities therefore do not differ much according to the presence of various comorbid conditions (eg, comparing Patient 1A to 2A or 1B to 2B).

Discussion

The prediction of long-term outcomes in kidney transplantation is a very important issue for a limited resource, not only for managing clinical decisions but also for adequate risk assessment. Predicting which candidate is most eligible and expected to have the greatest longevity for offered allograft kidney can be an extremely helpful tool for physicians making clinical decisions. In this paper, we presented a simple clinical score, which includes only variables available at the time of transplantation. All data captured from patients transplanted in the 21st century. This simple clinical score has better or at least the same prediction capability as other currently used prediction scores in the United States despite only pretransplant variables were used.

The main goal for developing this model was to help physicians make decision. The variables included in the model are those that are available to clinicians in everyday clinical practice. These models could help to compare predicted outcomes under various real-life circumstances; eg when a Nephrologist evaluates wait-listed patients with no knowledge of donor-specific information, or when a Surgeon needs an urgent determination about which of several potential recipients should receive a kidney once donor information becomes available. We believe the development and assessment of an objective prediction tool, based on systematic data collection and analysis, provides additional help to physicians. It goes without saying that the added value of a prediction tool is not intended to replace clinical judgment/knowledge, but rather to augment it.

Despite previous studies having recognized pretransplantation risk factors for kidney allograft loss or mortality[15,17–25], only few previous prediction score based solely on only these variables,[29,32,34,35] and none of them has been developed in the 21st century and focused on both graft and patients' survival. Additional calculations have been performed to calculate life years from transplant,[27,28] and scores have been developed for predicting coronary heart disease,[30] graft function at 1-year[33] or survival after discharge.[31] Only few previous scores have been developed based on data from 21st century,[26,33,35,39–41] however, none of them focused on both graft and patients' survival. Moreover, only a few efforts have been made to describe risk scores for use as prognostic tools to individualize risk of allograft loss or mortality in incident or prevalent transplant recipients.[26,38–41] For a prediction score to assume clinical utility, a number of conditions must be met. Of obvious importance, each component of the score should be statistically associated with the assessed clinical outcomes such as allograft loss and mortality. Nonetheless, exact quantification of an individual patient's risk of clinical events requires different statistical approaches from the approaches used to only examine the association between risk factor and event.[54,55] For instance, the prediction score should discriminate satisfactorily between the individuals who are experiencing vs. those who are not experiencing the clinical endpoints. The C statistic is an adequate method to assess this discrimination. Our new prediction score has acceptable C statistic, especially for the outcome of patient survival. Our score is also able to discriminate outcome risk across different waitlisted transplant candidates at the time of kidney transplantation (main score) or even before transplantation (score without donor variables). Even though our score includes only variables which are actually available at the time of transplantation, the C statistics of our prediction score was better or at least the same for all the studied endpoints (mortality, graft loss and combined of these) than the currently used EPTS score[36,37] or from Kasiske et al[41] or variables from iChoose Kidney model.[26] Although, it is important to note that EPTS allows for prediction of mortality in those with prior solid organ transplantation and the Kasiske et al model[41] included patients with preemptive kidney transplants and re-grafts. In addition, the iChoose Kidney score is based on logistic regression models, which did not take into account the time to event and did not censor for outcome events.[26] In our comparison we used the same variables used in the iChoose Kidney model, but applied a Cox regression model for comparison.[26] Another significant advantage of our prediction score is its ability to account for comorbidities, kidney donor related information and different important pretransplant laboratory values, which are associated with posttransplant outcomes.[20,21,24] Table S6 shows the variables

included in several currently avaliable prediction score models in transplant nephrology including our own. Although our score includes the use of more variables than other scores, our score can still be rapidly and efficiently calculated using our website at www.TransplantScore.com. Moreover, as clearly shown in Table 7, taking into account these additional variables results in significant improvement in the ability to predict long-term outcomes in kidney transplant recipients; as the currently used EPTS score[36,37] or the Kasiske et al[41] score are not able to distinguish between patients with and without comorbidites. Furthermore, while most of the other prediction scores were created to predict allograft loss[38– 40], our new prediction score was created to be able to predict not only allograft loss, but graft censored mortality as well.

Our new prediction score was designed to assist physicians in clinical decision making regarding kidney transplants even under urgent circumstances. In addition, we developed a prediction score without donor information, which can be helpful for physicians during the transplant evaluation as well. For prediction of posttransplant graft censored mortality and graft loss 10 predictors were used for each main model. These factors included: recipients' age, cause and length of ESRD, hemoglobin, albumin, selected comorbidities, race and type of insurance as well as donor characteristics such as donor age, ECD, diabetes status, number of HLA mismatches (Table S6). Based on the equations used to develop our new prediction score, we created a website at www.TransplantScore.com, where the predicted event probability for a patient can be calculated rapidly and efficiently. This webpage was designed to also be useful on mobile devices both online and off-line, and we also developed a mobile app, which makes our score applicable even at the patient's bedside.

Although our score has a marginal increase in the C-statistic over existing score, we note that unfortunately, most of the prediction scores used in transplant nephrology and in general nephrology have similarly low C-statistic. However, it is important to note that we used only pretransplant variables, while the rest of the scores used posttransplant variables (which makes the prediction easier). Furthermore, we point out that the C-statistic provides a single-number summary of overall prediction performance which clinical utility should not be solely based on. In addition to pretransplant variables, another important consideration in the fitness for clinical use is that the prediction model incorporates adequate key patient predictive factors able to structurally discriminate among patients' likelihood of death/graft failure event. For instance, a model with only baseline diabetes structurally cannot distinguish varying mortality probabilities for a patient with diabetes mellitus and coronary artery disease and peripheral vascular disease or abnormal laboratory results, for instance. A model with a higher C-statistic but which is limited structurally in making adequate individualized predictions may not be appropriate for some clinical applications.

Our study should be noted for several advantages other than those mentioned above. Our prediction score is the only novel score developed from data from the 21st century patients in the United States and focusing on both recipients' and graft survival while previous models such as the EPTS score,[36,37] the Kasiske et al prediction score[41] and the iChoose Kidney score[26] used older data or focused on only 1outcome. Moreover, we developed a score without donor data, which can help the dialysis physician to calculate the waitlisted patients expected posttransplant survival. In addition, our cohort size was much larger than the ones

used in previous studies to develop prediction scores.[38–40] Our score has been developed using data derived from several centers. Center-specific scores, based on data derived from any given center's data, could be more applicable for patients transplanted in the given center. Finally, we created a website www.TransplantScore.com and a mobile application to help physicians easily use our predictive model in everyday practice.

Our study should be qualified for several potential limitations. The prediction models are only as good as the data used in their derivation. In the development dataset in our analyses, data for continuous variables of recipients' albumin, alkaline phosphatase, hemoglobin and phosphorus were missing in 27–28% of patients, and data on organ preservation total cold ischemic time were missing in 20% of patients. We used multiple imputation (10 imputations) methods to address missing data, although potential bias remains. Additionally, although most demographic variables likely are accurate for recipients and donors, there is always potential nondifferential misclassification bias contributing to type II error in our analyses. Comorbidity data in our study were obtained from the CMS Medical Evidence Report (form CMS-2728), for which a previous validation study found that comorbid conditions were significantly underreported.[47] In addition, we do not have data for important predictors such as midodrine administration.[56] Most importantly, our prediction model has yet to be externally validated in other cohorts. To the best of our knowledge, only few previously developed prediction scores were externally validated,[35,38,39,57] and only 2 these scores was validated in a different center.[39,57] Moreover, neither of these externally validated scores were developed and validated in patients in the United States at the 21st century. Externally validating our score in other cohorts at both the multi-center and individual center level is necessary to ensure the applicability, reliability, and utility of our prediction model for use in potential kidney transplant recipient patients. Moreover, our score was developed using US data from 1large dialysis provider; consequently the applicability of our score for nonUS patients and US patients from other dialysis providers might be limited. Further external validation is necessary. Finally, our score can be used only in recipients with first deceased kidney transplantation.

Conclusion

A newly developed prediction tool, which uses 21st century data exclusively available prior to the time of transplantation to predict patients' and graft survival performs better than currently used tools such as EPTS. The predicted event risk varies sensibly according to patients' and donors' pretransplant characteristics as well as laboratory measurements and prediction scores accounting for these differences should be implemented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors extend their thanks to the teammates in DaVita clinics who work every day to take care of patients and also to ensure the extensive data collection on which our work is based. The authors also thank DaVita Clinical Research (DCR) for technical assistance in that regard. DCR is committed to advancing the knowledge and practice of kidney care.

Funding Sources

The work in this manuscript has been performed with the support of grant R21AG047306 (MZM, KKZ, RM, DVN and CPK). The project was partially supported by the National Center for Advancing Translational Sciences, National Institutes of Health, grant UL1 TR000153 and TR001414, through the UC Irvine Biostatistics, Epidemiology and Research Design Unit. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

List of abbreviations

AIC	Akaike's information criterion
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
ECD	Extended criterion donor
EPTS	Estimated Post-Transplant Survival
ESRD	End stage renal disease
GOF	Goodness-of-fit
HLA	Human Leucocyte Antigen
HR	Hazard ratios
IQR	Interquartile range
PAD	Peripheral vascular disease
PS	prognostic score
SD	Standard deviation
SRTR	Scientific Registry of Transplant Recipients
USRDS	United States Renal Data System

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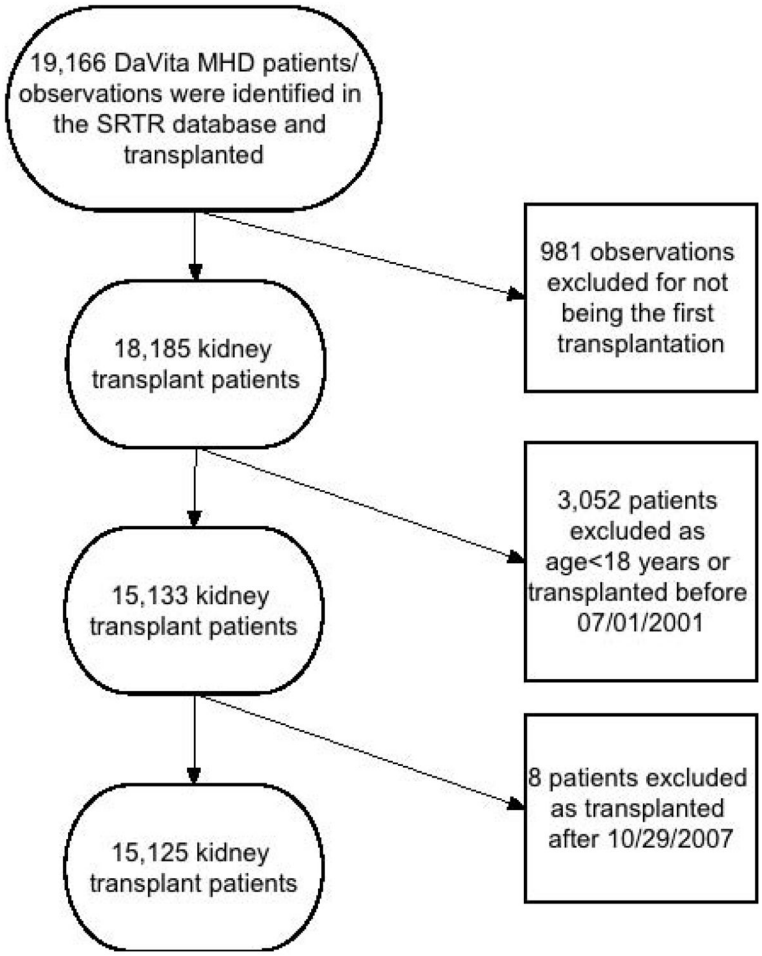
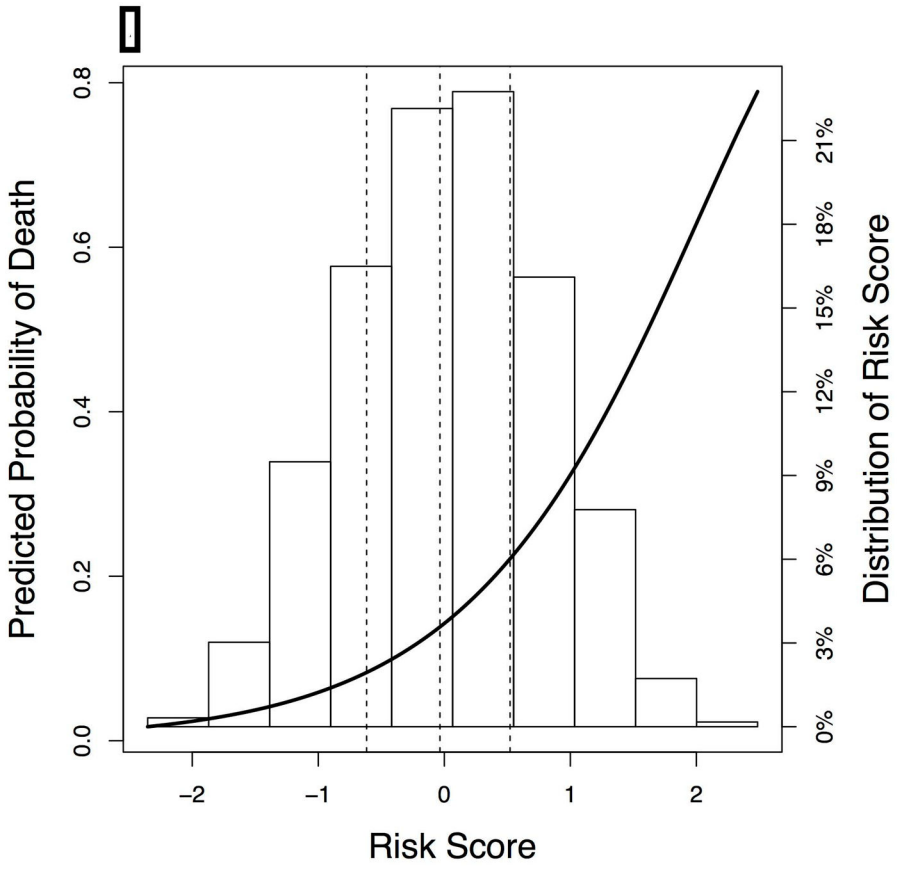
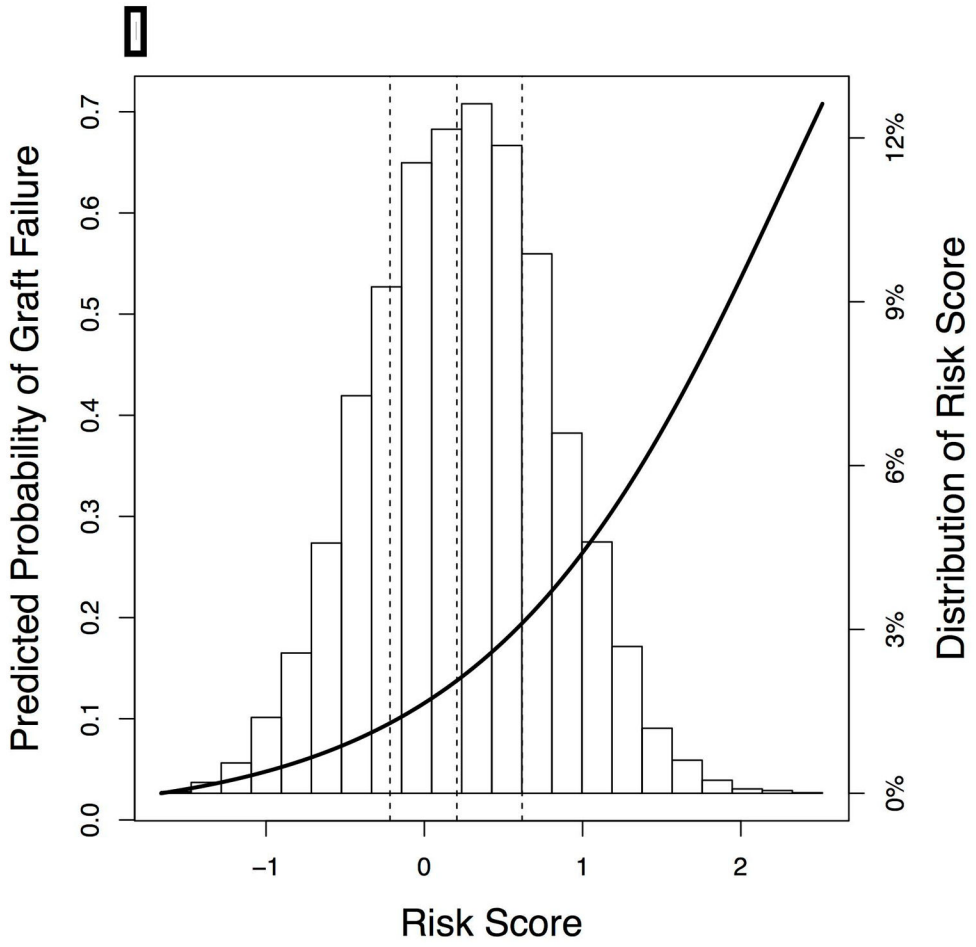


Figure 1.
Flow chart of patients' selection





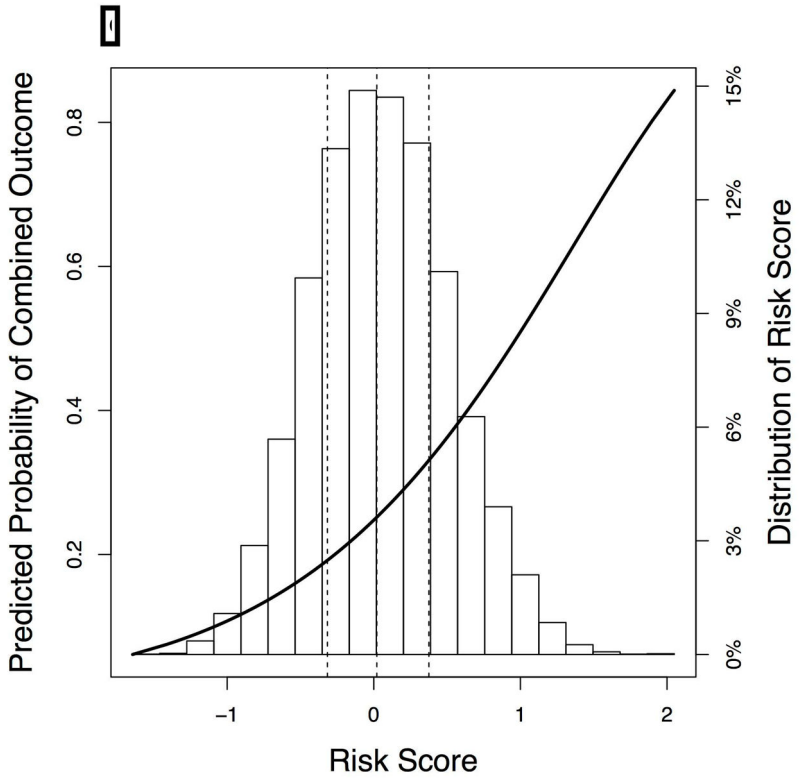


Figure 2.

Predicted probability of (Panel A) mortality, (Panel B) graft failure, and (Panel C) combined outcome (mortality or graft failure) within 5 years of transplant (solid black curve, left axis) as a function of risk score. Also given is distribution of the observed risk score (right axis) with quartiles indicated by dashed vertical lines. A patient's risk score is equal to the patient's linear predictor calculated from Tables 2, 3 and 4, respectively. The predicted probabilities at 25^{th}, 50^{th} and 75^{th} percentile of the risk level for mortality are 8.3%, 13.8% and 22.1%, respectively; for graft failure: 9.6% 13.8% and 19.4%; for combined outcome: 19.2%, 25.2% and 33.1%.

Table 1

Baseline characteristics of the patients

Recipients' characteristics	Entire cohort (n=15,125)	Development set (N=10,083)	Validation set (N=5,042)
Age (years)	50 ± 13	50 ± 13	50 ± 13
Gender (% male)	61	61	61
Race/ethnicity, %			
White	48	48	49
Hispanic	28	29	28
African American	15	14	15
Other/Unknown	9	9	8
Type of Primary Insurance, %			
Medicare	49	49	49
Medicaid	3	3	3
Other	36	36	36
Unknown	12	12	12
Primary cause of ESRD, %			
Diabetes	25	25	25
Hypertension	23	23	23
Glomerulonephritis	23	23	23
Cystic disease	8	8	8
Other/Unknown	21	21	21
Type of Renal Replacement Therapy, %			
No Dialysis	14	14	14
Hemodialysis	68	68	68
Peritoneal Dialysis	11	11	11
Unknown	7	7	7
Time on dialysis (years)	3.56 ± 3.14	3.51 ± 3.09	3.59 ± 3.17
Time on dialysis (years), %			
<1 year	18	18	17
1–3 years	34	35	34
3–5 years	25	24	25
>5 years	23	23	24
Comorbid conditions, %			
Diabetes mellitus	36	37	36
History of cancer	5	5	5
Coronary Artery Disease	7	7	7
Cerebrovascular disease	4	5	4
Peptic ulcer	5	4	5
Peripheral Vascular Disease	7	7	7
Hepatitis B Virus (DNA/core positivity)	9	8	9

Recipients' characteristics	Entire cohort (n=15,125)	Development set (N=10,083)	Validation set (N=5,042)
Cytomegalovirus positivity	62	63	62
Laboratory results			
Serum albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.4	4.0 ± 0.4
Serum alkaline phosphatase (U/L)	113 ± 78	112 ± 77	113 ± 79
Blood hemoglobin (g/dL)	12.2 ± 1.3	12.2 ± 1.3	12.2 ± 1.3
Serum phosphorus (mg/dL)	5.9 ± 1.5	5.9 ± 1.5	5.9 ± 1.5
Donors' characteristics			
Age (years)	39 ± 15	39 ± 15	39 ± 15
Gender (% male)	53	53	53
Race/Ethnicity, %			
White	66	66	66
Hispanic	14	14	14
African American	15	15	15
Other/Unknown	5	5	5
Comorbid conditions, %			
Diabetes mellitus (unknown) *	4 (32)	4 (32)	4 (32)
Hypertension (unknown) *	18 (33)	18 (33)	18 (33)
Smoker	23	22	23
Cytomegalovirus positivity	61	59	61
Inotropic support	38	38	38
Trauma as cause of death	28	28	28
Expanded criteria donor	14	14	14
Transplantation related data			
Number of HLA mismatches, %			
0	12	11	12
1,2,3	28	29	28
4,5,6	60	60	60
Cold Ischemic Time (hours)	14.15 ± 10.68	14.09 ± 10.73	14.19 ± 10.65

Data are presented in mean±SD or percentage as appropriate.

Abbreviations: ESRD: End Stage Renal Disease; HLA: Human Leucocyte Antigen

*: (percentage of patient with missing data on this variable)

Table 2

Cox regression model for predicting mortality with all variables (main model)

Predictors	Parameter[a]	Adjusted Hazard Ratios (95% Confidence Interval)	p-value
Recipients' characteristics			
Age categories			
18–34 years	−0.8993	0.41 (0.31–0.54)	<0.001
35–49 years	−0.5179	0.60 (0.50–0.71)	<0.001
50–64 years		1.00 (Reference)	
>=65 years	0.4880	1.63 (1.40–1.90)	<0.001
Race categories			
White		1.00 (Reference)	
Hispanic	−0.0868	0.92 (0.79–1.07)	0.26
African-American	−0.3664	0.69 (0.56–0.85)	<0.001
Other/Unknown	−0.2804	0.76 (0.59–0.97)	0.03
Type of insurance			
Medicare		1.00 (Reference)	
Medicaid	0.3414	1.41 (0.96–2.05)	0.08
Other	−0.3197	0.73 (0.62–0.85)	<0.001
Unknown	−0.1720	0.84 (0.70–1.01)	0.07
Time on dialysis			
<1 year		1.000 (Reference)	
1–3 years	0.2103	1.23 (1.00–1.52)	0.04
3–5 years	0.2991	1.35 (1.08–1.69)	0.009
>5 years	0.6025	1.83 (1.45–2.30)	<0.001
Comorbid conditions			
Diabetes mellitus (presence vs. absence (ref.))	0.4244	1.53 (1.34–1.74)	<0.001
Coronary Artery Disease (presence vs. absence (ref.))	0.3236	1.38 (1.15–1.65)	<0.001
Peripheral Vascular Disease (presence vs. absence (ref.))	0.3225	1.38 (1.13–1.69)	0.002
Laboratory results			
Serum albumin (+1 g/dL)	−0.4759	0.62 (0.52–0.75)	<0.001
Donors' characteristics			
Age (+1 year)	0.0087	1.01 (1.00–1.01)	<0.001
Diabetes mellitus			
Absence		1.000 (Reference)	
Presence	0.2393	1.27 (0.97–1.67)	0.09
Unknown	−0.3268	0.72 (0.61–0.85)	<0.001

[a]Model parameter estimate before application of shrinkage factor of 0.9312. Final coefficients are multiplied by this shrinkage parameter.

Estimated 5-year event probabilities can be obtained as: $1\text{-}0.857437^{\exp(PS^*)}$, where $PS^* = \gamma$ LP, γ is the shrinkage factor, and LP is the linear predictor using the given parameter estimates.

Table 3

Cox regression model for predicting graft failure with all variables (main model)

Predictors	Parameter[a]	Adjusted Hazard Ratios (95% Confidence Interval)	p-value
Recipients' characteristics			
Age categories			
18–34 years	0.4933	1.64 (1.37–1.96)	<0.001
35–49 years	0.2198	1.25 (1.07–1.45)	0.004
50–64 years		1.00 (Reference)	
>=65 years	−0.1970	0.82 (0.67–1.01)	0.06
Race categories			
White		1.00 (Reference)	
Hispanic	0.3286	1.39 (1.20–1.61)	<0.001
African-American	−0.1727	0.84 (0.69–1.02)	0.08
Other/Unknown	−0.6400	0.53 (0.39–0.72)	<0.001
Type of insurance			
Medicare		1.00 (Reference)	
Medicaid	−0.3227	0.72 (0.49–1.06)	0.10
Other	−0.4970	0.61 (0.52–0.70)	<0.001
Unknown	−0.6253	0.53 (0.44–0.65)	<0.001
Primary cause of ESRD			
Diabetes		1.00 (Reference)	
Hypertension	0.4139	1.51 (1.21–1.89)	<0.001
Glomerulonephritis	0.4576	1.58 (1.25–2.00)	<0.001
Cystic disease	0.1332	1.14 (0.83–1.58)	0.42
Other	0.5488	1.73 (1.39–2.15)	<0.001
Time on dialysis			
<1 year		1.00 (Reference)	
1–3 years	−0.5467	0.58 (0.49–0.68)	<0.001
3–5 years	−0.8588	0.42 (0.35–0.52)	<0.001
>5 years	−0.6523	0.52 (0.43–0.64)	<0.001
Comorbid conditions			
Diabetes mellitus (presence vs. absence (ref.))	0.3031	1.35 (1.14–1.61)	<0.001
Laboratory results			
Blood hemoglobin (+1 g/dL)	−0.0892	0.92 (0.87–0.97)	0.002
Donors' characteristics			
Diabetes mellitus			
Absence		1.00 (Reference)	
Presence	0.5145	1.67 (1.30–2.15)	<0.001
Unknown	−0.3680	0.69 (0.59–0.81)	<0.001

Predictors	**Parameter**[a]	**Adjusted Hazard Ratios (95% Confidence Interval)**	**p-value**
ECD (vs. non ECD (ref.))	0.5023	1.65 (1.41–1.94)	<0.001
Transplantation related data			
Number of HLA mismatches			
0		1.00 (Reference)	
1,2,3	0.5998	1.82 (1.42–2.33)	<0.001
4,5,6	0.5332	1.70 (1.35–2.15)	<0.001

[a]Model parameter estimate before application of shrinkage factor of 0.9167. Final coefficients are multiplied by this shrinkage parameter. Estimated 5-year event probabilities can be obtained as: $1\text{-}0.8845403^{\exp(PS^*)}$, where $PS^* = \gamma$ LP, γ is the shrinkage factor, and LP is the linear predictor using the given parameter estimates.

Table 4

Cox regression model for predicting combined outcome (mortality or graft failure) with all variables (main model)

Predictors	Parameter[a]	Adjusted Hazard Ratios (95% Confidence Interval)	p-value
Recipients' characteristics			
Age categories			
18–34 years	0.0993	1.10 (0.95–1.29)	0.20
35–49 years	−0.0784	0.92 (0.82–1.04)	0.20
50–64 years		1.00 (Reference)	
>=65 years	0.1881	1.21 (1.06–1.38)	0.01
Race categories			
White		1.00 (Reference)	
Hispanic	0.1609	1.17 (1.05–1.32)	0.01
African-American	−0.2554	0.77 (0.66–0.90)	0.001
Other/Unknown	−0.4475	0.64 (0.52–0.79)	<0.001
Type of insurance			
Medicare		1.00 (Reference)	
Medicaid	−0.1557	0.86 (0.63–1.16)	0.32
Other	−0.4287	0.65 (0.58–0.73)	<0.001
Unknown	−0.4112	0.66 (0.57–0.77)	<0.001
Primary cause of ESRD			
Diabetes		1.00 (Reference)	
Hypertension	0.1541	1.17 (0.99–1.38)	0.07
Glomerulonephritis	0.1447	1.16 (0.96–1.38)	0.12
Cystic disease	−0.1870	0.83 (0.64–1.07)	0.15
Other	0.3209	1.38 (1.17–1.62)	<0.001
Time on dialysis			
<1 year		1.00 (Reference)	
1–3 years	−0.2618	0.77 (0.67–0.88)	<0.001
3–5 years	−0.3747	0.69 (0.59–0.80)	<0.001
>5 years	−0.1432	0.87 (0.74–1.02)	0.08
Comorbid conditions			
Diabetes mellitus (presence vs. absence (ref.))	0.3021	1.35 (1.18–1.55)	<0.001
Coronary artery disease (presence vs. absence (ref.))	0.2617	1.30 (1.11–1.51)	<0.001
Laboratory results			
Serum albumin (+1 g/dL)	−0.2644	0.77 (0.67–0.88)	<0.001
Blood hemoglobin (+1 g/dL)	−0.0451	0.96 (0.91–0.99)	0.05
Donors' characteristics			
Age (+1 year)	0.0059	1.01 (1.00–1.01)	0.003

Predictors	**Parameter**[a]	**Adjusted Hazard Ratios (95% Confidence Interval)**	**p-value**
Diabetes mellitus			
Absence		1.00 (Reference)	
Presence	0.4596	1.58 (1.23–1.93)	<0.001
Unknown	−0.3308	0.72 (0.63–0.82)	<0.001
ECD (vs. non ECD (ref.))	0.2082	1.23 (1.05–1.44)	0.01
Transplantation related data			
Number of HLA mismatches			
0		1.00 (Reference)	
1,2,3	0.3241	1.38 (1.16–1.65)	<0.001
4,5,6	0.3115	1.36 (1.16–1.61)	<0.001

[a]Model parameter estimate before application of shrinkage factor of 0.9160. Final coefficients are multiplied by this shrinkage parameter. Estimated 5-year event probabilities can be obtained as: $1\text{-}0.752292^{\exp(PS^*)}$, where $PS^* = \gamma$ LP, γ is the shrinkage factor, and LP is the linear predictor using the given parameter estimates.

Table 5

Discrimination C statistics for (A) current model with all variables, (B) current model without donor variables, (C) model based on EPTS (Estimated PostTransplant Survival) score, (D) model based on equation of Kasiske's paper and (E) model based on variables from iChoose Kidney

Model/Outcome	Mortality	Graft failure	Combined
	Discrimination C (95% Confidence Interval of Discrimination C)		
(A) Current main model[#]	0.70 (0.67–0.73)	0.63 (0.60–0.66)	0.63 (0.61–0.66)
(B) Current model without donor variable[#]	0.70 (0.67–0.72)	0.59 (0.56–0.63)	0.61 (0.59–0.63)
(C) EPTS predictors[*]	0.66 (0.63–0.69)	0.59 (0.57–0.62)	0.57 (0.54–0.59)
(D) Kasiske Model[**]	0.68 (0.65–0.70)	0.66 (0.64–0.69)	0.62 (0.60–0.64)
(E) iChoose Kidney[***]	0.70 (0.67–0.72)	0.54 (0.50–0.57)	0.61 (0.58–0.63)

Models (A–E) included the following variables:

[#]: Model A and B are different across outcomes (mortality, graft failure, combined outcome), but the details of parameter estimations and variable information can be found in Tables 2–4 for Model A, Tables S1–S3 in supplemental material for Model B.

[*]: Model C: recipient age, presence of diabetes, duration on dialysis, previous solid organ transplantation (default: none)

[**]: Model D: donor age, donor history of hypertension, recipient age, race, recipient insurance, duration on dialysis, recipient cause of End Stage Renal Disease, HCV antibody, trauma as cause of death

[***]: Model E: recipient age, gender, race/ethnicity, presence of hypertension, cardiovascular disease, diabetes, serum albumin < 3.5 g/dL, duration on dialysis

Table 6

Predicted outcomes using our new main model (with all variables) for some typical clinical scenarios (www.TransplantScore.com; the webpage can be used as mobile application if it is opened on mobile device and agreed to download it)

Probability (%) of the event	**Mortality**				
	First year	***Second year***	***Third year***	***Fourth year***	***Fifth year***
Patient A	2	3	4	5	7
Patient B	12	19	26	35	42
Patient C	20	30	41	52	60
Probability (%) of the event	**Graft Failure**				
	First year	*Second year*	*Third year*	*Fourth year*	*Fifth year*
Patient A	7	10	14	16	18
Patient B	7	11	14	17	19
Patient C	12	18	24	28	31
Probability (%) of the event	**Combined Outcome (mortality or graft failure)**				
	First year	*Second year*	*Third year*	*Fourth year*	*Fifth year*
Patient A	7	11	15	19	22
Patient B	17	25	33	40	45
Patient C	25	36	47	55	61

Patient A: 33 years old White recipient with polycystic kidney disease, Medicare insurance, with no diabetes mellitus, peripheral vascular disease and coronary artery disease, has serum albumin 3.8 g/dL and blood hemoglobin 13.1 g/dL and on dialysis for 6 months *receiving kidney* from 30 years old standard criteria donor without diabetes with zero HLA mismatch

Patient B: 57 years old White recipient with hypertensive nephrosclerosis, Medicare insurance, with no diabetes mellitus, but has peripheral vascular disease and coronary artery disease, has serum albumin 3.2 g/dL and blood hemoglobin 11.1 g/dL and on dialysis for 24 months *receiving kidney* from 53 years old standard criteria donor without diabetes with 3 HLA mismatches

Patient C: 64 years old African American recipient with diabetic nephropathy, Medicare insurance, with diabetes mellitus and peripheral vascular disease, but free from coronary artery disease, has serum albumin 2.8 g/dL and blood hemoglobin 10.1 g/dL and on dialysis for 6 years *receiving kidney* from 50 years old extended criteria donor without diabetes with 5 HLA mismatches

Table 7

Predicted combined outcome using our new main model, EPTS (Estimated PostTransplant Survival) score and model based on equation of Kasiske's paper for 4 different patients

Probability (%) of the event	**Our new model with all variables**				
	First year	***Second year***	***Third year***	***Fourth year***	***Fifth year***
Patient 1A ("good"): **No comorbidities** and with relatively **low of albumin and hemoglobin**	8	12	17	21	24
Patient 1B ("good"): **No comorbidities** and with relatively **high of albumin and hemoglobin**	7	10	14	18	21
Patient 2A ("bad"): **With all comorbidities** and with relatively **low of albumin and hemoglobin**	33	47	58	67	73
Patient 2B ("bad"): **With all comorbidities** and with relatively **high of albumin and hemoglobin**	29	41	52	61	67
Probability (%) of the event	**EPTS model**				
	First year	*Second year*	*Third year*	*Fourth year*	*Fifth year*
Patient 1A ("good"): **No comorbidities** and with relatively **low of albumin and hemoglobin**	6	10	13	17	20
Patient 1B ("good"): **No comorbidities** and with relatively **high of albumin and hemoglobin**	6	10	13	17	20
Patient 2A ("bad"): **With all comorbidities** and with relatively **low of albumin and hemoglobin**	9	13	18	23	27
Patient 2B ("bad"): **With all comorbidities** and with relatively **high of albumin and hemoglobin**	9	13	18	23	27
Probability (%) of the event	**Kasiske et al model**				
	First year	*Second year*	*Third year*	*Fourth year*	*Fifth year*
Patient 1A ("good"): **No comorbidities** and with relatively **low of albumin and hemoglobin**	14	22	30	38	45
Patient 1B ("good"): **No comorbidities** and with relatively **high of albumin and hemoglobin**	14	22	30	38	45
Patient 2A ("bad"): **With all comorbidities** and with relatively **low of albumin and hemoglobin**	15	23	32	40	48
Patient 2B ("bad"): **With all comorbidities** and with relatively **high of albumin and hemoglobin**	15	23	32	40	48