A Simple Tool to Predict Outcomes After Kidney Transplant

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Background: Surprisingly few tools have been developed to predict outcomes after kidney transplant.

Study Design: Retrospective observational cohort study.

Setting & Participants: Adult patients from US Renal Data System (USRDS) data who underwent deceased donor kidney transplant in 2000-2006.

Predictor: Full and abbreviated prediction tools for graft loss using candidate predictor variables available in the USRDS registry, including data from the Organ Procurement and Transplantation Network and the Centers for Medicare & Medicaid Services End-Stage Renal Disease Program.

Outcomes: Graft loss within 5 years, defined as return to maintenance dialysis therapy, preemptive retransplant, or death with a functioning graft.

Measurements: We used Cox proportional hazards analyses to develop separate tools for assessment (1) pretransplant, (2) at 7 days posttransplant, and (3) at 1 year posttransplant to predict subsequent risk of graft loss within 5 years of transplant. We used measures of discrimination and explained variation to determine the number of variables needed to predict outcomes at each assessment time in the full and abbreviated equations, creating simple user-friendly prediction tools.

Results: Although we could identify 32, 29, and 18 variables that predicted graft loss assessed pretransplant and at 7 days and 1 year posttransplant ("full" models), 98% of the discriminatory ability and >80% of the variability explained by the full models could be achieved using only 11, 8, and 6 variables, respectively.

Limitations: Comorbidity data were from the Centers for Medicare & Medicaid Medical Evidence Report, which may significantly underreport comorbid conditions; C statistic values may indicate only modest ability to discriminate risk for an individual patient.

Conclusions: This method produced risk-prediction tools that can be used easily by patients and clinicians to aid in understanding the absolute and relative risk of graft loss within 5 years of transplant.
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INDEX WORDS: Death-censored graft loss; graft failure; mortality; registry analysis; risk prediction.

Editorial, p. 817

Several observational studies have attempted to define the risk of outcomes after kidney transplant.[1-20] Generally, these studies define one or more risk factors to better understand the pathogenesis of graft failure and identify factors that may be modified to improve outcomes. However, another important function of risk assessment is to aid clinicians in decision making. For example, assessing risk at the time of listing on the deceased donor waiting list may help determine the advisability of undergoing transplant or continuing on dialysis therapy. Assessing risk associated with different deceased donor characteristics may help clinicians advise patients about the suitability of a particular deceased donor kidney. Assessing risk posttransplant may help determine how much immunosuppressive medication to use. Given the importance of risk assessment, surprisingly few practical tools are available for this purpose. Most previous studies have published models that are difficult to use, with odds ratios or hazard ratios from many variables.

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We based risk-prediction tools on the minimal number of variables needed to maximize prediction, thereby reducing the amount of information needed for their application.

METHODS

Study Population and Variables

Data from the US Renal Data System (USRDS) were used for this analysis. All adult (aged ≥18 years) recipients of deceased donor kidneys transplanted between 2000 and 2006 initially were included. Multiorgan recipients and prior recipients of nonkidney organs were excluded. Recipients with a history of prior kidney transplant were included. Therefore, the prediction models apply to adult deceased donor kidney-only transplant recipients with no history of prior nonkidney organ transplant.

Three separate cohorts were created to develop prediction models: (1) at the time of transplant (n = 59,091), (2) 7 days posttransplant (n = 57,603), and (3) 1 year posttransplant (n = 43,743). The 7-day cohort was conditional on 7-day graft survival, and the 1-year cohort, on 1-year graft survival. Patients were followed up until the earliest of graft failure (defined as return to dialysis therapy or preemptive retransplant), death with a functioning graft, or December 31, 2007.

Candidate predictor variables were those readily available in the USRDS registry, including data from the Organ Procurement and Transplantation Network (OPTN) and the Centers for Medicare & Medicaid Services (CMS) End-Stage Renal Disease Program (Table S1, provided as online supplementary material available with this article at www.ajkd.org). Recipient comorbid conditions were ascertained from OPTN transplant candidate and recipient registration data and supplemented with information from the CMS End-Stage Renal Disease Medical Evidence Report (form CMS-2728) when appropriate.

Statistical Methods

Cox proportional hazards models were used to develop the risk-prediction equations. The primary outcome was graft loss within 5 years, defined as return to maintenance dialysis therapy, preemptive retransplant, or death with a functioning graft. Each cohort was subdivided into a development set and a validation set by using a 70% random sample of the full cohort. The 70% sample was used for initial model development, and the remaining 30% sample was used for model validation. Comparative models also were developed for death-censored graft failure (defined as return to dialysis therapy or preemptive retransplant) and death with a functioning graft; however, their presentation is beyond the scope of this report.

The univariate relationship between each candidate predictor variable and graft loss within 5 years was considered using Cox proportional hazards analyses. Second-order polynomial parameterizations were used for most continuous predictors. Mean values of continuous predictor variables were used when the predictor variable level was unknown: recipient body mass index (2% of the baseline population), donor age (<1%), donor body mass index (14%), cold ischemia time (13%), and donor terminal serum creatinine level (<1%). Results of using an imputed mean versus multiple imputation of the continuous predictors were compared and found to be similar. Continuous predictors were categorized into clinically meaningful groups if the distribution was highly skewed, as with panel-reactive antibodies. For estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD) stages were used to accommodate missing values. For categorical variables, missing levels were assigned to a separate level if univariate analyses found that the missing level did not satisfy missingness at random (eg, panel-reactive antibodies, HLA antigen mismatches, eGFR). If the analyses supported missingness at random, the missing level was assigned to the most common category (eg, viral serologic test results). Candidate predictors with no significant univariate association with graft loss ($P \geq 0.05$) were not considered in the full model development. All remaining candidate predictor variables were entered into a Cox proportional hazards model, and a backward-selection process was used with $\alpha = 0.10$ as the criterion to remain in the model. Backward selection was used to yield a reduced set of candidate predictor variables to be considered further for retention in the final prediction models.

Schemper's[21] V_2 statistic, a measure of the proportion of variation explained by the Cox model, and the index of concordance, a measure of the model's discriminatory ability, were calculated for the model with all candidate predictors retained by the stepwise selection process. Variables in the model then were ordered according to their relative contribution to the model, assessed using the P value associated with the type III Wald χ^2 test. The variable with the lowest relative contribution (largest type III P value) then was removed, and the process was repeated. The final full models were determined to be those that retained at least 99% of the percentage of variation explained by the full set of candidate predictors determined using the backward-selection process. This process allowed us to remove variables of borderline significance if their collective inclusion in the model resulted in a <1% improvement in the percentage of variation explained by the model. A secondary objective of the analysis was to construct abbreviated models that could be implemented more easily in clinical practice. The abbreviated models were determined to be those that retained at least 80% of the percentage of variation explained by the full set of candidate predictors determined using the backward-selection process.

When the final full and abbreviated models were determined, a linear shrinkage factor, determined using a bootstrap process, was applied to the final model coefficients. Two hundred bootstrapped samples of the development sets were taken. In each sample, the linear predictor ($X\beta$) was calculated by multiplying the model coefficients by the vector of covariate values for each patient. The outcome was regressed on $X\beta$ in a univariate Cox regression, yielding a coefficient on the $X\beta$ term, η_i, for i = 1-200. The linear shrinkage parameter then was estimated as the mean of the resulting set of η_i. This shrinkage parameter was used to adjust the final set of model coefficients in an effort to account for model overoptimism.[22,23]

Internal validation of the resulting models was assessed in the 30% validation set using measures of discrimination and calibration. Discrimination was assessed using the index of concordance, or C statistic, which measures the ability of the model to correctly discriminate patients who experienced graft loss within time t from those who did not. Calibration was assessed using the slope of the prognostic index, obtained by regressing the linear predictor for each patient against the outcome in a Cox proportional hazards model. A slope of the prognostic measure near 1.0 would occur if the observed probabilities agreed with the predicted probabilities from the model. Final model calibration and discrimination was assessed in 5 randomly selected transplant programs to show how the full model performance is likely to vary when applied to a single center's transplant population.

The final prediction models can be used to estimate predicted probability of all-cause graft failure within 5 years of transplant from each of 3 times: at the time of transplant, 7 days posttransplant, and 1 year posttransplant. These predicted probabilities of graft failure were estimated from the final prediction equations as: $1 - \widetilde{S}(t, X)$, where $\widetilde{S}(t, X) = \widetilde{S}_0(t)^{e^{X\beta}}$ and t was set to 5 years posttransplant.

RESULTS

Characteristics of the Study Populations

Recipient, donor, and transplant characteristics of the study populations used to develop the models predicting graft loss pretransplant and at 7 days and 1 year posttransplant are described in online supplementary material (Tables S1-S4).

Predicting Graft Loss Using Characteristics Known Before Transplant

A relatively large number of recipient, donor, and pretransplant characteristics (n = 38) were associated with graft loss using the backward-selection process with a retention criterion of 0.10. However, 32 predictor variables were adequate to account for 99% of the variation explained by the larger set of predictors (Table S2). In addition, 80% of the variation explained and 98% of the discriminatory power of these variables to predict graft loss (Schemper V_2 statistic; Fig 1) were achieved using only 11 variables (by order of contribution): donor age, recipient race, first versus subsequent transplant, prior years on renal replacement therapy, recipient age, primary cause of CKD, hepatitis C virus antibody status, donor history of hypertension, recipient primary insurance coverage, donor cause of death, and total HLA antigen mismatches (Table 1). Thus, a relatively simple formula can be used to predict most of the variability in posttransplant graft loss. The equation listed in Table 1 can be used to estimate the probability of graft loss within 5 years posttransplant, as shown in Fig 2.

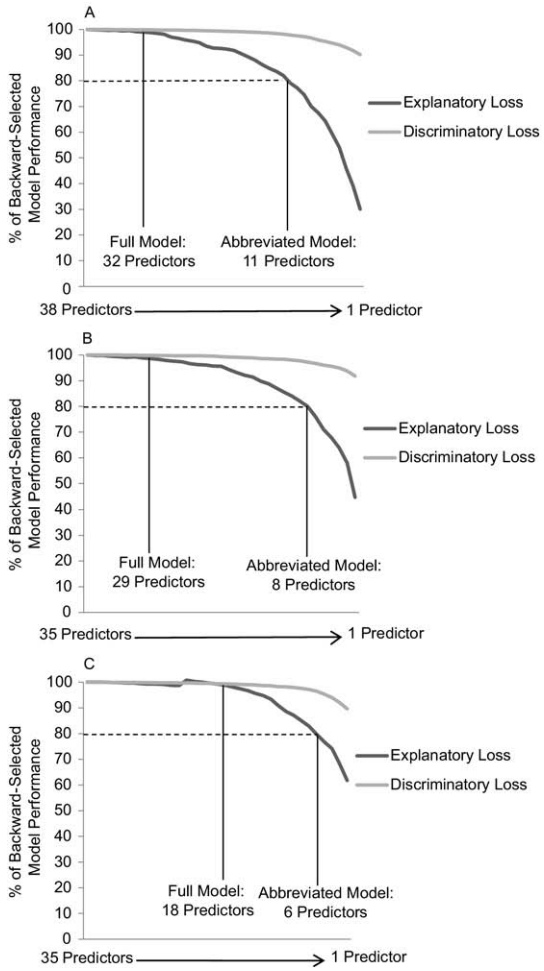

Figure 1. Performance of models for graft loss based on information available (A) pretransplant and at (B) 7 days and (C) 1 year posttransplant. The y-axes reflect the percentage of model performance obtained including all candidate predictors resulting from the backward-selection process. As the number of variables in each model is iteratively reduced (moving to the right on the x-axes), the lines depict loss of discriminatory ability and percentage of variation explained by the model. Final full models were defined when the percentage of variation explained was not <99% of the full candidate set; abbreviated models, when the percentage of variation explained was not <80% of the full candidate set. Of note, fewer variables are needed to attain the same model performance posttransplant compared with pretransplant.

Discrimination and calibration of the final models were assessed by applying the prediction equations to the 30% validation sample. The discriminatory ability of the full predic-

Table 1. Abbreviated Model for Predicting Graft Loss Within 5 Years Posttransplant, Prediction Made at Time of Transplant

Predictor	Mean ± SD or Percentage	Parameter[a]	HR (95% CI)	*P*
Donor age (y)	38 ± 17			
Donor age − 38		0.0088	1.01 (1.01-1.01)	<0.001
(Donor age − 38)^2		0.0003	1.00 (1.00-1.00)	<0.001
Race				
White	61.0		1.00 (reference)	
African American	30.8	0.1921	1.21 (1.16-1.27)	<0.001
Asian	5.8	−0.3168	0.73 (0.66-0.81)	<0.001
Other/unknown	2.4	−0.2059	0.81 (0.69-0.96)	0.01
RRT, if first Tx				
Preemptive Tx	5.3	−0.2883	0.75 (0.66-0.85)	<0.001
<1 y	8.7	−0.0797	0.92 (0.85-1.01)	0.07
1-<3 y	29.5		1.00 (reference)	
3-<5 y	23.7	0.0224	1.02 (0.96-1.08)	0.5
≥5 y	21.4	0.1565	1.17 (1.10-1.24)	<0.001
RRT, if subsequent Tx[b]				
<9 y	3.8	0.3815	1.46 (1.32-1.63)	<0.001
9-14 y	3.8	0.3392	1.40 (1.26-1.57)	<0.001
≥14 y	3.8	0.2631	1.30 (1.16-1.46)	<0.001
Recipient age	50 ± 13			
Recipient age − 50		0.0089	1.01 (1.01-1.01)	<0.001
(Recipient age − 50)^2		0.0006	1.00 (1.00-1.00)	<0.001
(Recipient age − 50) × (Donor age − 38)		−0.0001	1.00 (1.00-1.00)	0.03
Primary cause of CKD				
Diabetes	24.9		1.00 (reference)	
Hypertension	22.4	−0.1740	0.84 (0.79-0.89)	<0.001
Glomerulonephritis	25.2	−0.2555	0.77 (0.73-0.82)	<0.001
Cystic disease	8.8	−0.5202	0.59 (0.54-0.65)	<0.001
Other	18.7	−0.2097	0.81 (0.76-0.87)	<0.001
HCV antibody positive[c]	6.5	0.3978	1.49 (1.38-1.60)	<0.001
Donor history of hypertension	22.7	0.2009	1.22 (1.16-1.29)	<0.001
Primary insurance				
Medicare	57.0		1.00 (reference)	
Private	24.4	−0.1882	0.83 (0.78-0.88)	<0.001
Other	18.6	0.1016	1.11 (1.05-1.17)	<0.001
Trauma as donor cause of death	49.0	−0.1623	0.85 (0.81-0.89)	<0.001
HLA-A, -B, -DR mismatches[d]				
0	14.2		1.00 (reference)	
1-3	22.6	0.1466	1.16 (1.07-1.25)	<0.001
4-6	61.1	0.2376	1.27 (1.18-1.36)	<0.001
Unknown	2.1	0.3073	1.36 (1.18-1.57)	<0.001

Note: Ordered by level of contribution to model. N = 59,091.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HCV, hepatitis C virus; HR, hazard ratio; RRT, renal replacement therapy; SD, standard deviation; Tx, transplant.

[a]Parameter estimate before application of shrinkage parameter of 0.9876. Final coefficients are multiplied by this shrinkage parameter. Estimated 5-year event probabilities can be obtained as: $1 - 0.74666^{e^x}$, where x is equal to the linear predictor after applying the shrinkage parameter.

[b]Reference group is first transplant, 1 to less than 3 years of RRT.

[c]Reference group is HCV antibody negative or unknown.

[d]HLA-A, -B, and -DR mismatches were counted as a sum total.

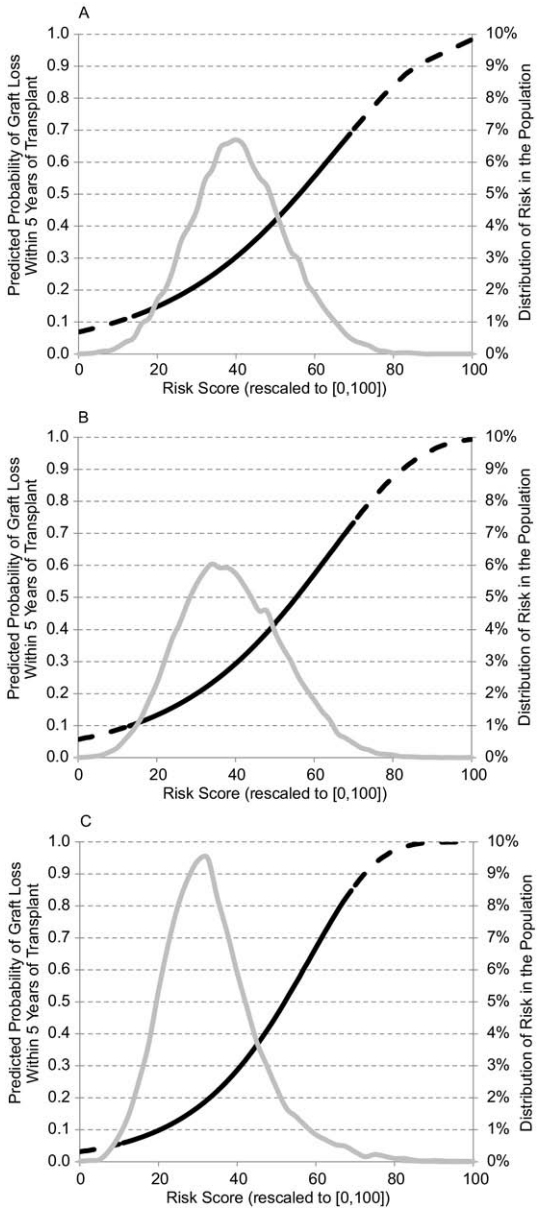

Figure 2. Conversion of risk level to predicted probability for the full models for graft loss within 5 years based on information available (A) pretransplant and (B) 7 days and (C) 1 year posttransplant. The distribution of risk in the population is shown in the histogram (gray lines, right axis). Predicted probabilities (black lines, left axis) associated with risk levels more extreme than the 1st and 99th percentiles are shown with dashed lines. A patient's risk score can be calculated as follows: (A) risk score = (x + 1.25)/4.05; (B) (x + 1.10)/4.46; (C) (x + 1.28)/5.94, where x is equal to the patient's linear predictor calculated from Tables 2, 3, and 4, respectively.

tion equation is modest, reflected by the C statistic of 0.649. However, 98% of the C statistic value was obtained by including only 11 of the 32 variables in the full model. The model was well calibrated, with a slope of the prognostic index of 1.04 ($P = 0.2$ for a test of whether the slope of the prognostic index = 1.0). The abbreviated model also was well calibrated, with a slope of 1.04 ($P = 0.3$).

Predicting Graft Loss Using Characteristics Known at 7 Days Posttransplant

Slightly fewer characteristics (n = 29) were associated with graft loss when the analysis was limited to patients with a functioning graft at 7 days posttransplant, allowing variables collected in the immediate posttransplant period (delayed graft function, eGFR at hospital discharge, and induction therapy) to be included (Table S3). Only 8 variables were needed to achieve 80% of the variation explained using the full model (Schemper V_2 statistic; Fig 1). These were (by order of contribution): eGFR at hospital discharge (by whether delayed graft function was reported), donor age, primary cause of CKD, recipient race, recipient age, and years on renal replacement therapy (by first vs subsequent transplant; Table 2).

The C statistic for the full model was 0.674, but 98% of its discriminatory power was obtained by including only 8 of the 29 variables in the full model. The model was well calibrated, with a slope of the prognostic index of 0.99 ($P = 0.7$ for a test of whether the slope of the prognostic index = 1.0). The abbreviated model also was well calibrated on average, with a slope of 1.00 ($P = 0.9$; Fig 3).

These models make clear that early graft function is an important predictor of subsequent graft loss (Table 2); delayed graft function and lower eGFR at discharge were associated with a higher likelihood of subsequent graft loss. Interestingly, the highest eGFR category (>90 mL/min/1.73 m^2) was associated paradoxically with higher risk of graft failure than eGFR of 60-89 mL/min/1.73 m^2 (Table 2).

Predicting Graft Loss Using Characteristics Known at 1 Year Posttransplant

Only 6 variables were needed to achieve 80% of the variation explained by the full model and

Table 2. Abbreviated Model for Predicting Graft Loss Within 5 Years Posttransplant, Prediction Made 7 Days Posttransplant

Predictor	Mean ± SD or Percentage	Parameter[a]	HR (95% CI)	*P*
Discharge eGFR, if no DGF[b] (mL/min/1.73 m^2)				
≥90	6.8		1.00 (reference)	
60-89	15.0	−0.0400	0.96 (0.85-1.09)	0.5
45-59	13.4	0.0467	1.05 (0.93-1.19)	0.5
30-44	15.9	0.1474	1.16 (1.03-1.31)	0.02
15-29	14.7	0.2394	1.27 (1.13-1.43)	<0.001
<15	9.9	0.5162	1.68 (1.48-1.89)	<0.001
Unknown	1.1	0.8726	2.39 (1.98-2.89)	<0.001
Discharge eGFR, if DGF[b,c] (mL/min/1.73 m^2)				
≥90	0.3	0.6705	1.96 (1.33-2.87)	<0.001
60-89	0.8	0.4773	1.61 (1.25-2.08)	<0.001
45-59	1.2	0.3583	1.43 (1.15-1.78)	0.001
30-44	2.3	0.6592	1.93 (1.64-2.27)	<0.001
15-29	5.2	0.6794	1.97 (1.73-2.25)	<0.001
<15	13.3	0.7930	2.21 (1.97-2.48)	<0.001
Unknown	0.3	1.7203	5.59 (4.27-7.31)	<0.001
Donor age (y)	38 ± 17			
Donor age − 38		0.0104	1.01 (1.01-1.01)	<0.001
(Donor age − 38)^2		0.0004	1.00 (1.00-1.00)	<0.001
Primary cause of CKD				
Diabetes	24.9		1.00 (reference)	
Hypertension	22.4	−0.2035	0.82 (0.77-0.87)	<0.001
Glomerulonephritis	25.2	−0.2824	0.75 (0.71-0.80)	<0.001
Cystic disease	8.8	−0.5822	0.56 (0.51-0.62)	<0.001
Other	18.6	−0.2394	0.79 (0.73-0.85)	<0.001
Race				
White	61.1		1.00 (reference)	
African American	30.7	0.2794	1.32 (1.26-1.39)	<0.001
Asian	5.8	−0.2771	0.76 (0.68-0.85)	<0.001
Other/unknown	2.4	−0.1379	0.87 (0.74-1.03)	0.1
Recipient age	50 ± 13			
Recipient age − 50		0.0101	1.01 (1.01-1.01)	<0.001
(Recipient age − 50)^2		0.0007	1.00 (1.00-1.00)	<0.001
(Recipient age − 50) × (Donor age − 38)		−0.0002	1.00 (1.00-1.00)	0.003
RRT, if first Tx				
Preemptive Tx	5.3	−0.1288	0.88 (0.77-1.00)	0.05
<1 y	8.8	−0.0702	0.93 (0.85-1.02)	0.1
1-<3 y	29.5		1.00 (reference)	
3-<5 y	23.7	0.0407	1.04 (0.98-1.11)	0.2
≥5 y	21.3	0.1866	1.21 (1.13-1.28)	<0.001
RRT, if subsequent Tx[d]				
<9 y	3.7	0.3885	1.47 (1.32-1.65)	<0.001
9-14 y	3.8	0.3138	1.37 (1.22-1.54)	<0.001
≥14 y	3.8	0.3238	1.38 (1.22-1.56)	<0.001

Note: Ordered by level of contribution to model. N = 57,603.

Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease; DGF, delayed graft function; eGFR, glomerular filtration rate (estimated using the 4 variable Modification of Diet in Renal Disease Study equation[24]); HR, hazard ratio; RRT, renal replacement therapy; SD, standard deviation; Tx, transplant.

[a]Parameter estimate before application of shrinkage parameter of 0.9862. Final coefficients are multiplied by this shrinkage parameter. Estimated 5-year event probabilities can be obtained as: $1 - 0.79965^{e^x}$, where x is equal to the linear predictor after applying the shrinkage parameter.

[b]Defined as need for dialysis in the first week posttransplant.

[c]Reference group is no DGF, eGFR ≥90 mL/min/1.73 m^2.

[d]Reference group is first transplant, 1 to less than 3 years of RRT.

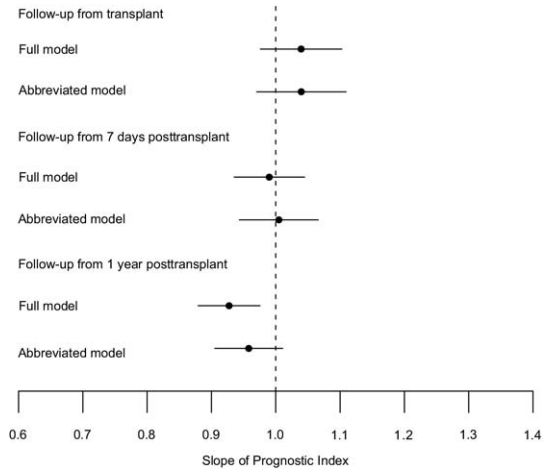

Figure 3. Calibration statistics (slopes of the prognostic index) for the full and abbreviated models for graft loss within 5 years based on information available pretransplant and 7 days and 1 year posttransplant. Slopes of 1.0 indicate good model calibration. Shown are calibration slopes and 95% confidence intervals.

maintain 98% of the discriminatory ability of the full 18-variable model (Table S4) for patients who survived with a functioning graft for at least 1 year (Schemper V_2 statistic; Fig 1). These were (by order of contribution): eGFR at 1 year posttransplant, recipient race, hospitalization during year 1 posttransplant, primary cause of CKD, recipient age, and recipient primary insurance coverage (Table 3).

The C statistic for the full model was 0.716, but 98% of its value was obtained by including only 6 of the 18 variables in the full model. The slope of the prognostic index for the full model was 0.93 ($P = 0.003$). Because this was significantly lower than 1.0, there is evidence that this model provides estimated probabilities too high on the upper end of the risk distribution and too low on the lower end (ie, predicted probabilities are overdispersed) when assessed against the validation set. The calibration slope of 0.93 indicates that predictions were within 5% of observed if the predicted probability was $\leq$0.22 and off by at most 10% if the predicted probability was $>$0.22. Understanding the magnitude of possible miscalibration can help interpret model results. The abbreviated model was well calibrated, with a slope of 0.96 ($P = 0.1$; Fig 3).

Predicting Death With Function and Death-Censored Graft Failure

In general, variables predicting death-censored graft failure and death with a functioning graft were similar to those predicting graft loss (data not shown). However, some differences were notable. For example, there was a linear relationship between recipient age and risk of death with function, but older recipient age was associated with lower risk of death-censored graft failure. Compared with the risk for white patients, the risk for African Americans was higher for death-censored graft failure, but lower for death with a functioning graft. For the most part, comorbidity (data from form CMS-2728) was associated with death with function, but not with death-censored graft failure.

DISCUSSION

We developed risk-prediction tools for graft loss, death-censored graft failure, and death with a functioning graft after deceased donor kidney transplant. Rather than including all of the many clinical variables that correlate with these outcomes in each model, we determined which variables could be used to account for $>$80% of the variation in outcomes explained by the larger set of candidate predictors, thereby limiting the models to a smaller number of readily available variables.

The interaction of total time on renal replacement therapy with first or subsequent transplants is noteworthy (and not previously reported, to our knowledge). For first transplant, the longer the dialysis therapy duration, the higher the risk of graft failure. However, risk of graft loss diminishes modestly for subsequent transplants for patients receiving renal replacement therapy for longer than 14 years versus less than 9 years. This result could reflect a "survivorship bias" or it could be caused by long-surviving patients being more likely to continue surviving.

During the past decade, several studies enumerated risk factors for outcomes after kidney transplant. We searched MEDLINE and bibliographies for publications reporting methods to predict posttransplant kidney function, graft failure, or death. We included only investigations published since 1999 with study populations of at least 500. We excluded studies reporting only

Table 3. Abbreviated Model for Predicting Graft Loss Within 5 Years Posttransplant, Prediction Made 1 Year Posttransplant

Predictor	Mean ± SD or Percentage	Parameter[a]	HR (95% CI)	*P*
eGFR, 1 y posttransplant (mL/min/1.73 m^2)				
≥90	13.6		1.00 (reference)	
60-89	35.8	0.1088	1.11 (0.99-1.25)	0.06
45-59	26.0	0.4072	1.50 (1.34-1.69)	<0.001
30-44	17.1	0.8788	2.41 (2.14-2.70)	<0.001
15-29	5.7	1.7310	5.65 (4.99-6.39)	<0.001
<15	0.6	2.8499	17.29 (14.21-21.02)	<0.001
Unknown	1.2	0.8140	2.26 (1.71-2.97)	<0.001
Race				
White	62.0		1.00 (reference)	
African American	30.0	0.3940	1.48 (1.39-1.58)	<0.001
Asian	5.8	−0.1517	0.86 (0.74-1.00)	0.05
Other/unknown	2.2	−0.0126	0.99 (0.79-1.24)	0.9
Hospitalized during y 1				
No	74.5		1.00 (reference)	
Yes	22.7	0.4498	1.57 (1.47-1.67)	<0.001
Unknown	2.9	0.2463	1.28 (1.07-1.53)	0.008
Primary cause of CKD				
Diabetes	24.4		1.00 (reference)	
Hypertension	22.0	−0.2088	0.81 (0.75-0.88)	<0.001
Glomerulonephritis	26.0	−0.3121	0.73 (0.67-0.79)	<0.001
Cystic disease	9.2	−0.6445	0.52 (0.46-0.60)	<0.001
Other	18.5	−0.3371	0.71 (0.65-0.78)	<0.001
Recipient age (y)	50 ± 13			
Recipient age − 50		0.0064	1.01 (1.00-1.01)	<0.001
(Recipient age − 50)^2		0.0008	1.00 (1.00-1.00)	<0.001
Primary insurance				
Medicare	56.7		1.00 (reference)	
Private	25.1	−0.3470	0.71 (0.65-0.76)	<0.001
Other	18.2	0.1346	1.14 (1.06-1.23)	<0.001

Note: Ordered by level of contribution to model. N = 43,743.

Abbreviations and definitions: CI, confidence interval; CKD, chronic kidney disease; eGFR, glomerular filtration rate (estimated by the 4-variable Modification of Diet in Renal Disease Study equation[24]); HR, hazard ratio; SD, standard deviation.

[a]Parameter estimate before application of shrinkage parameter of 0.9960. Final coefficients are multiplied by this shrinkage parameter. Estimated 5-year event probabilities can be obtained as: $1 - 0.86256^{e^x}$, where x is equal to the linear predictor after applying the shrinkage parameter.

immediate or early graft function, including delayed graft function. We thus identified 20 studies[1-20] (Table 4). All used logistic regression or Cox proportional hazards analysis to derive multivariate equations to predict one or more outcomes.

The goals of predicting outcomes in these studies varied (Table 4). Two used data collected at the time of wait listing for deceased donor kidney transplant to predict mortality on the waiting list compared with mortality posttransplant.[14,19] Nine predicted outcomes from deceased donor kidneys.[2,4-6,11,13,15,18,20] Six used information collected at the time of living donor transplant to predict outcomes.[7,10,12,14,16,20] Others predicted outcomes using data collected at the time of hospital discharge,[8] at 6 months posttransplant,[16] during the first year posttrans-

Table 4. Published Tools to Predict Outcomes After Kidney Transplant

Reference, Year Published	Population	No. of Study Participants	Transplant Dates	Outcomes[a]	Time of Assessment	Risk Prediction Method
Ojo et al,[1] 2000	USRDS, age ≥ 18 y, DD, LD	86,502	1988-1997	Death	Pretransplant[b]	HRs
Swanson et al,[2] 2002	USRDS, age ≥ 18 y, DD	20,309	1994-1998	DCGF	Pretransplant	HRs
Hariharan et al,[3] 2002	USRDS, age ≥ 18 y, DD, LD	105,742	1988-1998	GF	1 y posttransplant	HRs
Nyberg et al,[4] 2003	SRTR, age ≥ 18 y, DD	34,324	1994-1999	6-mo eGFR	Pretransplant	Points, from linear regression
Goldfarb-Rumyantzev et al,[5] 2003	SRTR, DD, kidney/pancreas	37,407	1990-1998	3-y GF	Pretransplant	ORs, tree-based algorithm[c]
Schold et al,[6] 2005	SRTR, age ≥ 18 y, first DD	45,850	1996-2002	GF	Pretransplant[c]	HRs
Jassal et al,[7] 2005	CORR, DD, LD	6,324	1988-1999	Death	Pretransplant	Tables, from HRs
Hernandez et al,[8] 2005	Single center, DD	1,293	1981-2001	Death	Hospital discharge[d]	HRs
Schaeffner et al,[9] 2006	Single center, DD, LD	710	1996-1998	Death, GF	5 y posttransplant[e]	HRs
Brennan et al,[10] 2006	SRTR, LD	8,603	1999-2002	1 y SCr > 1.5 mg/dL	Pretransplant	ORs
Baskin-Bey et al,[11] 2007	UNOS, age ≥18 y, DD	36,201	1995-2002	GF	Pretransplant	HRs
Krikov et al,[20] 2007	USRDS	92,844	1990-1999	DCGF	Pretransplant	Tree-based modeling
Akl et al,[12] 2008	Single center, LD	1,900	1976-2007	GF	Pretransplant[f]	Nomogram, from HRs
Rao et al,[13] 2009	SRTR, age ≥ 18 y, first DD	69,440	1995-2005	GF	Pretransplant	Points, from HRs
Schold et al,[14] 2009	SRTR, age ≥18 y, first DD, LD	108,928	1995-2000	Death	Listing for DD	HRs
Moers et al,[15] 2009	UNOS, age > 11 y, DD	99,860	1994-2006	Death, GF	Pretransplant[g]	ORs, HRs
Tiong et al,[16] 2009	UNOS, LD	20,085	2000-2003	1 y eGFR, GF	Pretransplant,[h] 6 mo posttransplant	Nomogram, from HRs
Hernandez et al,[17] 2009	Single center, DD	4,928	1990-2002	Death	1 y posttransplant	Points, from HRs
Machniki et al,[18] 2009	USRDS, DD, Medicare	25,270	1995-2002	GF, death	Pretransplant	HRs
van Walraven et al,[19] 2010	USRDS	169,393	1995-2006	Death	Time of wait-listing	Points, from HRs

Note: Studies published since 1999 including at least 500 patients and reporting 1 or more methods for predicting graft function, death, or GF. Studies reporting only delayed graft function were not included.

Abbreviations: CORR, Canadian Organ Replacement Registry; DCGF, death-censored graft failure; DD, deceased donor; eGFR, estimated glomerular filtration rate from serum creatinine level; GF, graft failure; HR, hazard ratio; LD, living donor; OR, odds ratio; SCr, serum creatinine; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing; USRDS, US Renal Data System.

[a]Death is death with graft function; GF includes deaths, return to dialysis therapy, or retransplant.

[b]Posttransplant variables delayed graft function and acute rejections up to 6 months were included, but nothing indicated that all patients analyzed had survived at least 6 months without rejection.

[c]Readers cannot use the results presented to predict outcomes with the information provided.

[d]Includes information from initial hospitalization.

[e]Convenience sample of patients attending clinic a mean of 5 years after transplant.

[f]Posttransplant variables delayed graft function and acute rejections up to 3 months after transplant were included, but nothing indicated that all patients analyzed had survived at least 3 months with a functioning graft.

[g]The posttransplant variable delayed graft function was included, but nothing indicated that all patients analyzed had survived with functioning grafts beyond when they may have had delayed graft function (eg, excluding primary nonfunction).

[h]Includes information for initial immunosuppressive medications used after transplant.

Table 5. Risk Factors for Reduced Function or Graft Failure

Risk Factors	Previous Studies, Reference Numbers	Present Study	
		Full Models	Abbreviated Models
Recipient characteristics			
Age	3, 5, 10, 12, 15, 16, 18	Yes	Yes
Sex	3, 5, 9, 10, 16, 18	Yes	—
Race/ethnicity	3, 10, 16, 18	Yes	Yes
Body surface area	10, 16	—	—
Obesity or BMI	5, 9, 18	Yes	—
HCV		Yes	Yes
Congestive heart failure	18	Yes	—
Atherosclerotic heart disease	18	Yes	—
Hypertension	18	Yes	—
Diabetes	3, 18	Yes	—
COPD	18	Yes	—
Tobacco use	18	Yes	—
Substance abuse	18	Yes	—
Limitations in ADLs	18	Yes	—
Cause of CKD	3, 16, 18	Yes	Yes
Preemptive transplant	3	Yes	Yes
Pretransplant transfusions	3	NE	NE
Dialysis modality		Yes	—
Prior transplant	3, 5, 15	Yes	Yes
Time on waiting list	15	NE	NE
Duration of RRT	18	Yes	Yes
Insurance coverage		Yes	Yes
HLA antigen mismatches	3, 5, 6, 13, 15, 16, 18	Yes	Yes
Cross-match positive		Yes	—
Panel-reactive antibody	3, 15, 18	Yes	—
Cytomegalovirus D^+/R^-	6, 18	Yes	—
Donor characteristics			
Deceased vs living[a]	3	NA	NA
Related vs unrelated[a]	10	NA	NA
Haplotype[a]	12	NA	NA
Laparoscopic[a]	16	NA	NA
Right kidney used		—	—
En bloc vs sequential	5, 13	—	—
Double kidney transplant	13	NA	NA
Donation after cardiac death	13, 15	Yes	—
Expanded criteria donor	15	—	—
Cause of death	4, 6, 13, 15	Yes	Yes
Age	3-6, 10, 12, 16, 18	Yes	Yes
Sex	16	Yes	—
Race/ethnicity	16, 18	Yes	—
Body surface area	10	NE	NE
Obesity/BMI	16, 18	Yes	—
Height and weight	13	NE	NE
Diabetes	15, 18	Yes	—
Hypertension	15, 18	Yes	Yes
HCV antibody positive	13	Yes	—
Cocaine use		—	—
No intravenous drug use	18	—	—
Terminal SCr/eGFR	16	Yes	—
Machine perfusion	15	NE	NE
Cold ischemia time	15	Yes	—

(Continued)

Table 5 (Cont'd). Risk Factors for Reduced Function or Graft Failure

Risk Factors	Previous Studies, Reference Numbers	Present Study	
		Full Models	Abbreviated Models
Posttransplant events			
Induction used	16	Yes	—
Total steroid dose	12	NE	NE
Mycophenolate mofetil used	16	NE	NE
Tacrolimus used	12	NE	NE
Calcineurin inhibitor used	16	NE	NE
Sirolimus used	16	NE	NE
Delayed graft function	16	Yes	Yes
Posttransplant SCr or eGFR	16	Yes	Yes
Acute rejection	16	Yes	—
Hospitalization		Yes	Yes
Disease recurrence		—	—
Treatment nonadherence		Yes	—
Malignancy		Yes	—
Proteinuria		—	—
Recipient functional status		Yes	—
Center volume	5	NE	NE

Abbreviations and definitions: ADLs, activities of daily living; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; D^+, donor positive; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; NA, not applicable; NE, not examined; R^-, recipient negative; RRT, renal replacement therapy; SCr, serum creatinine.

[a]Applicable to only studies including living donor transplants.

plant,[3,17] or (using cross-sectional data) at a mean of 5 years posttransplant.[9]

None of these studies attempted to define a minimal set of variables that would risk-stratify patients, and most did not provide tools to allow readers to readily apply prediction equations to individual patients. Two developed nomograms.[12,16] Two published tables that allowed readers to look up the risk for an individual patient.[7,8] Six provided point systems[4,10,11,17,19] or used a formula to calculate points.[13] The remaining 10 provided no mechanism to predict outcomes for individual patients.[1-3,5,6,9,14,15,18,20]

In the present study, we focused on predicting posttransplant outcomes for deceased donor kidney recipients from 3 different vantage points: (1) pretransplant, (2) at 7 days posttransplant, and (3) at 1 year posttransplant. The 1-year model included the occurrence of delayed graft function, acute rejection, and hospitalization and 1-year eGFR (based on serum creatinine level). We did not compare outcomes on the waiting list with transplant outcomes, which could inform the decision of whether to remain on dialysis therapy or undergo transplant. We also did not examine living donor transplant outcomes.

Thirty-two, 29, and 18 variables predicted graft failure assessed pretransplant and at 7 days and 1 year posttransplant, respectively. However, 80% of the variability in prediction (Schemper V_2 statistic) and 98% of the discriminatory ability of the full models could be accounted for by 11, 8, and 6 variables, respectively. Interestingly, variables generally associated with higher immunologic risk, such as HLA antigen mismatches, positive cross-match, and high panel-reactive antibody titer, were associated with graft loss at the time of transplant or at hospital discharge, but not at 1 year posttransplant. However, these immunologic risk variables were "replaced" by acute rejection in the first year and eGFR at 1 year (Table 3). Also of interest, several donor factors tended to become less important predictors with time. At the time of transplant, donor age, donor hypertension, and donor cause of death each independently predicted graft survival (Table 1). However, none of these factors remained in the model using information known at 1 year posttransplant to predict subsequent graft survival (Table 3). Possibly, the effects of these factors were manifest at different levels of graft function, which were included in the 1-year

model, but were not yet known at the time of transplant.

Variables used to predict risk in this study are similar to, albeit more numerous than, the variables generally reported by others (Table 5). Key variables in the abbreviated models (Tables 1-3), such as recipient age, recipient race/ethnicity, donor age, and number of HLA antigen mismatches, often have been reported to be important predictors of posttransplant graft function and graft failure (Table 5).

There are some important limitations to this study. The prediction models are only as good as the data used in their derivation. Although most demographic variables likely are accurate for recipients and donors, many other data are suspect. For example, we used comorbidity data from the CMS Medical Evidence Report (form CMS-2728) to supplement comorbidity data available in the OPTN data. A recent validation study found that comorbid conditions were significantly underreported on this form.[25] Thus, although specificity was good (>0.95 for most comorbid conditions), sensitivity was low, averaging 0.59 for 17 comorbid conditions.[25] Better comorbidity data could increase the predictive ability of our models.

In general, models with C statistic values <0.70, with 0.50 being random and 1.00 being perfect, should be considered to have only modest ability to discriminate risk for an individual patient. In the prediction models, it is interesting and perhaps not surprising that the C statistic improved slightly from 0.649 pretransplant to 0.674 at hospital discharge and 0.716 at 1 year posttransplant, despite fewer variables (only 7) being included in the prediction model at 1 year. The pretransplant models and models from day 7 were well calibrated on average, whereas the model from 1 year appears to provide risk estimates that are overdispersed by about 5% at the level of risk at which most patients were observed to be and by at most 10% at the high end of risk. Recognizing these limitations, these models can provide a general assessment of risk, including estimated probabilities of events along with percentiles of risk based on a national sample of kidney transplant patients.

Table 6. Model Performance in 5 Randomly Selected Transplant Centers

Transplant Center	No. of Patients	Calibration		Discrimination C Statistic (95% CI)
		Calibration Slope (95% CI)	*P*[a]	
		Model 1. Time of Transplant		
A	58	1.18 (−0.08-2.44)	0.8	0.70 (0.57-0.82)
B	256	1.03 (0.42-1.63)	0.9	0.62 (0.55-0.70)
C	235	0.73 (0.20-1.27)	0.3	0.61 (0.54-0.68)
D	151	1.64 (0.52-2.75)	0.3	0.69 (0.56-0.82)
E	451	1.07 (0.60-1.54)	0.8	0.63 (0.57-0.69)
		Model 2. Day 7 Posttransplant		
A	54	1.21 (0.01-2.41)	0.7	0.72 (0.52-0.92)
B	253	0.83 (0.35-1.32)	0.5	0.63 (0.55-0.71)
C	229	0.85 (0.31-1.39)	0.6	0.63 (0.55-0.71)
D	149	1.64 (0.59-2.68)	0.2	0.69 (0.53-0.85)
E	443	0.73 (0.30-1.17)	0.2	0.60 (0.53-0.67)
		Model 3. 1-Year Posttransplant		
A	41	1.26 (−0.18-2.69)	0.7	0.65 (0.55-0.76)
B	170	0.68 (0.32-1.04)	0.08	0.68 (0.60-0.77)
C	436	0.94 (0.53-1.34)	0.8	0.66 (0.58-0.73)
D	206	0.89 (0.22-1.56)	0.8	0.64 (0.51-0.78)
E	162	1.34 (0.90-1.78)	0.1	0.78 (0.70-0.86)

Abbreviation: CI, confidence interval.
[a]Test of calibration slope = 1.

Including immunosuppressive medication in models derived from retrospective observational data is problematic because it is difficult, if not impossible, to adequately account for selection bias. Maintenance immunosuppressive medications in particular often are started, stopped, and switched at different times posttransplant as patients assume different levels of risk. We chose to include only induction therapy because its use is discretely determined in the first 7 days posttransplant. Nevertheless, the potential remains for unaccounted bias in the use of induction agents. However, use of induction agents was not an independent predictor in the final limited models (Tables 2 and 3).

One limitation of risk-prediction models derived from large multicenter data sets is in knowing how applicable the prediction models are for individual centers. We addressed this important issue by testing the models in 5 randomly selected single centers. Calibration slopes, although varying around 1.0, were not significantly different from 1.0 in any of the centers or models assessed. Discrimination statistics also varied by center, but generally were close to those achieved in the full population (Table 6).

In conclusion, we developed a practical system for predicting the risk of graft loss, death-censored graft failure, and mortality after deceased donor kidney transplant. A clinician can estimate the risk pretransplant, at the time of hospital discharge, and at 1 year posttransplant by entering the information into a web-based calculator to determine risk (www.txscores.org). We believe that this tool provides the best available information for predicting risk and that it may help clinicians make important decisions regarding selection of deceased donor kidneys and posttransplant management strategies.

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SUPPLEMENTARY MATERIALS

Table S1. Recipient, Donor, and Transplant Characteristics Included in the Analysis.

Table S2. Full Model for Predicting Graft Loss Within 5 Years Posttransplant, Prediction Made at Time of Transplant.

Table S3. Full Model for Predicting Graft Loss Within 5 Years Posttransplant, Prediction Made 7 Days Posttransplant.

Table S4. Full Model for Predicting Graft Loss Within 5 Years Posttransplant, Prediction Made 1 Year Posttransplant.

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