A Simplified Donor Risk Index for Predicting Outcome After Deceased Donor Kidney Transplantation

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Background. We sought to determine the deceased donor factors associated with outcome after kidney transplantation and to develop a clinically applicable Kidney Donor Risk Index.
Methods. Data from the UK Transplant Registry on 7620 adult recipients of adult deceased donor kidney transplants between 2000 and 2007 inclusive were analyzed. Donor factors potentially influencing transplant outcome were investigated using Cox regression, adjusting for significant recipient and transplant factors. A United Kingdom Kidney Donor Risk Index was derived from the model and validated.
Results. Donor age was the most significant factor predicting poor transplant outcome (hazard ratio for 18–39 and 60+ years relative to 40–59 years was 0.78 and 1.49, respectively, $P<0.001$). A history of donor hypertension was also associated with increased risk (hazard ratio 1.30, $P=0.001$), and increased donor body weight, longer hospital stay before death, and use of adrenaline were also significantly associated with poorer outcomes up to 3 years posttransplant. Other donor factors including donation after circulatory death, history of cardiothoracic disease, diabetes history, and terminal creatinine were not significant. A donor risk index based on the five significant donor factors was derived and confirmed to be prognostic of outcome in a validation cohort (concordance statistic 0.62). An index developed in the United States by Rao et al., *Transplantation* 2009; 88: 231–236, included 15 factors and gave a concordance statistic of 0.63 in the UK context, suggesting that our much simpler model has equivalent predictive ability.
Conclusions. A Kidney Donor Risk Index based on five donor variables provides a clinically useful tool that may help with organ allocation and informed consent.

Keywords: Kidney transplantation, Deceased donation, Graft survival.

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The severe shortage of deceased donor (DD) organs available for transplantation has led to increased use of kidneys from suboptimal donors with potentially less good transplant outcome. Categorizing such kidneys according to anticipated outcome is important because it enables clinicians to be better informed when making decisions about organ allocation and allows appropriate counseling of potential recipients.

Kidneys from suboptimal donors are variously referred to as marginal, extended criteria, or expanded criteria organs. While the criteria for a "marginal" organ are not well defined, expanded criteria kidneys have been carefully defined based on an analysis of data held by the Scientific Registry of Transplant Recipients (SRTR) (*1*). Expanded criteria kidneys are those which have a relative risk of graft loss greater than 1.7 when compared with kidneys from young donors (aged 10–39 years) with a normal creatinine at death (less than 1.5 mg/dL) and without a history of hypertension or death from a cerebrovascular accident (CVA). However, the binary division of donor kidneys into those of standard and expanded criteria is an oversimplification. For example, the relative risk of graft loss for expanded criteria kidneys varies from 1.74 (age 50–59 years with hypertension and a raised creatinine) to 2.69 (age more than 60 years with hypertension, raised creatinine, and dying from a CVA). Likewise, the risk of graft loss for kidneys that were defined as standard criteria is not uniform, with relative risks of graft loss ranging up to 1.66 for donors aged 40 to 49 years with a raised creatinine who died from a CVA.

Although categorizing DD kidneys as either standard or expanded criteria has the advantage of simplicity, it does

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TABLE 1. Significant donor factors in a risk-adjusted Cox proportional hazards transplant survival model after adult deceased donor, adult recipient, and first kidney only transplants performed in the United Kingdom, January 1, 2000, to December 31, 2007

Variable	Category	Overall (n=4342)		0 to 3 mo (n=4342)		3 mo to 3 yr (n=4003)		Over 3 Years (n=2412)	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Donor age (yr)	18–39	0.78 (0.66–0.93)	**<0.0001**	0.87 (0.65–1.16)	**0.003**	0.67 (0.50–0.91)	**<0.0001**	0.80 (0.60–1.08)	**0.015**
	40–59	1.00		1.00		1.00		1.00	
	≥60	1.49 (1.27–1.74)		1.51 (1.16–1.98)		1.57 (1.23–2.02)		1.38 (1.02–1.88)	
History of hypertension	Yes	1.30 (1.12–1.51)	**0.0006**	1.11 (0.85–1.44)	0.45	1.45 (1.14–1.84)	**0.003**	1.37 (1.03–1.81)	**0.035**
	No	1.00		1.00		1.00		1.00	
Donor weight	Continuous (per 10 kg)	1.03 (0.98–1.07)	0.26	1.12 (1.05–1.20)	**0.001**	1.00 (0.93–1.08)	0.96	0.93 (0.85–1.01)	**0.072**
Days in hospital	Continuous	1.01 (1.00–1.01)	0.29	1.02 (1.01–1.02)	**0.009**	1.00 (0.98–1.02)	0.66	0.99 (0.97–1.01)	0.44
Epinephrine / adrenaline	Yes	1.05 (0.89–1.24)	0.59	1.08 (0.81–1.44)	0.59	1.37 (1.05–1.79)	**0.026**	0.76 (0.54–1.05)	**0.087**
	No	1.00		1.00		1.00		1.00	

Hazard ratios are adjusted for all other donor factors in the table, and recipient age, ethnicity, primary renal disease, whether or not transplantation preempted the need for dialysis, HLA mismatch, cold ischemia time, and year of transplant.

Statistically significant *P*-values are shown in bold.

HR, hazard ratio; CI, confidence interval; HLA, human leukocyte antigen.

not adequately reflect the wide spectrum of donor kidney quality, and this has led to the development of more refined approaches to assessing the quality of DD kidneys. The most comprehensive of these is the Kidney Donor Risk Index (KDRI) developed by Rao et al. (*2*) based on a larger subset of patients in the SRTR than that used in the original analysis to define expanded criteria. Previous indices, such as those of Nyberg et al. (*3*) and Schold et al. (*4*), were derived from a smaller group of potential donor factors. The KDRI was developed and validated on US data alone and its applicability to DD kidneys outside the United States is not clear. We have undertaken an in-depth analysis of UK Transplant Registry data to determine donor factors that predict poorer transplant outcome in the United Kingdom and propose a simplified and clinically applicable donor risk index to aid decision making with respect to organ offering and allocation.

RESULTS

To determine the factors that influence transplant survival, the time from transplant to the earlier of graft failure or patient death, we analyzed UK Transplant Registry data from 7620 first adult kidney only recipients of adult DD kidney transplants performed between January 1, 2000, and December 31, 2007.

Modeling and Validation Datasets

A donor risk index was developed by dividing the transplant dataset randomly into modeling and validation datasets comprising 4570 (60%) and 3050 (40%) transplants, respectively. There were no significant differences between the distributions of each of the donor factors between the modeling and validation datasets, although donors in the modeling dataset were slightly heavier ($P=0.09$) (see **Table 1, SDC 2,** http://links.lww.com/TP/A577). Analysis of demographic data for recipients of kidneys from the modeling and validation cohorts showed that only male gender (60.9% vs. 63.4%, $P=0.03$) and recipient age (median 50 years vs. 49 years; $P=0.01$) differed between the two groups (see **Table 2, SDC 3,** http://links.lww.com/TP/A578); all other factors were similar.

Factors Influencing Kidney Transplant Outcome

Of the recipient and transplant factors considered for inclusion in the model for transplant survival, the following were significant in the modeling data set: recipient age, ethnicity, primary renal disease, whether or not transplantation preempted the need for dialysis, human leukocyte antigen (HLA) mismatch, cold ischemia time, and year of transplant.

Donor factors were then considered for inclusion in this model, and of these, donor age group and history of hypertension were found to affect overall survival. To investigate whether some factors influence transplant survival in different time periods, the significance of each factor in the three posttransplant periods from 0 to 3 months, 3 months to 3 years, and over 3 years, was examined.

Donor age group was the most significant factor predicting poor transplant outcome (hazard ratio [HR] for 18–39 and 60+ years relative to 40 to 59 years was 0.78 and 1.49, respectively; $P<0.001$). This effect persisted through all transplant follow-up epochs (Table 1). The donor age categories chosen were found to better reflect the effect of donor age on outcome than consideration of age as a continuous variate. A donor history of hypertension was associated with an overall increase in risk of transplant failure (HR 1.30, $P=0.001$). Although it had little effect in the first 3 months after transplant, donor hypertension had a significant association thereafter (3 months to 3 years, HR 1.45, $P=0.003$; over 3 years, HR 1.37, $P=0.035$). Other donor factors that were associated with inferior transplant outcome included increased donor weight, an effect that was only significant in the first 3 months (HR 1.12 for each 10 kg, $P=0.001$). Conversely, there was a trend toward increased donor weight being associated with improved

transplant outcomes beyond 3 years (HR 0.93 for each 10 kg weight increase, $P=0.072$). Neither the last serum creatinine before donor death nor death from a cardiovascular accident were significant predictors of transplant outcome, although a weak association between creatinine and outcome ($P=0.08$) was observed.

Longer duration of hospital stay before donor death was associated with inferior early transplant outcome (HR 1.02, $P=0.009$) but had no influence on long-term outcome. The use of either noradrenaline or vasopressin in the donor did not affect transplant outcome. However, the use of adrenaline was associated with an inferior transplant survival between 3 months and 3 years (HR 1.37, $P=0.026$), but there was no association in the immediate posttransplant period or in the long term. There was no evidence for including other than linear effects of duration of hospital stay and donor weight, and there were no interactions between the donor factors.

A UK donor risk index was derived from the parameter estimates of the donor factors in the Cox model developed for overall transplant survival. This gives the following index:

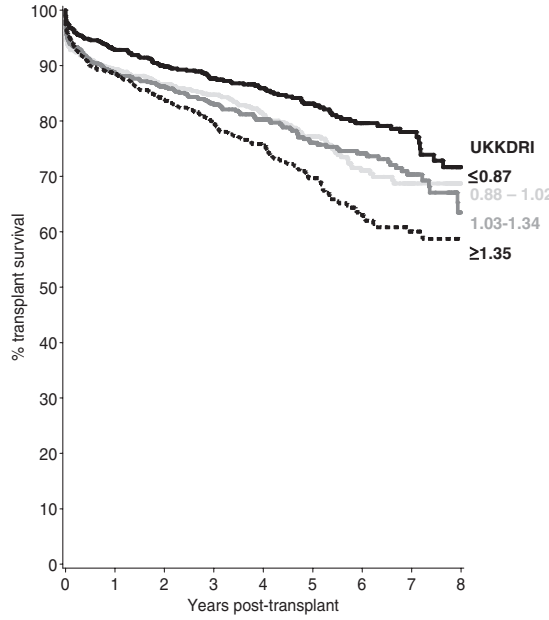

FIGURE 1. Survival curves according to quartiles of the UKKDRI in the validation cohort. UKKDRI, United Kingdom Kidney Donor Risk Index.

UK Kidney Donor Risk Index

$$\begin{aligned}\text{UKKDRI} = \exp\{&-0.245\times(\text{donor age} < 40)+\\ &0.396\times(\text{donor age} \geq 60)+\\ &0.265\times(\text{history of hypertension})+\\ &0.0253\times[\text{donor weight(kg)}-75]/10)+\\ &0.00461\times(\text{days in hospital})+\\ &0.0465\times(\text{adrenaline})\}\end{aligned}$$

where donor age less than 40 years is 1 if donor age is less than 40 years and 0 otherwise, donor age ≥60 is 1 if donor age is 60 years or more and 0 otherwise, history of hypertension=1 for a positive history and 0 otherwise, and adrenaline=1 if the donor was on adrenaline and 0 otherwise.

The United Kingdom Kidney Donor Risk Index (UKKDRI) is equal to 1.0 for a donor aged 40 to 59 years, weighing 75 kg, with no history of hypertension, a hospital stay less than1 day, and not given adrenaline. An index less than 1 indicates a lower risk donor and a risk index more than 1 indicates a higher risk donor.

Validation of UKKDRI

The UKKDRI was validated by fitting it to the validation cohort of 3050 kidney transplants. The change in the log-likelihood ratio statistic (−2 log L) on adding UKKDRI to the model was highly significant ($P<0.001$), confirming that the index is strongly associated with transplant survival. There was no evidence of a nonlinear effect of UKKDRI on transplant outcome.

Values of the Akaike's Information Criterion statistic for the model that contains (i) the variables in the UKKDRI and relevant transplant and recipient factors and (ii) the additional donor factors that are in the United States derived Kidney Donor Risk Index (USKDRI) were 5103.9 and 5104.8, showing that the additional donor factors in the USKDRI do not improve model fit.

To assess the predictive ability of the Cox model that was used to derive the UKKDRI, the concordance statistic (c-statistic) is 0.62 (se=0.011), which indicates that the model has some predictive ability.

To further examine the ability of UKKDRI to predict transplant survival, the index was divided into quartiles, based on data in the modeling data set, giving the ranges ≤0.87, 0.88–1.02, 1.03–1.34, and ≥1.35. Transplant survival curves for patients with UKKDRI values in these four groups were then obtained for the validation data set and shown in

TABLE 2. Transplant survival after adult deceased donor, adult recipient, and first kidney only transplants in the validation cohort according to UK Kidney Donor Risk Index

UK Kidney Donor Risk Index	No. at risk on day 0	% transplant survival (95% confidence intervals)			
		90 d	1 yr	3 yr	5 yr
≤0.87	718	95.5 (93.8–96.8)	92.8 (90.7–94.5)	87.6 (84.9–89.9)	83.1 (79.7–86.0)
0.88–1.02	761	92.4 (90.3–94.1)	89.3 (86.9–91.3)	84.7 (81.8–87.2)	77.2 (73.4–80.4)
1.03–1.34	734	93.2 (91.1–94.8)	88.7 (86.2–90.8)	83.0 (80.0–85.6)	76.1 (72.1–79.5)
≥1.35	689	92.6 (90.4–94.3)	88.6 (86.0–90.8)	79.7 (76.2–82.7)	70.0 (65.3–73.6)
Overall	2902	93.4 (92.5–94.3)	89.9 (88.7–90.9)	83.8 (82.4–85.2)	76.7 (74.8–78.5)

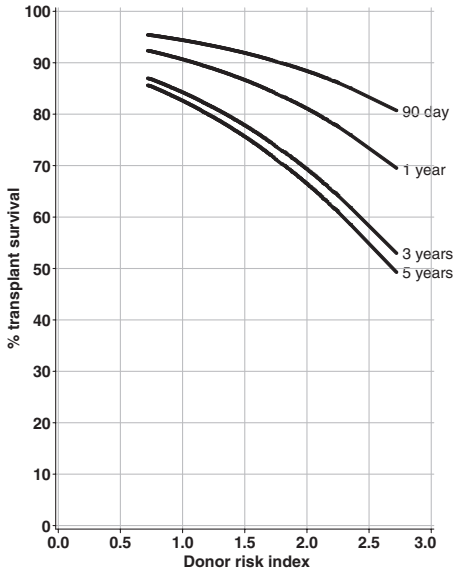

FIGURE 2. Predicted transplant survival rates at 90 days, 1, 3, and 5 years posttransplant according to United Kingdom kidney donor risk index and based on a recipient with "baseline " values (age 50 years, white, on dialysis, with glomerulonephritis, 000 HLA-A, B, DR mismatched transplant, and cold ischemia time 17 hr).

Figure 1. This clearly shows that the UKKDRI does distinguish between the survival of patients; the difference in the 75% survival rate ranges from 4.0 to 7.1 years. Table 2 shows the transplant survival rates for patients in the validation cohort stratified into the four groups of the risk index.

Transplant survival rates were also estimated according to various values of the UKKDRI for 3 months, and 1, 3, and 5 years and are illustrated in Figure 2. The estimates were based on a standardized recipient who was white, aged 50 years, on dialysis before transplantation, with glomerulonephritis, and receiving a 000 HLA-A, B, DR mismatched transplant with a cold ischemia time of 17 hr. The difference in transplant survival at 5 years between donor kidneys with the highest and lowest UKKDRI is estimated to be over 40%.

Comparison of the UKKDRI With the USKDRI

We next compared the UKKDRI with the USKDRI (*2*) for each transplant in the validation dataset. Adding either the UKKDRI or the USKDRI to a Cox model fitted to the validation data set that contains all the significant recipient and transplant factors, the change in -2 log L reveals that both indices are highly significant prognostic indicators ($P<0.0001$) for the UK data. For models that contained UKKDRI or USKDRI, the c-statistic was 0.62 and 0.63, respectively, so that the predictive ability of the two models is practically identical. However, the UKKDRI has the advantage of simplicity as it is derived from just five donor factors, whereas the USKDRI incorporates 15 factors.

DISCUSSION

To provide a clinical tool for predicting the likely outcome of DD kidney transplantation, we have derived a UKKDRI based on donor factors readily available to the transplant surgeon at the time of donor organ offer. Of the 19 donor variables considered for inclusion in the UKKDRI, the two most important were donor age group and hypertension, of which donor age had the largest influence on transplant outcome.

Neither terminal donor serum creatinine nor death from CVA predicted transplant outcome which contrasts with findings from the SRTR analysis where these were two of the four factors used to define expanded criteria (*1*). Our finding that terminal serum creatinine is not independently associated with transplant outcome is not perhaps surprising; any potential effect is likely to be dominated by donor age, because renal function deteriorates progressively with age. Moreover, where kidneys were used from donors with a high serum creatinine, it is probable that the decision to proceed was based on additional information suggesting acute recoverable renal injury and a recent near-normal premorbid creatinine.

Donation after circulatory death was not found to be an adverse factor for transplant outcome in the United Kingdom in this analysis, nor in another recent UK analysis (*5*). Similarly, donor diabetes did not predict poor transplant outcome although this may be because of the small number of donors with diabetes. In the first analysis of the SRTR database, donor diabetes was not an adverse factor, but subsequent analysis of a larger data set showed it to be a significant risk factor (*1*, *2*). It was notable that in this study, neither a history of smoking nor donor ethnicity was associated with transplant outcome, although the number of ethnic minority DD was small.

Dividing the transplant follow-up period into three distinct posttransplant epochs allowed us to assess the role of individual donor factors on transplant outcome in more detail. Donor age was the most important predictor of poor transplant outcome in all three epochs studied. Donor history of hypertension remained a significant risk factor affecting medium and long-term outcome (3 months onward) but was not associated with early posttransplant outcome.

Three other donor factors had significant effects on outcome in different epochs. Donor weight had a deleterious effect in the early posttransplant period but favored long-term graft survival. Obese donors have more perirenal fat, and one potential explanation for the deleterious effect of increased donor body weight in the short term may be a rewarming effect at the time of organ retrieval. Perinephric fat does not cool down quickly during in situ cold perfusion and may rewarm the kidneys after perfusion stops contributing to ischemic injury. In addition, dissection in an obese donor is more challenging and there is a greater risk of kidney damage that may also affect early outcome.

The duration of inpatient stay before organ donation, particularly stay in intensive care, is generally believed to be associated with poor transplant outcome, but surprisingly, this variable has not been included in previous registry studies of kidney, liver, and pancreas transplantation (*2*, *6*, *7*). In this study, length of hospital stay before organ donation was related to transplant outcome only in the early posttransplant period. The use of adrenaline (epinephrine) in the donor at the time of organ donor referral also influenced transplant outcome, but only between 3 months and 3 years. It is not clear why the use of adrenaline or the length of hospital stay had effects on transplant outcome that were limited to their respective epochs.

When establishing the UKKDRI, we adjusted for recipient and transplant-related factors, but chose to incorporate in the index itself only factors that characterized the donor kidney, and not recipient or transplant-related factors, such as cold ischemic time that are unknown at the time of organ offer for transplantation. There was no evidence of any interaction effect between UKKDRI and recipient factors, so the risk index can be used independently to aid understanding about donor organ quality at the time of offering and in gaining informed consent. It can also be used in conjunction with other factors in risk-adjusted outcome analyses.

In summary, the UKKDRI provides a simple, clinically useful tool that allows prediction of transplant outcome. It will aid transplant surgeons and others in organ allocation and gaining fully informed consent from potential transplant recipients.

MATERIALS AND METHODS

We analyzed data submitted to the UK Transplant Registry held by National Health Service Blood and Transplant. The registry records mandatory data on all kidney transplants performed in the United Kingdom supplied by all 23 adult UK kidney transplant centers.

Data from 7620 adult recipients of adult DD kidney transplants performed between January 1, 2000, and December 31, 2007, were analyzed. A number of donor variables were studied, all of which were routinely available to the recipient center at the time of the kidney offer for transplantation: donor age group (18–39, 40–59, and 60+ years), gender, ethnicity, donor type (donation after brain death or circulatory death), terminal creatinine (the last value measured before the offer), cause of death (trauma, intracranial hemorrhage, and other), weight, height, body mass index, abdominal girth, length of time in hospital, urine output in the hr before the offer, whether on adrenaline (epinephrine), noradrenaline (norepinephrine) or vasopressin, and history of cardiothoracic disease (unspecified), smoking, diabetes, or hypertension.

To develop a valid donor risk model, it was necessary to adjust for recipient and transplant factors that may influence transplant survival. Factors considered were recipient age, renal disease (glomerulonephritis, polycystic kidney disease, diabetes, "not reported," or "other"), gender, ethnicity (white, Asian, black, or other), preemptive transplantation, HLA mismatch (according to the four levels used in the UK 2006 Kidney Allocation Scheme [*8*] but ignoring the defaulting of rare antigens to more common counterparts), year of transplant, cold ischemia time, donor-recipient cytomegalovirus match, and donor-recipient gender match.

To develop a donor risk index, the transplant dataset was randomly divided into a modeling dataset comprising 4570 (60%) transplants and a validation dataset comprising 3050 (40%) transplants. The randomization and all other statistical analyses were carried out using SAS (version 9.1, SAS Institute Inc., NC).

Statistical Methodology

The distribution of donor, recipient, and transplant factors in the modeling and validation data sets were compared using a chi-square test. In cases where there were large numbers of missing values, a *P* value is also given for comparing the two data sets excluding the unknowns. Where continuous variables were grouped, the median values were compared using the Mann-Whitney *U* test.

The outcome variable was transplant survival, defined as time from transplant to the earlier of graft failure or patient death. Donor factors influencing transplant survival were investigated using Cox proportional hazards regression, adjusting for significant recipient and transplant factors identified. Survival times were stratified by transplant center to allow for possible differences between centers. The coefficients of the significant donor factors in the Cox model (that also included the relevant recipient and transplant factors) were used to construct the donor risk index.

Transplant survival was considered over the full follow-up period of up to 9 years (overall survival) and, to identify donor factors that are important in different time periods, in three distinct posttransplant epochs: 0 to 3 months (censoring survival times over 90 days); 3 months to 3 years (omitting observations with survival times under 90 days and censoring survival times over 1095 days); and over 3 years (omitting observations with survival times less than 1095 days). Data on two transplants with missing survival times were excluded, as were transplants where the donor weight and number of days in hospital were missing (n=160).

Alternative models were compared using the log-likelihood ratio statistic ($-2 \log L$) and Akaike's Information Criterion. The extent of any nonlinearity in continuous variables was examined using martingale residuals (*9*) and by grouping the variable and plotting log HRs for each group against the mid point. The linearity of the UKKDRI was also examined by testing for nonlinearity across the four quartiles of the distribution of UKKDRI values.

Predictive ability of Cox models was assessed using a c-statistic due to Gönen and Heller (*10*). This statistic is based on the observed survival times of all pairs of patients. The two times in a pair are said to be concordant if the patient with the lower risk score (the linear part of the Cox model) has the longer survival time, and the c-statistic is the estimated proportion of pairs for which this is the case. The value of the statistic, c, is equal to 0.5 when a model has no utility.

Comparison of the UK and US Donor Risk Indices for UK Data

The KDRI of Rao et al. (*2*) was also applied to the UK validation dataset to compare its performance with that of the newly derived UKKDRI. To render the Rao formula applicable to our data, black ethnic origin was substituted for African American ethnicity, and donors who died of intracranial hemorrhage, intracranial thrombosis, or "intracranial event, type unclassified" were classified as deaths from CVA. Values of USKDRI were calculated after reestimating coefficients of variables in the USKDRI using the UK data.

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