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Prediction of Three-Year Mortality After Deceased Donor Kidney Transplantation in Adults with Pre-Transplant Donor and Recipient Variables

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Background: Prognostic models for 3-year mortality after kidney transplantation based on pre-transplant donor and recipient variables may avoid futility and thus improve donor organ allocation.

Material/Methods: There were 1546 consecutive deceased-donor kidney transplants in adults (January 1, 2000 to December 31, 2012) used to identify pre-transplant donor and recipient variables with significant independent influence on long-term survival (Cox regression modelling). Detected factors were used to develop a prognostic model for 3-year mortality in 1289 patients with follow-up of >3 years (multivariable logistic regression). The sensitivity and specificity of this model's prognostic ability was assessed with the area under the receiver operating characteristic curve (AUROC).

Results: Highly immunized recipients [hazard ratio (HR: 2.579, 95% CI: 1.272–4.631], high urgency recipients (HR: 3.062, 95% CI: 1.294–6.082), recipients with diabetic nephropathy (HR: 3.471, 95% CI: 2.476–4.751), as well as 0, 1, or 2 HLA DR mismatches (HR: 1.349, 95% CI: 1.160–1.569) were independent and significant risk factors for patient survival. Younger recipient age ≤42.1 years (HR: 0.137, 95% CI: 0.090–0.203), recipient age 42.2–52.8 years (HR: 0.374, 95% CI: 0.278–0.498), recipient age 52.9–62.8 years (HR: 0.553, 95% CI: 0.421–0.723), short cold ischemic times ≤11.8 hours (HR: 0.602, 95% CI: 0.438–0.814) and cold ischemic times 11.9–15.3 hours (HR: 0.736, 95% CI: 0.557–0.962) reduced this risk independently and significantly. The AUROC of the derived model for 3-year post-transplant mortality with these variables was 0.748 (95% CI: 0.689–0.788).

Conclusions: Older, highly immunized or high urgency transplant candidates with anticipated longer cold ischemic times, who were transplanted with the indication of diabetic nephropathy should receive donor organs with no HLA DR mismatches to improve their mortality risk.

MeSH Keywords: Kidney Transplantation • Mortality • Prognosis • Regression Analysis

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Background

Kidney transplantation is the best replacement therapy for patients with kidney failure [1]. In comparison to dialysis, kidney transplantation offers advantages like higher quality of life and longer survival [1]. Meanwhile the disparity between the number of patients who need a kidney graft and appropriate donors is still growing [2], as is the demand for expanding the number of donors. This situation can force identification of potentially hazardous donors and recipients with inherent covariables that pose high risks for unfavorable outcomes after transplantation. The United Network of Organ Sharing has implemented a definition of Expanded Criteria Donors that are defined by being older than 60 years of age or by age 50–59 years, plus at least 2 criteria out of the following 3: cerebrovascular accident as cause of death, serum creatinine greater than 1.5 mg/dL, or history of hypertension [3]. Eurotransplant organization reacted to the increasing waiting list by developing the Eurotransplant Senior Program (ESP) which includes donors aged ≥65 years [4].

The Kidney Transplant Morbidity Index was used by Pieloch et al. to determine the 3-year graft and patient survival rate by recipient's pre-transplant comorbidities [5]. Laging et al. recently proposed the Rotterdam Comorbidity in Kidney Transplantation Score to predict post-transplant mortality risk [6]. Interestingly, in the population investigated by Laging et al., 50% of those patients with the highest comorbidity scores survived more than 10 years [6]. Patients with comorbidities are likely those patients with a greater long-term survival benefit afforded by transplantation when compared to dialysis. This notion has been further underlined by the recent findings published by Sørensen et al. which demonstrated a survival benefit for kidney transplantation despite high comorbidity [7].

The current study aims to identify risk factors for patient mortality and prognostic factors for 3-year post-transplantation mortality based on pre-transplant donor and recipient variables excluding comorbidities that cannot be altered at the time of organ allocation to ensure optimal transplant benefit by improved donor organ allocation.

Material and Methods

Setting and data collection

A university hospital in Germany within the Eurotransplant community provides the setting. This single center retrospective analysis has been based on a comprehensive clinical data base which has been complemented by additional retrospective data from clinical charts for the purpose of this study.

Ethics statement

This study has been approved by the Ethics Committee at Hannover Medical School (reference number 2375-2014). Patients gave general informed consent for the analysis of their data in medical research. All data were anonymized prior to research.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are summarized in Figure 1. It includes all consecutive deceased-donor kidney transplants performed at Hannover Medical School between the January 1, 2000 and December 31, 2012. Pediatric (age ≤17 years) with combined transplants as well as simultaneously performed double kidney transplants were excluded. Study Cohort 1 was used to identify independent risk factors for survival (multivariable Cox regression modelling). Study Cohort 2 was defined after additional exclusion of survivors who had a period of less than 3 years for follow-up with the goal to assess those independent risk factors for survival identified in Study Cohort 1 as prognostic factors for observed 3-year morality using multivariable logistic regression modelling (Figure 1).

Definitions of variables

The investigated variables on the urgency of kidney transplantation are defined by the waiting list status immediately prior to transplantation according to the organ allocation rules established by the German Medical Council (Bundesärztekammer) [8]. These allocation rules are executed by Eurotransplant for Germany [8]. Patients listed as high urgency were defined with an imminent lack of access for either hemodialysis or peritoneal dialysis; severe (uremic) polyneuropathy, inability to cope with dialysis with a high risk for suicide; severe bladder problems (hematuria, cystitis, etc.) due to kidney graft failure. Patients declared as highly-immunized were those who suffered from an end-stage renal disease and who were transplantable with a panel reactive allo-antibodies (PRA) range of ≥85%. Immunized listed recipients who had an end-stage renal disease, were transplantable and had a measured PRA range of ≥6% to <85%. Marked as transplantable were those recipients with an end-stage renal disease who were transplantable and had a PRA range of <6% [9].

Study end-points

Long-term patient survival (Study Cohort 1) and 3-year observed survival status versus death (Study Cohort 2) regardless of graft function were defined as primary study endpoints. For those patients who were lost to clinical follow-up, the German legal registration offices provided us with information on their current survivor status. As we have reported before, all changes of address and all deaths have to be reported to the legal registration offices in Germany. This information

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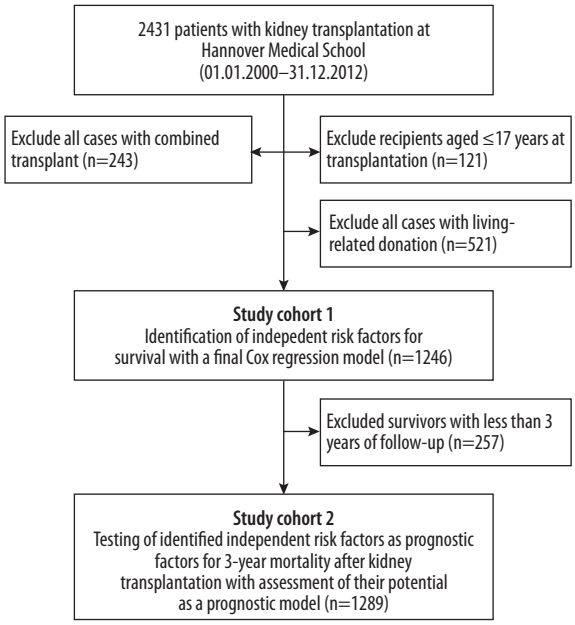

Figure 1. Shown is the patient study inclusion and exclusion flow chart.

is accessible for our institution within the current legal framework in Germany [10].

Statistical methods

The complete data set from Hannover was used for a brain storming session that included experienced kidney transplant specialists in order to define pre-transplant prognostic factors that are commonly known prior to transplantation. These factors were used as candidate variables for the prognostic model design. The next step was statistical evaluation of all the potential prognostic factors using univariable Cox regression analysis with the goal to determine the relevance of variables for long-term survival.

Variables with more than 5% missing values were submitted to an assessment of a potentially significantly different distribution of missing data between patients with 3-year mortality and those without 3-year mortality using the chi-squared test. For the assessed variables with more than 5% missing values a significant difference ($P<0.05$) in distribution of missing data could not be detected. Patients with missing values for variables that were critical for prognostic modelling were eliminated.

The influence of significant categorical variables on survival over time was further assessed in exploratory analyses using Kaplan-Meier curves and log rank tests (data not shown).

Principal component analyses were applied for better understanding of the underlying data structure and avoiding multi-collinearity in regression. Principal component analyses and multivariable Cox regression analyses were performed for donor and recipient variables [11].

The Shapiro-Wilk W test was used to assess normal distribution of variables. Not normally distributed variables were included into multivariable regression using only their quartiles which were used as nominal variables (Supplementary Table 1).

In Study Cohort 1, all uncorrelated variables with P values ≤0.250 in univariable Cox regression analysis were included in multivariable regression modelling as previously described [10]. An initial stepwise backwards likelihood elimination process of the least significant variables was performed. A threshold of >20% change between each of the steps in one or multiple betas of the investigated variables was chosen for the anticipation of potentially significant factor interactions [10].

The finally reached multivariable Cox regression model in Study Cohort 1 with pre-operative donor and recipient variables was used for the construction of a 3-year mortality prognostic model. Identified variables with significant independent influence on long-term survival were used for multivariable logistic regression analysis for the purpose of building a prognostic model for 3-year mortality using stepwise backwards likelihood elimination.

Lack of fit of the derived prognostic model was assessed with the Hosmer-Lemeshow test. Additional evaluation of the derived prognostic model included determination of the area

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Table 1. Influences of pre-transplant recipient variables on long-term survival in Study Cohort 1 (univariable Cox analysis, significant *P* values in bold numbers).

Univariable Cox Regression Analysis Influence of pre-transplant recipient variables on long-term survival (n=1546)				
	Evaluated parameters	Hazard ratio	Hazard ratio (95%-CI)	p-Value
Clinical characteristics of the recipient	Age in years	1.059	1.049–1.069	**<0.001**
	Age in years (quartiles 1–4)	1.798	1.624–1.993	**<0.001**
	Sex female yes	0.813	0.654–1.005	0.056
	Weight in kg	1.008	1.000–1.015	**0.034**
	Weight in kg (quartiles 1–4)	1.140	1.039–1.251	**0.006**
	Height in cm	0.995	0.985–1.005	0.311
	Height in cm (quartiles 1–4)	0.969	0.883–1.063	0.501
	BMI in kg/m^2	1.048	1.020–1.076	**0.001**
	BMI in kg/m^2 (quartiles 1–4)	1.177	1.072–1.293	**0.001**
	Pre-transplant waiting time in years	0.978	0.940–1.017	0.269
	Pre-transplant waiting time in years (quartiles 1–4)	0.926	0.843–1.017	0.106
	Time since first dialysis in years	0.997	0.959–1.035	0.869
	Time since first dialysis in years (quartiles 1–4)	0.860	0.861–1.037	0.230
	Current PRA in%	1.002	0.996–1.007	0.569
	Current PRA in% (quartiles 1–4)	1.004	0.901–1.111	0.934
	Highest PRA in%	1.001	0.998–1.005	0.492
	Highest PRA in% (quartiles 1–4)	1.016	0.938–1.097	0.698
	Cold ischemic time in hours	1.013	0.995–1.030	0.152
	Cold ischemic time in hours (quartiles 1–4)	1.122	1.015–1.242	**0.025**
	Warm ischemic time in minutes	1.000	0.992–1.008	0.991
	Warm ischemic time in minutes (quartiles 1–4)	0.969	0.872–1.076	0.552
	Pre-Tx dialysis yes	0.559	0.214–2.256	0.360
	First transplantation (yes)	0.900	0.689–1.193	0.454
	Second transplantation (yes)	1.144	0.839–1.527	0.385
	Third transplantation (yes)	0.867	0.414–1.579	0.665
	Forth transplantation (yes)	1.496	0.248–4.648	0.595
	Fifth transplantation (yes)	1.520e-8	6.313–6.313	0.435
	Sixth transplantation (yes)	3.469	0.198–15.373	0.303
	Urgency of waiting list status: T-KI (yes)	0.851	0.640–1.154	0.291
	Urgency of waiting list status: I-KI (yes)	0.929	0.637–1.308	0.684
	Urgency of waiting list status: HI_KI (yes)	1.554	0.773–2.761	0.199
	Urgency of waiting list status: HU_KI (yes)	2.648	1.264–4.825	**0.013**
	Blood group A (yes)	1.094	0.888–1.346	0.339
	Blood group B (yes)	1.135	0.811–1.546	0.450
	Blood group AB (yes)	0.845	0.507–1.316	0.476
	Blood group 0 (yes)	0.897	0.723–1.109	0.317
	HLA A mismatches (0, 1, 2)	1.234	1.057–1.440	**<0.001**
	HLA B mismatches (0, 1, 2)	1.088	0.942–1.257	0.252
	HLA DR mismatches (0, 1, 2)	1.158	0.997–1.346	0.055

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Table 1 continued. Influences of pre-transplant recipient variables on long-term survival in Study Cohort 1 (univariable Cox analysis, significant *P* values in bold numbers).

Univariable Cox Regression Analysis Influence of pre-transplant recipient variables on long-term survival (n=1546)				
	Evaluated parameters	Hazard ratio	Hazard ratio (95%-CI)	p-Value
Indications for transplantation	Chronic glomerulonephritis (yes)	0.780	0.592–1.012	0.062
	Congenital anomalies of the kidney and urinary tract (yes)	0.556	0.323–0.886	**0.012**
	Diabetic nephropathy (yes)	3.487	2.544–4.468	**<0.001**
	IgA nephropathy (yes)	0.662	0.537–0.960	**0.029**
	Interstitial nephritis (yes)	1.450	0.941–2.130	0.089
	Nephrocalcinosis (yes)	1.910	0.815–3.733	0.125
	Other (yes)	5.578e-9	2.154–2.154	0.181
	Polycystic diseases (yes)	0.871	0.629–1.177	0.379
	Pyelonephritis (yes)	0.661	0.282–1.291	0.246
	Renal manifestations of systemic diseases (yes)	1.038	0.648–1.571	0.869
	Unknown etiology of kidney failure (yes)	0.895	0.632–1.231	0.507
	Vascular nephropathy	1.192	0.889–1.569	0.233

PRA – panel reactive antibody; T-KI – transplantable; I-KI – immunized; HI_KI – highly immunized; HU_KI – high urgency.

under the receiver operating characteristic curve (AUROC) to assess the sensitivity and specificity of the model's predictions of 3-year mortality after transplantation (bootstrap 95% CI: 1000 iterations; random number seed: 978). AUROCs >0.700 are widely regarded as a prerequisite for clinically useful prognostic models [12,13]. The best Youden index (Youden index=sensitivity+specificity–1) [14] was used to determine the cutoff value with the best sensitivity and specificity for the prediction of 3-year mortality with the logit of the developed prognostic model. The relevance of this cutoff value for long-term survival was investigated with Kaplan-Meier analysis using the log rank test.

JMP Pro 11.0 Software (SAS Institute, Cary, NC, USA) was used to perform statistical analyses with P values <0.050 defined as significant.

Results

Clinical and demographic characteristics and descriptive statistics

The hospital mortality rate in Study Cohort 1 was 1.5% and in Study Cohort 2 it was 1.6%. A total of 359 patients (23.2%) in Study Cohort 1 died during follow-up and 332 patients (27.8%) in Study Cohort 2 died. Further details of the observed pre-transplant donor and recipient variables in Study Cohort 1 and Study Cohort 2 are summarized in Supplementary Tables 1–5.

Risk factor analysis with univariable Cox regression analysis

Tables 1 and 2 summarize the influence of observed pre-transplant variables on long term survival as evaluated by univariable Cox regression.

Independent risk factors for long-term survival

While recipient weight, recipient body mass index, the number of HLA A mismatches, as well as the indications of congenital anomalies of the kidney and urinary tract and IgA nephropathy had a significant impact on earlier death in the univariable Cox regression; however, the significance of these factors for earlier death could not be confirmed in multivariable Cox regression modelling (Table 1). Several donor variables, including donor age, last potassium, last urea, hypertension reported, smoking, as well as respirational donor cause of death had a significant influence on earlier recipient death in univariable Cox regression. The significance of these influences could not be confirmed in multivariable analyses (Table 2).

The urgency of the waiting list status highly immunized-KI did not display a significant impact on earlier death in the univariable Cox regression (Table 1) but gained an independently significant influence on earlier death in multivariable regression modelling (HR: 2.579; 95% CI: 1.272–4.631; *P*=0.011) (Table 3).

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Table 2. Influences of pre-transplant donor variables on long-term survival in Study Cohort 1 (univariable Cox analysis, significant *P* values in bold numbers).

Univariable Cox regression analysis Influence of pre-transplant donor variables on long-term survival (n=1546)				
	Evaluated parameters	Hazard ratio	Hazard ratio (95%-CI)	p-Value
Clinical characteristics of the donor	Age in years	1.020	1.012–1.027	**<0.001**
	Age in years (quartiles 1–4)	1.333	1.211–1.468	**<0.001**
	Sex female (yes)	0.964	0.782–1.186	0.728
	Weight in kg	1.000	0.993–1.006	0.905
	Weight in kg (quartiles 1–4)	1.007	0.922–1.099	0.882
	Height in cm	0.996	0.987–1.007	0.479
	Height in cm (quartiles 1–4)	0.943	0.852–1.041	0.245
	BMI in kg/m2	1.008	0.982–1.032	0.556
	BMI in kg/m2 (quartiles 1–4)	1.027	0.935–1.127	0.582
	Duration on the ICU in days	0.997	0.980–1.002	0.505
	Duration on the ICU in days (quartiles 1–4)	0.985	0.879–1.103	0.788
	Ventilation time in hours	0.100	0.999–1.000	0.509
	Ventilation time in hours (quartiles 1–4)	0.972	0.883–1.071	0.571
	Duration urine catheter in days	1.000	1.000–1.001	0.216
	Duration urine catheter in days (quartiles 1–4)	0.982	0.877–1.099	0.749
	Duration since hypertension diagnosis in years	0.989	0.936–1.039	0.679
	Duration since hypertension diagnosis in years (quartiles 1–4)	1.039	0.770–1.398	0.803
	Duration since diabetes mellitus diagnosis in years	0.938	0.825–1.029	0.215
	Duration since diabetes mellitus diagnosis in years (quartiles 1–4)	0.685	0.362–1.228	0.207
	Duration of smoking in pack years	0.995	0.929–1.038	0.847
	Duration of smoking in pack years (quartiles 1–4)	1.105	0.447–2.809	0.822
	Last potassium value in mmol/l	1.170	1.003–1.359	**0.045**
	Last creatinine value in µmol/l	1.000	0.998–1.000	0.624
	Last creatinine value in µmol/l (quartiles 1–4)	1.039	0.947–1.141	0.415
	Last urea value in mmol/l	0.997	0.987–1.004	0.496
	Last urea value in mmol/l (quartiles 1–4)	1.102	1.004–1.211	**0.041**
	Blood group A (yes)	1.634	0.863–1.309	0.564
	Blood group B (yes)	1.058	0.730–1.484	0.756
	Blood group AB (yes)	0.861	0.500–1.373	0.551
	Blood group 0 (yes)	0.948	0.768–1.168	0.618
	Hypertension reported	1.463	1.142–1.875	**0.003**
	Hypertension treated (yes)	0.825	0.479–1.486	0.507
	Diabetes mellitus reported	1.374	0.887–2.051	0.150
	Diabetes mellitus treated (yes)	2.221	0.640–13.985	0.235
	Smoking (yes)	0.687	0.527–0.889	**0.004**

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Table 2 continued. Influences of pre-transplant donor variables on long-term survival in Study Cohort 1 (univariable Cox analysis, significant *P* values in bold numbers).

Univariable Cox regression analysis Influence of pre-transplant donor variables on long-term survival (n=1546)					
		Evaluated parameters	Hazard ratio	Hazard ratio (95%-CI)	p-Value
Clinical characteristics of the donor	Donor cause of death	Circulatory (yes)	0.973	0.554–1.574	0.917
		CNS infarction (yes)	1.025	0.653–1.529	0.908
		CNS trauma (yes)	0.855	0.635–1.129	0.276
		CNS tumor (yes)	2.043e-9	1.124–1.124	0.064
		CVA bleeding (yes)	1.225	0.944–1.572	0.125
		CVA: Cerebro Vascular Accident Not Otherwise Specified (yes)	1.260	0.965–1.625	0.088
		Meningitis / Encephalitis (yes)	1.050	0.260–2.741	0.934
		Not otherwise specified (yes)	0.840	0.230–1.821	0.690
		Anoxic brain damage, not elsewhere classified (yes)	0.774	0.421–1.293	0.347
		Cerebral oedema (yes)	1.110	0.438–2.276	0.804
		Respirational (yes)	0.362	0.090–0.946	**0.036**
		Subdural Hematoma (yes)	0.953	0.236–2.488	0.933
		Subarachnoid haemorrhage (yes)	0.844	0.635–1.105	0.222
		Trauma (yes)	1.238	0.763–1.892	0.369

CVA – cerebrovascular accident.

Table 3. Influences of pre-transplant recipient and donor variables on long-term survival as identified in the final multivariable Cox regression model of recipient risk factors for survival in Study Cohort 1.

Multivariable Cox Regression Model			
Evaluated parameters	Hazard ratio	Hazard ratio (95%-CI)	P values
Urgency of waiting list status: HI_KI (yes)	2.579	1.272–4.631	0.011
Urgency of waiting list status: HU_KI (yes)	3.062	1.294–6.082	0.014
Recipient diabetic nephropathy	3.471	2.476–4.751	<0.001
Recipient Age in years (quartile 1)	0.137	0.090–0.203	<0.001
Recipient Age in years (quartile 2)	0.374	0.278–0.498	<0.001
Recipient Age in years (quartile 3)	0.553	0.421–0.723	<0.001
Cold ischemic time in hours (quartile 1)	0.602	0.438–0.814	0.001
Cold ischemic time in hours (quartile 2)	0.736	0.557–0.962	0.025
HLA DR mismatches (0, 1, 2)	1.349	1.160–1.569	<0.001

HI_KI – highly immunized; HU_KI – high urgency; HLA – human leucocyte antigen.

The final result of multivariable Cox regression modelling demonstrated that the following variables had a statistically significant and independent impact on the risk of earlier death after kidney transplantation: Urgency of waiting list status highly immunized, urgency of waiting list status high-urgency, recipient diabetic nephropathy, recipient age in years ≤42.1 years (quartile 1), recipient age in years 42.2–2.8 years (quartile 2), recipient age in years 52.9–62.8 years (quartile 3), cold ischemic time in hours ≤11.8 hours (quartile 1), cold ischemic time in hours 11.9–15.3 hours (quartile 2) and 0, 1, or 2 HLA DR mismatches (Table 3).

Factor interactions could not be detected in multivariable Cox regression modelling for donor and recipient variables during

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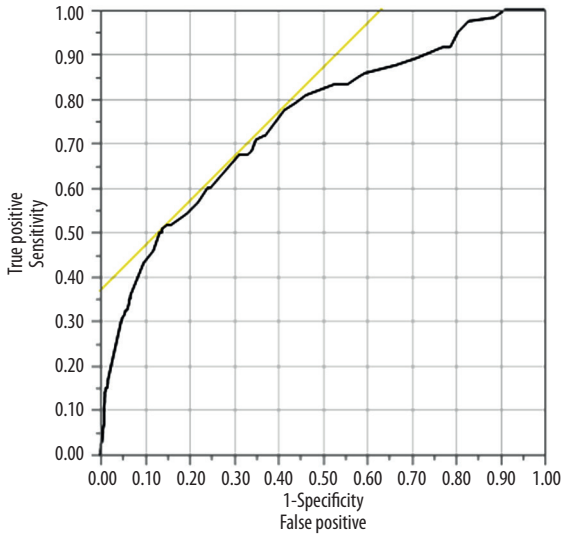

Figure 2. Shown is the ROC curve of the proposed prognostic model for the prediction of 3-year mortality after kidney transplantation. The AUROC is 0.748 (AUROC 95% CI: 0.689–0.788, best Youden index: sensitivity of prediction: 50.8%; specificity of prediction: 86.1%; overall correctness of prediction: 68.5%). ROC – receiver operating characteristic; AUROC – area under the receiver operating characteristic curve.

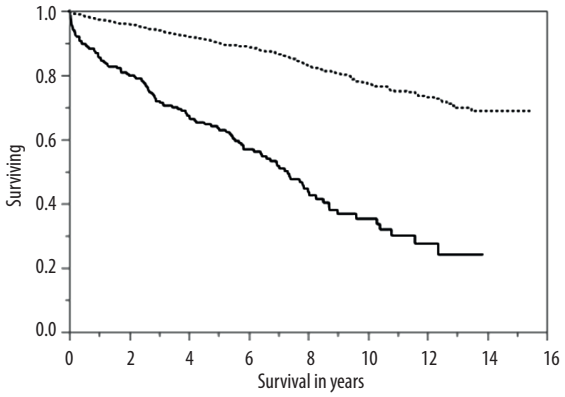

Figure 3. Shown is the Kaplan-Meier curve demonstrating significantly worse long-term survival for those patients with a predicted risk of 3-year mortality greater than 15.7% (continuous line, n=214) as had been determined with the proposed prognostic model for 3-year mortality when compared to those patients with a lesser predicted risk of 3-year mortality in Study Cohort 2 (dotted line, n=1012) (P<0.001, log rank test). Patients with lacking data for variables that are contained in the proposed prognostic model have been excluded due to inability to calculate the predicted risk (n=63).

stepwise backwards likelihood elimination. The final multivariable model is summarized in Table 3.

Prognostic factors for 3-year post-transplant mortality

Prognostic factors for 3-year mortality demonstrated an AUROC larger than 0.700 (AUROC=0.748, bootstrap 95% CI=0.689–0.788) (Figure 2). This model demonstrated no significant lack of model fit (P=0.132) and was defined as follows:

$$Risk\ of\ 3-year\ mortality\ in\ \% = \frac{1}{(1\ +\ Exp(\ -(Lin[1])\ ))}$$

Lin[1]=–1.957
+ Urgency code HI (if yes→0.538; else→–0.538)
+ Urgency code high urgency (if yes→1.056; else→–1.056)
+ Diabetic nephropathy (if yes→0.698; else→–0.698)
+ Age ≤42.1 years, first quartile (if yes→–0.996; else→0.996)
+ Age 42.2–52.8 years, second quartile (if yes→–0.661; else→0.661)
+ Age 52.9–62.8 years, third quartile (if yes→–0.346; else→0.346)
+ CIT ≤11.8 hours, first quartile (if yes→–0.221; else→0.221)
+ CIT 11.9–15.3 hours, second quartile (if yes→–0.226; else→0.226)
+ (0.397×[number of HLA-DR mismatches])

The sensitivity of prediction of 3-year mortality with this model was 50.8% and the specificity 86.1% with an overall correctness of prediction 68.5%. Sample size calculation for external validation of the proposed prognostic model for 3-year mortality with a power >80% was determined to require a total of 8464 cases with 847 cases with 3-year mortality estimated to be at 10.0%.

Significantly worse long-term survival for those patients with a predicted risk of 3-year mortality greater than 15.7% as had been determined with the proposed prognostic model for 3-year mortality was detected when compared to those patients with a lesser predicted risk of 3-year mortality in Study Cohort 2 (P<0.001, log rank test). Due to the inability to calculate the predicted risk, patients without data for variables that were contained in the proposed prognostic model were excluded (n=63) (Figure 3). Statistically significant effects of the number of HLA-DR mismatches regarding patient survival (P<0.001, log rank test) were calculated using Kaplan-Meier analysis as shown in Figure 4.

Discussion

This study identified independent pre-transplant donor and recipient risk factors for patient mortality. The developed prognostic model for 3-year mortality based on these results is potentially clinically useful for recipient counselling and donor

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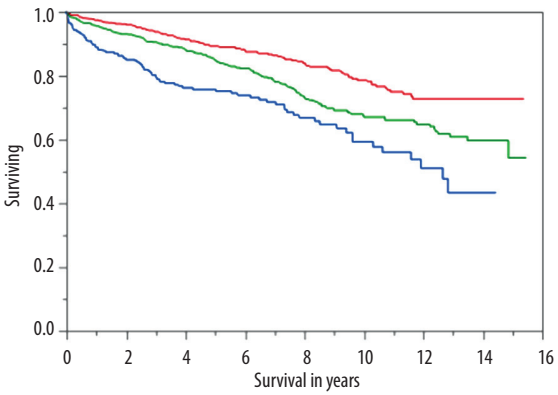

Figure 4. Shown are the Kaplan-Meier curves demonstrating statistically significant effects of the number of HLA-DR mismatches on patient survival (P<0.001, log rank test). Zero mismatches result in the red line, 1 mismatch in the green line and 2 mismatches in the blue line.

organ acceptance decisions (AUROC >0.700, Figure 2) and has a cutoff with a highly significant influence on earlier death after transplantation (Figure 3). The derived prognostic model demonstrated that older recipients with longer cold ischemic time, who suffer from diabetic nephropathy and who are either highly immunized or urgent recipients can be transplanted with a lower risk of early mortality, if they are transplanted with a donor kidney without any HLA-DR mismatches. The highly significant impact of the number of HLA-DR mismatches on patient survival is shown in Figure 4. Transplantation of patients with more favorable recipient risk profiles could be justifiably transplanted with donor kidneys that result in 1 or 2 HLA-DR mismatches. Such a decision should be based on the individual weighing of recipient risk factors (Table 3). The proposed prognostic model and the underlying Cox regression model both provide tools for such a weighing of individual recipient risk profiles.

It is striking that this study externally confirms the prognostic relevance of an older recipient age and pre-existing recipient diabetes for an increased risk of mortality after kidney transplantation in a European cohort as has been published before in a report from a large registry trial from the United States which has proposed a predictive score for post-transplant mortality [15].

It has been reported before that both, the age of the donor and the age of the recipient have an influence on patient survival after transplantation, although these results have not been explicit. Dempster et al. for example found no significantly increased recipient mortality at one year after transplantation even when donors were 65 years or older [16]. In this study donor age demonstrated a significant impact on early recipient mortality in univariable analysis (Table 2) which could not be confirmed in multivariable Cox regression analysis. This is likely due to the fact that older recipients tended to receive older donor kidneys. Dempster et al. found in a similar setting where older patients tended to receive older donor kidneys more complications after transplantation defined as delayed graft function, kidney failure in the first year after transplantation and higher serum creatinine at one year after transplantation [16]. In this context, McCaughan et al. have shown that patients with graft failure who needed to return to dialysis had worse survival rates when compared to patients who underwent dialysis and never had transplantation or when compared to patients who had functional kidney grafts [17]. Additionally, Frei et al. detected delayed graft function as a relevant risk factor for graft and patient survival [18]. This study has shown that cold ischemic time is an independent and significant risk factor for patient survival. Long CITs are known to increase the risk of delayed graft function and early graft failure [18].

Recipient age has been identified to have a significant influence on post-transplant survival. These findings agree with clinical experience and could be explained with increased comorbidity of older patients [5] as well as with decreasing life expectancy that naturally decreases with increasing age. Because of an increasing frequency and percentage of older recipients and donors, Eurotransplant established the ESP which allocates kidneys from deceased donors older than 65 years to recipients in the same age range by keeping the CIT as short as possible by ignoring HLA matching [8]. The findings of this study describe an increased mortality risk for patients who were transplanted with higher numbers of HLA-DR mismatches (Table 3, Figure 4). Therefore, the practice of ignoring HLA matching in the ESP should be regarded with great caution.

Jacobi et al. have proposed to define patients transplanted in the ESP as a high-risk population who need careful evaluation and selection for transplantation and close clinical surveillance after transplantation [19]. Frei et al. could not find a negative influence on graft and patient survival for patients transplanted in the ESP in comparison to standard allocation [18]. In contrast to the aforementioned results, the current study identified higher recipient age as an independent risk factor for 3-year mortality. The first, second and third quartile of recipient age were independent and significant protective factors in the proposed prognostic model for 3-year mortality demonstrating that lower age quartiles were more protective when compared to the fourth quartile of recipient age (≥62.9 years) (Table 3). This study clearly showed that recipient age had a non-linear influence on early mortality risk after kidney transplantation with increasing risk of earlier death per unit of older age (Supplementary Figure 1).

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The Dempster et al. study showed a higher mortality rate in the first year after transplantation for older patients [16]. While older recipients have been shown to be at higher risk for complications after transplantation [16,19,20], the only alternative to transplantation would be dialysis, which has been shown to have even worse results concerning survival, quality of life, and economic factors [16,19,21,22].

The study by Orlandi et al. did not find recipient age as an independent risk factor for negative outcomes but found recipient diabetic state was a relevant and independent risk factor for earlier death [21]. This is particularly important, as the increasing diabetes prevalence in the population leads to an increase in the frequency of diagnosed end-stage renal disease cases [22]. Foucher et al. found that age-related mortality after kidney transplantation was not significantly increased, whereas the diabetic state of the recipient was shown to be a risk factor for excess mortality when compared to a general population [23]. These findings are in line with our findings that a recipient's diabetic nephropathy was a highly significant risk factor for early mortality after kidney transplantation with a hazard ratio of 3.471 (95% CI: 2.476–4.751) independent of the recipient age at transplantation (Table 3).

This study showed that cold ischemic time was a relevant risk factor for early death. Especially for older patients who receive an expanded criteria organ may be negatively influenced by long cold ischemic time [24]. This is why the ESP aims to keep cold ischemic time as short as possible [19]. Van der Vliet and Warlé found cold ischemic time to be an independent risk factor for delayed graft function and acute rejection, but not for long-term outcomes [24]. Frei et al. showed that every hour of cold ischemic time increased the risk of graft loss by 3% [18]. However, Jacobi et al. and Giessing et al. could not find any negative impact of longer cold ischemic time, not even using expanded criteria for donor kidneys by comparing the outcome of successfully and subsequently transplanted kidneys from one donor with just low differences in cold ischemic time [19,25]. The results of our study clearly point to the clinical relevance of cold ischemic time for post-transplant patient survival.

Concerning HLA mismatches, 1 or 2 HLA DR mismatches had a statistically significant impact on survival (Figure 4) which was confirmed in multivariable Cox regression modelling (Table 3). This result is in line with previously published findings [26]. Laging et al. found that all HLA mismatches were relevant factors for graft survival [28]. Furthermore, Frei et al. revealed higher rates of acute and late rejection for ESP patients with shorter cold ischemic time and explained these findings by more HLA mismatches leading to antibody-mediated rejection as a consequence [18]. We propose, based on our findings as well as previously published reports to consider HLA DR mismatches for donor kidney allocation while keeping the cold ischemic time as short as possible. This concept has been realized in the Eurotransplant Senior DR-compatible Program (ESDP), which includes full HLA DR compatibility and reduced cold ischemic time [8] in comparison to the ESP [4].

The proposed prognostic model for 3-year mortality requires external validation with data from other centers before allocation rules can be adapted. Sample size calculation based on the results of this study revealed that the data of a total of 8464 transplanted patients with an estimated 3-year mortality rate of 10.0% would be needed for external validation of the proposed prognostic model with a power >80%.

This study investigated the independent influences of pre-transplant recipient and donor risk factors on post-transplantation survival beyond recipient comorbidity. The recently defined Kidney Transplant Morbidity Index with its demonstrated significant influence on 3-year patient survival [5] and the Rotterdam Comorbidity in Kidney Transplantation Score used to predict post-transplant mortality risk [6] were intentionally not used as analyzed risk factors in this study. Laging et al. showed that patient death was significantly influenced by cardiovascular disease, other organ transplantation, and total comorbidity scores [6]. However, in the population investigated by Laging et al., 50% of the patients with the highest comorbidity scores survived more than 10 years. Laging et al. suggested that a high comorbidity score should not be seen as a contraindication for kidney transplantation [6]. In addition, patients on the waiting list for kidney transplantation with comorbidities that increased post-transplant mortality risk were those patients with greater long-term survival benefit afforded by transplantation when compared to continued dialysis [6]. This notion has been further underlined recently by Sørensen et al., who demonstrated a survival benefit in kidney transplantation despite high comorbidity [7]. Thus, patients with high comorbidity should not be excluded from kidney transplantation. The current study showed how donor kidneys could be matched to recipients to reduce the 3-year mortality risk while the recipients' comorbidity burden could not be possibly reduced at the time when donor organ offers are made and a decision on the acceptance of such an offer for an individual patient is made responsibly.

Predicting an unfavorable outcome using the proposed prognostic model, allows the offered donor organ to be used for more favorable donor-recipient combinations, while keeping urgency aspects in mind. This weighing of options has profound ethical implications in the dimension of distributive justice. The current study clearly showed that HLA-DR mismatches should be taken into account, even though they are not available before listing. Unfavorable combinations of pre-transplant donor and recipient variables and increased recipient risk profiles should at least trigger heightened clinical vigilance after transplantation.

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The presented study had several limitations including a possible center-bias which may have influenced the findings in this single-center study. A further limitation of the current study was that cold ischemic time can only be estimated prospectively by transplantation surgeons prior to actual transplantation for each patient. However, in our clinical experience, the estimation of the quartiles of cold ischemic time, which were identified as significant factors in the proposed prognostic model, would usually be possible with sufficient accuracy.

Conclusions

The main conclusion of this study was that especially older, highly immunized, or high urgency transplantation candidates with anticipated longer cold ischemic times, who are transplanted with the indication of diabetic nephropathy, should not receive donor organs with 1 or 2 HLA DR mismatches. The proposed prognostic model was able to weigh the risk of 3-year post-transplant mortality that was associated with different individual expressions of these identified risk factors. In case of predicting an unfavorable outcome with the proposed prognostic model, the offered donor organ could be used for more favorable donor-recipient combinations, while keeping urgency aspects in mind. This weighing has profound ethical implications in the dimension of distributive justice.

Conflicts of interest

None.

Supplementary Files

Supplementary Table 1. Shown are the distributions of non-normally distributed continuous variables in quartiles of those variables that were included into multivariable Cox regression modelling in Study Cohort 1.

Variables		Quartile 1	Quartile 2	Quartile 3	Quartile 4
Recipient	Age in years	≤42.1	42.2–52.8	52.9–62.8	≥62.9
	Weight in kg	≤62.5	62.6–72.0	72.1–82.0	≥82.1
	BMI in kg/m^2	≤21.8	21.9–24.4	24.5–27.1	≥27.2
	CIT in hours	≤11.8	11.9–15.3	15.4–19.6	≥19.7
Donor	Age in years	≤41.0	41.1–52.0	52.1–61.0	≥61.1
	Urea in mmol/l	≤3.3	3.4–5.3	5.4–8.2	≥8.3

Supplementary Table 2. Shown is the distribution of analyzed preoperative recipient variables in Study Cohort 1 determined prior to transplantation (all values rounded to one decimal).

Pre-transplant recipient variables and their distribution (n=1546)					
	Continuous data	Mean (median)	Range	Standard deviation	Missing values in %
Clinical characteristics	Age in years	52.4 (53.70)	17.3–76.4	13.0	0
	Weight in kg	73.1 (72.05)	20–124	14.4	0
	Height in cm	73.1 (72.05)	81-206	10.3	0
	Transplant-waiting since in years	4.3 (4.54)	0–18.51	2.7	0.1
	Time since first dialysis in years	6.2 (6.42)	0.03–27.4	2.8	0.1
	Rest diuresis in ml	538.5 (200)	0–4000	713.6	83.8
	Current PRA in%	6.4 (0)	0–100	19.8	0.1
	Highest PRA in%	13.8 (0)	0–100	28.0	0.1
	Cold ischaemic time (CIT) in minutes	938.2 (882)	127–2430	361.8	4.2
	Warm ischaemic time in minutes	36.4 (35)	7–126	13.3	14.7

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	Binary data	n	%	n.a.	Missing values in%
Clinical characteristics	Sex (Female/Male)	630/916	40.8/59.3	Not applicable (n.a.)	0
	Pre-Tx dialysis (yes/no)	1537/8	99.5/0.5		0.1
	First transplantation (yes)	1299	84.0		0
	Second transplantation (yes)	194	12.5		0
	Third transplantation (yes)	44	2.8		0
	Forth transplantation (yes)	7	0.5		0
	Fifth transplantation (yes)	1	0.1		0
	Sixth transplantation (yes)	1	0.1		0
	Urgency of waiting list status: T-KI (yes)	1333	86.2		0
	Urgency of waiting list status: I-KI (yes)	158	10.0		0
	Urgency of waiting list status: HI_KI (yes)	37	2.4		0
	Urgency of waiting list status: HU_KI (yes)	18	1.2		0
	Blood group A (yes)	659	42.6		0
	Blood group B (yes)	177	11.4		0
	Blood group 0 (yes)	620	40.1		0
	Blood group AB (yes)	90	5.8		0
HLA mismatch with donor	0 HLA A mismatches (yes)	714	46.2		0
	1 HLA A mismatch (yes)	647	41.9		0
	2 HLA A mismatches (yes)	185	12.0		0
	0 HLA B mismatches (yes)	529	34.1		0
	1 HLA B mismatch (yes)	672	43.5		0
	2 HLA B mismatches (yes)	345	22.3		0
	0 HLA DR mismatches (yes)	571	36.9		0
	1 HLA DR mismatch (yes)	712	46.1		0
	2 HLA DR mismatches (yes)	263	17.0		0
Indications for transplantation	Chronic glomerulonephritis (yes)	327	21.2		0
	Congenital anomalies of the kidney and urinary tract (yes)	116	7.5		0
	Diabetic nephropathy (yes)	98	6.4		0
	IgA nephropathy (yes)	169	11.0		0
	Interstitial nephritis (yes)	80	5.2		0
	Nephrocalcinosis (yes)	18	1.2		0
	Other (yes)	3	0.2		0
	Polycystic diseases (yes)	224	14.5		0
	Pyelonephritis (yes)	38	2.5		0
	Renal manifestations of systemic diseases (yes)	85	5.5		0
	Unknown etiology of kidney failure (yes)	167	10.8		0
	Vascular nephropathy (yes)	221	14.3		0

PRA – panel reactive antibody; T-KI – transplantable; I-KI – immunized; HI_KI – highly immunized; HU_KI – high urgency; n.a. – not applicable.

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Supplementary Table 3. Shown is the distribution of analyzed preoperative donor variables in Study Cohort 1 determined prior to transplantation (all values rounded to one decimal).

Pre-transplant donor variables and their distribution (n= 1546)					
	Continuous data	**Mean (median)**	**Range**	**Standard deviation**	**Missing values in% of all cases except as indicated otherwise**
Clinical characteristics	Age in years	51.0 (53)	4–88	16.4	0
	Weight in kg	78.3 (78)	15–180	15.7	0
	Height in cm	173.3 (175)	85–200	10.1	0
	Duration on the ICU in days	6.7 (3.57)	0.17–1098	32.7	19.8
	Ventilation time in hours	146.8 (83.5)	3.1–26351	770.5	0.8
	Duration urine catheter in days	12.8 (3.6)	0.3–3773	155.6	20.9
	Duration since hypertension diagnosis in years	8.4 (7.9)	0.1–39.88	6.8	60.5 of all patients with hypertension
	Duration since diabetes mellitus diagnosis in years	8.8 (7.9)	0.3–56.59	9.5	58.7 of all patients with diabetes
	Duration of smoking in pack years	21.2 (18)	1–99	22.7	7.5
	Last potassium value in mmol/l	4.1 (4.1)	1.7–7.9	0.6	0.8
	Last creatinine value in µmol/l	103.7 (79.6)	17.7–725	87.4	0.6
	Last urea value in mmol/l	8.0 (5.3)	0.05–334	13.3	1.9
	Binary data	**n**	**%**	**n.a.**	
Clinical characteristics	Sex Female/Male	713/833	46.1/53.9	Not applicable (n.a.)	0
	Blood type A (yes)	648	42.0		0
	Blood Type B (yes)	159	10.2		0
	Blood Type 0 (yes)	661	42.8		0
	Blood Type AB (yes)	78	5.1		0
	Hypertension (yes)	484	31.3		67.0
	Hypertension treated (yes)	230	47.5 of all patients with hypertension		37.6
	Diabetes mellitus (yes)	104	17.6		64.4
	Diabetes mellitus treated (yes)	59	56.7 of all patients with Diabetes		
	Smoking (yes)	520	33.6		20.6
	Last urine glucose value (yes)	85	5.5		26.1
	Last urine protein value (yes)	411	26.6		26.6
	Last urine leukocytes value (yes)	126	8.2		45.8
	Last urine bacteria value (yes)	39	2.5		70.8
	Last urine epithelium value (yes)	9	0.6		86.2
	Last urine cylinders value (yes)	15	1.0		80.1

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	Binary data	n	%	n.a.	
Most probable causes of death	Cerebro Vascular Accident Not Otherwise Specified (yes)	196	12.7	Not applicable (n.a.)	0
	Circulatory (yes)	49	3.2		0
	CNS infarction (yes)	119	7.7		0
	CNS trauma (yes)	250	16.2		0
	CNS tumor (yes)	5	0.3		0
	CVA bleeding (yes)	330	21.3		0
	Meningitis / Encephalitis (yes)	13	0.8		0
	Not otherwise specified (yes)	18	1.2		0
	Other disorders of brain: Anoxic brain damage, not elsewhere classified (yes)	100	6.5		0
	Other disorders of brain: Cerebral oedema (yes)	33	2.1		0
	Respirational (yes)	24	1.6		0
	Sub Dural Hematoma (yes)	13	0.8		0
	Subarachnoid haemorrhage (yes)	335	21.7		0
	Trauma (yes)	61	3.9		0

ICU – Intensive Care Unit; CNS – central nervous system; CVA – cerebrovascular accident; n.a. – not applicable.

Supplementary Table 4. Shown is the distribution of analyzed preoperative recipient variables determined prior to transplantation in Study Cohort 2 (all values rounded to one decimal).

Pre-transplant recipient variables and their distribution (n=1289)					
	Continuous data	Mean (median)	Range	Standard deviation	Missing values in%
Clinical characteristics	Age in years	51.8 (52.8)	17.4–76.4	12.8	0
	Weight in kg	72.5 (72.0)	20–124	14.3	0
	Height in cm	171.1 (172)	114-206	10.1	0
	T-wait since in years	4.4 (4.7)	0–18.5	2.6	0.1
	Time since first dialysis in years	6.2 (6.4)	0–27.4	2.7	0.5
	Current PRA in%	5.6 (0)	0–100	18.7	0.1
	Highest PRA in%	13.1 (0)	0–100	27.3	0.1
	Cold ischemic time (CIT) in minutes	969.7 (915)	197–2430	366.9	4.7
	Warm ischaemic time in minutes	37.1 (35)	7–160	14.1	14.4

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	Binary data	n	%	n.a.	Missing values in%
Clinical characteristics	Sex (Female/Male)	527/726	40.9/59.1	Not applicable (n.a.)	0
	Pre-Tx dialysis (yes/no)	1282/7	99.5/0.5		0
	First transplantation (yes)	1082	83.9		0
	Second transplantation (yes)	160	12.4		0
	Third transplantation (yes)	40	3.1		0
	Forth transplantation (yes)	5	0.4		0
	Fifth transplantation (yes)	1	0.1		0
	Sixth transplantation (yes)	1	0.1		0
	Urgency of waiting list status: T-KI (yes)	1126	87.4		0
	Urgency of waiting list status: I-KI (yes)	121	9.4		0
	Urgency of waiting list status: HI_KI (yes)	25	1.9		0
	Urgency of waiting list status: HU_KI (yes)	17	1.3		0
	Blood group A (yes)	563	43.7		0
	Blood group B (yes)	145	11.2		0
	Blood group 0 (yes)	501	38.9		0
	Blood group AB (yes)	80	6.2		0
HLA mismatch with donor	0 HLA A mismatches (yes)	614	47.6		0
	1 HLA A mismatch (yes)	533	41.3		0
	2 HLA A mismatches (yes)	142	11.0		0
	0 HLA B mismatches (yes)	461	35.8		0
	1 HLA B mismatch (yes)	561	43.5		0
	2 HLA B mismatches (yes)	267	20.7		0
	0 HLA DR mismatches (yes)	474	36.8		0
	1 HLA DR mismatch (yes)	592	45.9		0
	2 HLA DR mismatches (yes)	222	17.2		0
Indications for transplantation	Chronic glomerulonephritis (yes)	273	21.2		0
	Congenital anomalies of the kidney and urinary tract (yes)	90	7.0		0
	Diabetic nephropathy (yes)	82	6.4		0
	IgA nephropathy (yes)	141	10.9		0
	Interstitial nephritis (yes)	63	4.9		0
	Nephrocalcinosis (yes)	17	1.3		0
	Other (yes)	2	0.2		0
	Polycystic diseases (yes)	181	14.0		0
	Pyelonephritis (yes)	36	2.8		0
	Renal manifestations of systemic diseases (yes)	71	5.5		0
	Unknown etiology of kidney failure (yes)	146	11.3		0
	Vascular nephropathy (yes)	187	14.5		0

PRA – panel reactive antibody; T-KI – transplantable; I-KI – immunized; HI_KI – highly immunized; HU_KI – high urgency; n.a. – not applicable.

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Supplementary Table 5. Shown is the distribution of analyzed preoperative donor variables determined prior to transplantation in Study Cohort 2 (all values rounded to one decimal).

Pre-transplant donor variables (n= 1289)						
	Continuous data	**Mean (Median)**		**Range**	**Standard deviation**	**Missing values in% of all cases**
Clinical characteristics	Age in years	50.1	(52)	5–86	16.3	0
	Weight in kg	78.0	(77.5)	15–180	15.5	0
	Height in cm	173.4	(175)	85–200	10.2	0
	Length of ICU stay in days	5.9	(3.6)	0.2–244.9	11.1	23.1
	Ventilation time in hours	127.4	(82.5)	3.1–2258.2	767.6	6.0
	Duration urine catheter in days	14.6	(3.6)	0.3–3773	149.5	24.1
	Last potassium value in mmol/l	4.2	(4.1)	2.0–6.6	0.6	1.1
	Last creatinine value in µmol/l	104.3	(79.6)	17.7–725	89.2	0.6
	Last urea value in mmol/l	7.5	(5.3)	0.04–110	8.8	2.4
	Binary data	**n**		**% of all cases except as indicated otherwise**	**n.a.**	
Clinical characteristics	Sex Female/Male	591/698		45.8/54.2	Not applicable (n.a.)	0
	Blood group A (yes)	553		42.9		0
	Blood group B (yes)	128		9.9		0
	Blood group 0 (yes)	539		41.8		0
	Blood group AB (yes)	69		5.4		0
	Hypertension reported	387		46		0
	Hypertension treated (yes)	157		40.6 of all patients with hypertension reported		0
	Diabetes mellitus reported	75		15.0		0
	Diabetes mellitus treated (yes)	38		50.6 of all patients with diabetes reported		0
	Smoking reported (yes)	402		40.0		0
	Positive urine glucose value reported	82		9.3		0
	Positive urine protein value reported	133		14.8		0
	Positive urine leukocytes value reported	112		16.0		0
	Positive urine bacteria value reported	33		8.8		0
	Positive urine epithelium value reported	8		4.5		0
	Positive urine cylinders value reported	13		5.2		0

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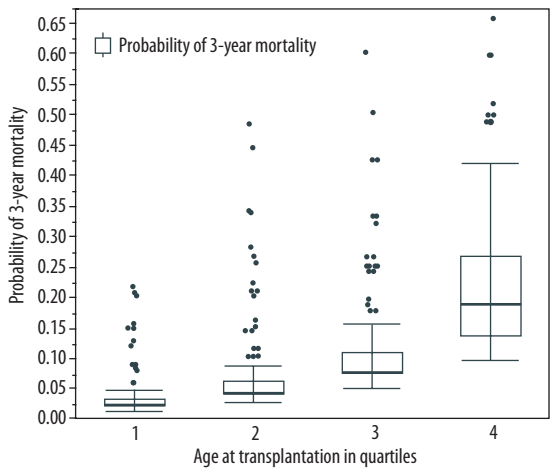
	Binary data	n	% of all cases except as indicated otherwise	n.a.	
Most probable causes of death	Cerebro Vascular Accident Not Otherwise Specified (yes)	189	14.7	Not applicable (n.a.)	0
	Circulatory (yes)	47	3.6		0
	CNS infarction (yes)	88	6.8		0
	CNS trauma (yes)	215	16.7		0
	CNS tumor (yes)	5	0.4		0
	CVA bleeding (yes)	252	19.6		0
	Meningitis / Encephalitis (yes)	11	0.9		0
	Not otherwise specified (yes)	17	1.3		0
	Other disorders of brain: Anoxic brain damage, not elsewhere classified (yes)	67	5.0		0
	Other disorders of brain: Cerebral oedema (yes)	29	2.2		0
	Respirational (yes)	23	1.8		0
	Sub dural Hematoma (yes)	13	1.0		0
	Subarachnoid haemorrhage (yes)	278	21.6		0
	Trauma (yes)	57	4.4		0

PRA – panel reactive antibody; T-KI – transplantable; I-KI – immunized; HI_KI – highly immunized; HU_KI – high urgency; n.a. – not applicable.



Supplementary Figure 1. Shown is the non-linear influence of recipient age in quartiles on the predicted risk of 3-year post-transplant mortality in percent divided by 100 (quartile 1=recipient age ≤42.1 years, quartile 2=recipient age 42.2–52.8 years, quartile 3=recipient age 52.9–62.8 years, quartile 4=recipient age ≥62.9 years).

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