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PREDICTION MODELING OF KIDNEY TRANSPLANT OUTCOME

by

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A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Biomedical Informatics

The University of Utah

December 2010

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The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Although renal transplant is the preferred modality for end-stage renal disease, it brings with it a number of challenges primarily associated with lack of individualized approach. The goals of the present project were: (1) to determine the most significant and clinically practical predictors of kidney transplant outcomes (patient survival, allograft survival, posttransplant complications) using United States Renal Data System (USRDS) data; (2) based on the selected predictors, to generate prediction models of renal transplant outcomes.

Our initial study developed prediction models using logistic regression and tree-based algorithms derived from data provided by the United Network of Organ Sharing (UNOS). A series of follow-up projects, using data supplied by the United States Renal Data System (USRDS), was performed. We were able to capture significant associations between donor, recipient, and transplant procedure variables (that could not be derived from UNOS data) and the allograph and recipient survival. Among our important findings, compared to peritoneal dialysis (PD), hemodialysis is associated with increased risk of graft failure and recipient death; preemptive retransplantation is associated with an increased risk of graft failure; increased time on dialysis between transplants is associated with a negative effect upon graft and recipient survival in most patient subgroups; short-term (6 months or less) dialysis had no negative effect on graft survival compared to preemptive transplants; certain socioeconomic factors, such as higher education level, citizenship, and type of insurance coverage, influenced graft and recipient outcomes, independent of racial differences; and that one particular

immunosuppressive medication regimen was superior to others in prolonging graft and recipient survival.

Based on these results, we developed a more comprehensive prediction model of the graft outcome using URSDS data using logistic regression and tree-based models. The new models included both deceased and living donor graft recipients, was based on the longer list of pertinent predictors while still being practical in the clinical setting, and addressed the probability of graft failure at five different time points (1, 3, 5, 7, and 10- year allograft survival). The models have been validated on the independent dataset and demonstrated performance suggesting implementation in the clinical decision support system.

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ACKNOWLEDGMENTS

I am grateful to the Dialysis Research Foundation for partially supporting this project

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1. INTRODUCTION

1.1. Statement of the problem

Renal transplant recipients represent a large subgroup of patients with chronic kidney disease (CKD). Renal transplant is a preferred modality of treatment for end-stage renal disease (ESRD), as it is associated with lower comorbidity, better recipient survival [1-3], improved quality of life [4], and lower medical expenses [5] than those of patients remaining on the transplant waiting list [6, 7]. However, since organ transplantation requires surgical intervention, aggressive immunosuppression, frequent blood sampling, patient monitoring, and other diagnostic studies, it is associated with serious complications mostly attributed to therapy [8, 9]. In particular, immunosuppressive therapy, a core method required of successful transplantation, has a narrow therapeutic window. Insufficient immunosuppression might predispose recipients to acute organ rejection and shortened allograft survival, while overaggressive immunosuppression might cause complications due to toxicity (e.g, cancers, diabetes mellitus [DM], hypercholesterolemia, osteoporosis) [10-13] or life-threatening opportunistic infections (e.g., bacterial infections, Epstein-Barr virus [EBV], cytomegalovirus [CMV], and polyoma BK virus) [14-16].

If the probability of specific outcomes (e.g., allograft failure, infection, cancers, diabetes) could be estimated by reliable risk-stratification tools, the patient-specific estimates would be very useful for individualizing therapeutic approaches. While individual factors associated with allograft survival and posttransplant complications (acute rejections, infections, cancers, diabetes) are to some extent known, in complex,

real-life situations where several factors are at play, it is difficult to estimate the risks of particular outcomes.

Developing risk stratification tools (i.e., a scoring systems and a decision support system [DSS]) based on predicted long-term outcomes of transplantation for individual patients might accomplish several important goals: (1) indicating donor-recipient combinations that predict favorable or poor outcomes; (2) identifying adjustment of modifiable factors that are highly predictive of allograft survival; and (3) identifying immunosuppressive strategies that predict improved allograft survival and limited complications in specific patients. Predicting important clinical events with subsequent risk-stratification of long-term posttransplant outcomes would represent a very important step towards individualized patient therapy, as opposed to protocol-driven approaches, where the individual factors of the recipient, donor, and transplant procedure are not considered in combination. However, the actual prediction of the outcome is impossible without using mathematical tools due to complexity of the associations and their interactions.

Using informatics tools it is possible to develop the prediction model of long-term kidney allograft survival, that can be used in the development of a decision support system.

1.2. The need for outcome prediction in renal transplantation

1.2.1. Transplantation is a preferred method of renal-replacement therapy

The number of patients with ESRD in the USA is approaching half-a-million; in most of the cases, the kidney function is being replaced by dialysis [17]. Mortality in patients on dialysis is 10 to 20 times higher than that of the general population [18, 19]. Renal transplantation, limited by a shortage of kidney donors [20], significantly improves survival of the patients [17]. With the introduction of new immunosuppressive

medications, short-term allograft outcomes have improved considerably [21], while long-term survival and chronic allograft nephropathy still present a problem [22].

Increased patient survival [1-3], quality of life [4], and decreased medical expenses [5] occur as a result of kidney transplantation compared to patients remaining on the transplant waiting list (usually on chronic dialysis). At the same time, the transplant procedure and the posttransplant course carry their own risks (e.g., surgery and anesthesia, immunosuppressive medications, lipid abnormalities, hyperglycemia, cancers, infections) that may shorten the life span of the recipient.

1.2.2. Predicting the outcome of transplantation is difficult

Health care providers and patients face several important questions before a transplant such as: is transplantation always beneficial compared to dialysis?; should one receive a transplant now and have the benefit of shorter time on dialysis, or wait for the kidney with a better match?; should a patient with multiple comorbidities receive a kidney transplant at all, and if so, how it is going to affect his/her life expectancy?; if there are several living donors available, who is the optimal choice for a particular patient (based on body size, gender, antigen match, comorbidities, and their interaction, etc.)?; what is the best immunosuppressive strategy?

Ideally, a computer-based DSS would integrate a large number of variables, allow modeling of specific constellations of predictors (i.e., issues associated with donor, recipient, and the transplant procedure) to reach a tailored prediction. This tool would be extremely valuable in the pre- and posttransplant setting, as it would help clinicians and patients alike to decide on the ESRD management strategy. Such a system could be used successfully if it predicted the degree of allograft survival, patient survival, and potential complications during the posttransplant course. The critical issue here is that patients and clinicians alike approach a transplant with virtually no sense of the patient-

specific expected outcome. Historically, the decision has been “transplant, yes or no?” The reality of posttransplant is much more of a gray area than this simple question suggests.

Several modifiable factors were found to be broadly associated with transplant outcome. These include body size match, type of recipient immunosuppressive therapy, the timing of the transplant in relation to the ESRD course, HLA antigen match, etc. [23-34]. Some of these factors have established optimal criteria (e.g., a living kidney is better than deceased, a preemptive transplant is advantageous compared to postdialysis transplant, a shorter organ cold-ischemia time is preferable, and close antigen matches are considered beneficial). However, clinically relevant, patient-specific treatment questions are difficult to answer based on these predictors in isolation. Since the number of variables is large, and their interactions are complex, it would be unrealistic to expect clinicians to reach an optimized decision unaided. To demonstrate the complexity of determining an optimal strategy, consider the following example: a potential recipient who is nearing ESRD is offered a well-matched *deceased* kidney available *immediately*. Should the patient accept the deceased organ to avoid *dialysis* or go on dialysis for an indefinite period in the hopes of receiving a living organ, missing the opportunity for a *preemptive* transplant? The complex nature of interactions between predictors of the kidney transplant outcome, as well as their intricate relationship to the outcome itself, makes manual prediction of allograft outcome daunting.

1.2.3. Individualized prediction would improve patient management

The personalized medicine paradigm proposes the diagnostic and therapeutic approaches to be tailored to the specific patient as opposed to “one-size-fits-all” approach [35, 36]. Usually considered in association with genomic information, personalized medicine also requires consideration of environmental factors of the

recipient and donor that, when considered in combination, may help in individualizing therapeutic approaches. Currently in organ transplantation, use of immunosuppressive medications is mostly based on general clinical protocols, rather than on individual differences between the patients. At the same time, the therapeutic window for most of the immunosuppressive medications is very narrow, where under-use may cause rejection, while overaggressive dosing schedule may cause long-term and life-threatening complications (e.g., posttransplant infections, cancers, diabetes, and osteoporosis) [10, 13, 15]. Individual patients respond differently to immunosuppression and the level of the drug is not always a good predictor of the response [37]. In addition to drug levels, other factors pertinent to the recipient, donor, and transplant procedure clearly affect the response to therapy and the rate of complications [23, 38-40].

While posttransplant management of the patients in most transplant centers is protocol-driven, predicting the duration of allograft and recipient survival and risk stratification for different outcomes (including posttransplant complications) might dramatically modify patient care. Knowing the quantified risks of allograft failure, patient death, acute rejection, cancers, infections, and other posttransplant complications for an individual patient may significantly affect several decision processes, including the following: whether to transplant, who is the best donor, what is the preferable immunosuppressive regimen. Prediction models were proposed in other areas of medicine, such as liver transplantation [41, 42], cancer [43-45], and cardiovascular disease [46-48]. NIH awarded a grant (1R01HL087115-01A1 Clinical Risk Factors for Primary Graft Dysfunction) to study clinical factors affecting posttransplant lung graft dysfunction and to develop a prediction model based on these factors. Interestingly, there is another R01 grant awarded by NIH (2R01DK034238-21A1 Models for Optimal Liver Transplant Outcomes) to predict renal function in liver transplant recipients. At the same time, in the area of kidney transplantation, aside from a few reports [49-52]

including those by our group [40, 53], the development and use of outcome prediction models are largely lacking.

1.3. Prediction models in liver transplantation

A Child-Turcotte-Pugh scoring system has been used in the past and has been recently modified to predict mortality in patients with advanced liver failure [54]. Other prediction models have been proposed to predict recurrent hepatitis C [55] and liver fibrosis [56] in liver transplant recipients. An artificial neural network (ANN) has been used to predict the allograft failure in patients with liver transplantation [57]. Finally, in liver transplantation, a model for end-stage liver disease (MELD) based on outcomes of transjugular intrahepatic portosystemic shunt (TIPS) is used for prediction of liver failure [58] and to determine priorities in organ allocation, [41]. However, while factors associated with survival after liver transplantation have been evaluated [59], attempts to use MELD to predict the outcome of liver transplant recipients (recipient and allograft survival at 1 year) were unsuccessful [60]. This illustrates the need to utilize a large data set of data that is directly related to the outcome of interest, as opposed to the use of proxies (e.g., data from TIPS outcomes used to predict transplant outcomes).

1.4. Prior efforts to predict kidney transplant outcome

Outcome prediction is becoming increasingly important in medicine, but when a resource is scarce, the need for accurate prediction becomes even more evident. There is extensive literature dedicated to identifying predictors and risk factors of kidney transplant outcomes in adults [23, 61] and children [62], including the work published by our group [23, 63-71].

In addition to conventional environmental factors associated with renal transplant outcome, new biomarkers are currently being proposed. To name a few, ELISpot assay for interferon-gamma is associated with renal function in recipients at 6 and 12 months

posttransplant [72]. IL-12 and IL-10 elevated pretransplant are associated with acute rejection [73]. Gene expression studies were also performed and showed association of some transcripts with acute rejection [74] and early [75] allograft function. Renal artery resistance index measured by Doppler has been associated with allograft survival [76]. However, actual prediction studies in this area are limited. In his New England Journal of Medicine editorial "Predicting outcomes after renal transplantation--new tools and old tools," Marsden [77] describes specific markers of the renal transplant outcome. However, to our knowledge, there is no comprehensive model taking advantage and benefiting from several predictors taken together.

Several published reports focus on the prediction of the drug kinetics or differential diagnoses. Prediction analysis and, specifically, an ANN were used in transplant patients to predict both pharmacokinetic parameters of cyclosporine [78, 79], tacrolimus [80], and mycophenolate mofetil [81]. An ANN was also used to differentiate between acute rejection and acute tubular necrosis based on the results of renogram and clinical parameters [82], and to assist in pathological diagnosis of acute rejection [83]. In addition, decision analysis models were used to assist decision making for specific clinical questions (e.g., treatment of ESRD in insulin-dependent diabetics) [84-86].

Literature dedicated specifically to the *general* prediction of the clinical outcomes in kidney transplantation is scarce. In an early effort, Opelz et al. concluded that time-dependent renal function and clinical grades can be used in prediction of late allograft failure [87]. ANNs have been used to identify patients who risk the development of posttransplant cytomegalovirus disease [88]. Brier et al. used an ANN to predict the occurrence of delayed allograft function in kidney transplant recipients [51]. They found that ANNs were more sensitive, but less specific, than logistic regression in predicting delayed graft function. Delayed graft function is a short-term outcome, where the event

is reached in a few days after transplant. This makes prediction less challenging than the task of predicting long-term outcome since there are very few censored data points and a limited chance for unaccounted factors to adversely affect the model. Shoskes used an ANN to predict short-term renal transplant outcome and reported results in a non-peer-reviewed journal [49]. In the early work by Hennige [50], the authors used a multivariate model and data from 924 patients to predict 1-year survival.

Several scoring systems predicting short-term outcomes have been proposed:

- Scoring systems for deceased donor kidneys (deceased donor score) predicting short and long-term outcome were studied.[89-91]. In a recent paper based on 217 transplantations, three prediction scores were evaluated in their performance of predicting short-term allograft outcome. They demonstrated moderate predictive ability [92].
- De Bruijne et al. used Cox modeling with time-dependent renal function covariates for prediction of late allograft failure [52]. The project was based on a relatively small sample size (n=692) and a short list of predictors. Another clinical tool predicting mortality after kidney transplantation based on the Cox model [93] has been proposed based on 6,324 Canadian renal transplant recipients. In our proposed project, we will have access to almost 200,000 records of renal transplant recipients in the USA with hundreds of variables, which provides an excellent opportunity to develop a comprehensive and robust prediction model and risk-stratification tools for several important renal transplant outcomes.

1.5. Published reports by the author

The results discussed here were previously reported in peer-reviewed publications. In particular, the preliminary model discussed in Chapter 3 has been presented in publication [23] and is also protected by US patent [94]. Studies discussed

in Chapter 4 were reported as follows: The role of the renal replacement therapy modality discussed in Section 4.3. was published in [66]. In a follow-up project, we reported the role of previous renal transplantation [65] (presented here in Section 4.4), while the role of ESRD duration prior to transplantation was presented in [64] and discussed below in Section 4.5. In more recent papers, we discussed the role of recipient socioeconomic status [95] (presented here in Section 4.6.) and the role of immunosuppressive medications [96] (presented in Section 4.7). Finally, we reported the results of tree-based modeling presented in Chapter 5 [97].

1.6. Specific aspects of medical informatics applicable to this project

1.6.1. Manipulating a large dataset

In this project, the data were obtained from several separate USDRS files that had to be linked to each other. Some of the medical data format had to be changed. We performed data cleaning and validation. Finally, we performed imputation procedures to prepare the dataset for analysis.

1.6.2. Knowledge discovery in the databases

We used specific KDD techniques, including recursive partitioning, artificial neural networks, as well as more traditional logistic regression to establish the feasibility of the prediction modeling and by comparing different models to select the optimal statistical approach.

1.6.3. Variable selection for the prediction modeling

Variable selection for the prediction modeling is an integral part of machine learning, and was performed prior to the construction of the prediction models.

1.6.4. Creation and validation of the prediction model: The core of the decision support system

In this project, we generated several mathematical models predicting the probability of the kidney allograft failure at different time points of the posttransplant period. Prediction models represent either a regression model or a recursive partitioning algorithm that can be easily coded and can be used as a core for the decision support system.

2. SPECIFIC AIMS

2.1. Hypothesis

Clinically useful individualized estimates of long-term kidney transplant outcomes can be generated by using mathematical models to combine standardized data collected on recipient characteristics, donor characteristics, and transplant procedures.

2.2. Project aims

The specific goals of the present project are the following:

1) To determine the most significant and clinically practical predictors of kidney transplant outcomes (patient survival, allograft survival, posttransplant complications) using United States Renal Data System (USRDS) data.

2) Based on the selected predictors, to generate prediction models of renal transplant outcomes.

2.3. Impact on patient care

While realizing the potential caveats concerning observational and retrospective studies, employing prediction models and developing risk-stratification tools may be used successfully in clinical practice to accomplish the following:

(1) manipulate modifiable factors (e.g., donor selection, diet, behavior, medications) in pretransplant and posttransplant periods to potentially prolong allograft and patient survival;

(2) create evidence-based recipient and donor counseling regarding pre- and posttransplant strategies and range of likely outcomes;

(3) individualize selection of immunosuppressive regimens in order to minimize the risk of allograft rejection and posttransplant complications, and thus to expand overall allograft and patient survival;.

(4) extend the predictive models to predict long-term outcome in the general population of patients with CKD. (Here, the infrastructure designed to collect and analyze the data used in this project will also be configured to accommodate new data types).

(5) to advance future research through utilizing the hypotheses generated in this study and by using research resources (including data collection and DNA storage) developed at the end of this project;

(6) generate hypotheses and provide important targets for future interventional studies by identifying important predictors of patient outcome;

(7) and finally, employing the proposed study to address the Healthy People 2010 statement to improve kidney transplant outcomes, and thereby accomplishing the goal of reducing the consequences of CKD.

3. PRELIMINARY MODEL: 3-YEAR ALLOGRAFT SURVIVAL

3.1. Introduction and project goal

Attempts have been made to develop prediction models of graft survival (mostly short-term) [98] based on data available using different statistical models such as Cox regression [50] and artificial neural networks [49]. The goal of this initial study was to evaluate the set of United Network of Organ Sharing (UNOS) records (1990-1998) to identify pretransplant factors affecting 3-year allograft survival in order to generate a prediction model that would accurately identify patients at risk for 3-year allograft failure using logistic regression and a tree-based algorithm. To assure practical use of the prediction model in pretransplant evaluation and recipient counseling, only variables available in the pretransplant period were used.

3.2. Methods

3.2.1. Dataset

Between the years 1990 and 1998, from the U.S. Scientific Registry of Transplant Recipients (supplied by UNOS), we selected patients with ESRD who had undergone kidney or kidney-pancreas transplantation. The dataset includes transplants done in infants and young children as well as old age (minimal age below 1 year, and maximum age 98 years). To protect patient privacy, follow-up dates and transplant dates were shifted randomly by ± 1 to 180 days. Dates were shifted by the same amount for any given record so that the difference between the dates is preserved. Independent variables available for analysis included age, gender, race, height and weight for both

donor and recipient, recipient cause of end-stage kidney disease, type of pretransplant renal replacement therapy, number of previous kidney transplants and pretransplant blood transfusions, recipient most recent creatinine and donor terminal creatinine, history and duration of diabetes in hypertension in the donor, number of HLA match and mismatch, cold ischemia time, kidney or kidney and pancreas transplant, and transplant center code. The outcome variable was 3-year graft survival, and the end point was defined as allograft failure. Patient death with functioning graft was not included in the definition of graft failure. Information regarding most of the variables used in our analysis was collected by UNOS beginning October 1, 1987. However, several variables (donor history and duration of diabetes and hypertension, recipient most recent serum creatinine and donor terminal creatinine) were collected by UNOS only since 4/1/1994. Furthermore, donors' most recent creatinine levels were collected only for nondialyzed patients between 4/1/94 and 10/25/99 with collections from all patients beginning only after 10/25/99 [23].

3.2.2. Data cleaning and imputation

The initial dataset consisted of 102,686 records. Independent variables initially planned to be included in the analysis, but missing a large number of entries, were either eliminated (recipient creatinine levels were missing in 89.2% of the entries) or categorized (previous number of kidney transplants, donor terminal creatinine levels, donor duration of diabetes, and donor duration of hypertension were missing in 87.3%, 60.6%, 63.7%, and 60.7% of the entries, respectively, and were converted into categorical variables with a separate code for missing values). The following variables were considered erroneous and were replaced with blank values: cold ischemia time =0 (n=376), cadaveric donor creatinine >3 mg/dl or 26.5 mmol/dl (n=923), donor or recipient height <45 cm or >210 cm (n=211, n=6), donor or recipient weight <1 kg or >340 kg

(n=21, n=29). A number of records with critical information being incomplete or deemed to be unreliable or erroneous had to be eliminated. Records missing both height and weight (for either donor or recipient) were eliminated. In the remaining missing records, donor and recipient height and weight were imputed using a tree-based model with height (for weight imputation), weight (for height imputation), age, gender, and race as independent variables. The imputation algorithm for recipient height (missing 90% of the values) was tested using 8,282 USRDS patients with complete data for age, weight, height, gender, and race from DMMS Waves 3 and 4 studies. The dataset consists of a random sample of all ESRD patients on January 1, 1994. As a test of reliability, the intra-class correlation coefficient was calculated using SPSS (SPSS Inc., Chicago, IL). Based on the Landis and Koch guideline for evaluation of the reliability coefficient [99], our correlation coefficient of 0.76 for the predicted height values has substantial agreement with the actual observed heights. Records with missing and indeterminate 3-year outcome were deleted; therefore, the dataset was biased towards a higher proportion of failed grafts. As a result, values of the percent survival have only relative meaning and are used for the purpose of comparison between groups studied. Two of the categorical variables had more than 34 levels (transplant center code, cause of ESRD). Based on the possibility that transplant center volume may have an effect on the outcome, a five category variable was created: transplant centers codes were grouped into quintiles according to total number of transplants done between ’90 and ’98 (1= 1-83; 2= 84-209; 3= 210-355; 4= 356-615; 5= 616-2529). Causes of ESRD were grouped into deciles by total number of transplants with known 3-year survival. The final dataset consisted of 37,407 records.

3.2.3. Statistical analysis

Bivariate analysis was performed using cross-tabulation and comparison of graft survival in the subgroup using the Chi-square test. The Friedman supersmoothing method was used to fit the curve in bivariate analysis. Discrimination was determined by area under receiver operating characteristic (ROC) curve and Chi-square for logistic regression models. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. For the purpose of prediction analysis, all records were randomly assigned either to a "training" set (n=25,000), used for knowledge acquisition and model development, or to a "testing" set (n=12,407), used to validate the models. Predicted probabilities of 3-year graft survival were generated on a testing set and were compared with the actual patient outcomes. The predicted probability of the graft survival with group-average observed graft survival was used to compare the performance of the models. Also, 2x2 contingency tables were used to determine positive and negative predictive values.

Multivariate statistical models used in the analysis included logistic regression and classification trees. In certain situations, traditional statistical methods are poorly suited for complex interactions or detecting patterns in the data. Many possible predictor variables may violate the normality assumptions necessary for parametric analysis. In addition, the results of traditional methods sometimes may be difficult to use. Therefore, along with a traditional regression model that assumes linear relationship between predictors and the outcome, we decided to use a less commonly used tree-base model, which does not require the linearity assumption, and was used in clinical prediction before [100]. Tree-based modeling is an exploratory technique for uncovering structure in data which generates a collection of many rules displayed in the form of a binary tree [101]. We used the S-Plus statistical software package (MathSoft, Inc., Seattle,

Washington) for bivariate analysis and tree-based modeling and SAS (SAS Institute, Cary, North Carolina) for logistic regression.

3.3. Results

3.3.1. Comparison between initial and final datasets

The elimination of the large number of records could potentially bias the dataset; therefore, after completing the data cleaning described in the previous section, we compared the final dataset (n=37,407) to the initial one (n=102,686). The final dataset had the same donor and recipient mean age, height, weight, number of matched and mismatched antigens, and cold ischemia time as the initial dataset, as well as the same distribution of donors and recipients by gender, dialysis type, race, presence of DM and HTN in donors' number of pretransplant transfusions, and transplant procedure (data not shown). Compared to the initial dataset number, the number of transplant centers in the final datasets has not changed. Therefore, we concluded that even after the elimination of a large number of records, the final dataset is still representative of the initial sample.

3.3.2. Bivariate analysis

3.3.2.1. Donor and recipient characteristics

Young as well as elderly donors and recipients have lower 3-year graft survival ($p<0.001$). There were differences in outcome associated with donor and recipient gender and race. Kidneys from the donors with both DM and HTN had the worst 3-year survival (59.3%), while those from the donors without either had the best outcome (76.3%). Kidneys from either diabetic or hypertensive donors were roughly in the middle (66.2% and 64.3%, respectively) ($p<0.001$). Increased duration of HTN and/or diabetes (from 1 to 5 years by 1 year increments) in the donor was associated with worse outcome ($p<0.001$ for both). There is no relationship between donor terminal creatinine

and graft survival. There were differences in outcome associated with different etiologies of renal failure (data not shown). Patients with no dialysis history (preemptive transplant) had the best 3-year graft survival (81.3%, n=1,940) followed by those with history of peritoneal dialysis (76.1%, n=4,591) and then hemodialysis (73.0%, n=11,542) ($p<0.001$). A previous transplant history worsened 3-year survival in almost a linear fashion with 76.7% survival in recipients with no previous transplant history: 70.9%, 62.1%, and 56.9% in those with one, two and more than two previous transplants, respectively ($p<0.001$). The number of pretransplant transfusions did not significantly affect graft survival in bivariate analysis.

3.3.2.2. Transplant procedure: Matching donor and recipient

Three--year survival improves and declines in a linear fashion with increasing numbers of matched and mismatched antigens, respectively ($p<0.001$). Donor/recipient BMI vs. 3-year graft survival looks almost like a bell-shaped curve with the best outcome associated with the donor/recipient BMI equal to 1. The worst survival was in grafts from relatively small donors to large recipients ($p<0.001$). Transplant centers with a low volume of transplants had variable outcomes, while in those with a high number of transplants, the outcome was relatively uniform. There was a slight downward trend in the relation of 3-year graft survival to cold ischemia time. Recipients of kidney-pancreas transplants had better 3-year kidney survivals (82.5%, n=3,243) than those receiving a single (i.e., kidney) transplant (75.7%, n=33,526) or en-bloc kidneys (68.2%, n=638) ($p<0.001$).

3.3.3. Mulitvariate analysis

The entire dataset (n=37,407) was initially included in a logistic regression model predicting 3-year graft survival. Using stepwise forward selection, we set a significance level of 0.05 for independent variables to enter the model. The variables and model

information are presented in Table 1. Odds ratios with 95% confidence intervals for the binary variables identified by the model are presented graphically (Figure 1). Deciles 6 and 7 of ESRD causes were identified as having a significantly higher risk of allograft failure, and the odds ratios of 3-year graft survival were 0.75 (95% CI 0.6-0.9) and 0.78 (95% CI 0.7-0.9), respectively [23].

Causes of ESRD in these categories that demonstrated less than 70% 3-year survival are membranous nephropathy (66.2%), cyclosporin nephrotoxicity (68.3%), analgesic nephropathy (68.8%), type II insulin dependent diabetes mellitus (65.6%), Henoch-Schönlein purpura (69.7%), mesangio-capillary type 1 glomerulonephritis (68.5%), and hemolytic uremic syndrome (54.8%).

Model discrimination using the c index (area under the receiver operating characteristic curve) was 0.653. This is the probability that for a randomly chosen pair of patients, the predicted and observed graft survivals are concordant. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. Since the p-value, p=0.63, of this test was not significant, the model's estimated probabilities of 3-year graft survival are not significantly different from the actual survival of patients over groups spanning the entire range of probabilities.

3.3.4. Prediction analysis

To generate the prediction model, we randomly selected 25,000 records as the training set, while the remaining 12,407 records were designated as a testing set and were used to compare predicted and observed 3-year allograft survival. A logistic regression model was again generated on the training set only. This model was 65% concordant and 34.5% discordant, while the c index was 0.653. Using the variables and parameter estimates generated with the training set, we calculated the probability of 3-year graft survival in the testing set. All records were divided into 10 groups based on

Table 1. Predictors of the outcome (3-year graft survival) identified by logistic regression for the whole dataset (n=37,407)

Independent variable	Coefficient	Chi-Square	p	Odds ratio	95% confidence interval
Intercept	1.332	89.474	<.0001		
Donor age	-0.0145	297.87	<.0001		
Donor BMI	0.0015	9.0748	0.0026		
Recipient BMI	-0.0121	42.774	<.0001		
Recipient age	0.0146	231.46	<.0001		
HLA match	0.1336	206.65	<.0001		
Cold ischemia time	-0.0079	35.701	<.0001		
Recipient is male	0.0648	6.4246	0.0113	1.067	1.015-1.122
Donor is male	0.1467	30.611	<.0001	1.158	1.099-1.22
Terminal donor creatinine 0.1-0.5	-0.2087	10.343	0.0013	0.812	0.715-0.922
Terminal donor creatinine >1.5-2	-0.2389	12.579	0.0004	0.787	0.69-0.899
Terminal donor creatinine >2-2.5	-0.4012	8.8319	0.003	0.67	0.514-0.872
Previous number of transplants =1	-0.4078	11.241	0.0008	0.665	0.524-0.844
Previous number of transplants =2	-0.8534	35.723	<.0001	0.426	0.322-0.564
Previous number of transplants >2	-1.1078	25.17	<.0001	0.33	0.214-0.509
Previous number of transplants unknown	-0.0454	0.1503	0.6982	0.956	0.76-1.202
Donor is Black	-0.3229	66.57	<.0001	0.724	0.67-0.782
Donor is Hispanic	-0.1247	7.1664	0.0074	0.883	0.806-0.967
Recipient is Black	-0.4726	263.48	<.0001	0.623	0.589-0.66
Recipient is Asian	0.2201	8.065	0.0045	1.246	1.071-1.451
Recipient was never dialyzed	0.2001	9.7585	0.0018	1.222	1.077-1.385
Recipient dialysis modality is unknown	0.1754	33.774	<.0001	1.192	1.123-1.264
Donor: HTN (but not DM)	-0.3701	32.775	<.0001	0.691	0.608-0.784
Donor: no diabetes	-0.571	13.845	0.0002	0.565	0.418-0.763
Donor: duration of DM >= 5 years	-0.5702	14.815	0.0001	0.565	0.423-0.756
Donor: duration of HTN >= 5 years	0.1856	4.7968	0.0285	1.204	1.02-1.421
Simultaneous kidney-pancreas transplant	0.3052	30.044	<.0001	1.357	1.217-1.513
Transplant procedure: en-block transplant	-0.6445	47.954	<.0001	0.525	0.437-0.63
Transplant procedure: double kidney	-12.727	0.021	0.8849	<0.001	>999.99

Table 1. Continued

Independent variable	Coefficient	Chi-Square	p	Odds ratio	95% confidence interval
Transplant procedure: whole pancreas / right kidney	-1.413	3.9032	0.0482	0.243	0.06-0.989
Transplant center volume (>83-209)	-0.1436	8.2045	0.0042	0.866	0.785-0.956
Transplant center volume (>355-615)	-0.1115	14.812	0.0001	0.895	0.845-0.947
Number of transplants for this diagnosis >46-77 (6^{th} decile)	-0.2942	7.2995	0.0069	0.745	0.602-0.922
Number of transplants for this diagnosis >77-196 (7^{th} decile)	-0.2435	7.9364	0.0048	0.784	0.662-0.929

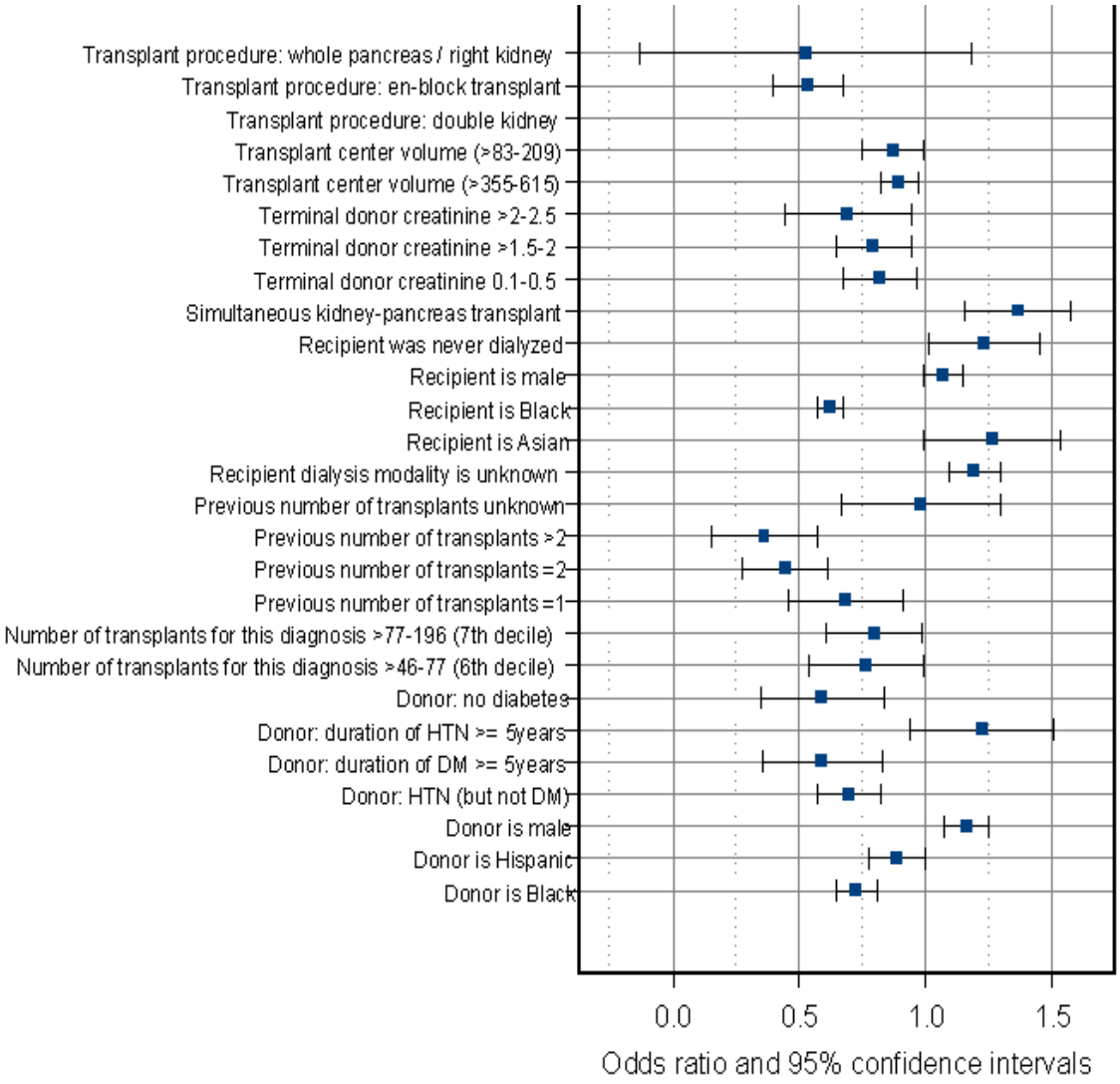


Figure 1. Odds ratios of the 3-year graft survival based on the logistic regression model

deciles of predicted probability of graft survival (0-10%, >10-20%, >20-30%, etc.). The observed percentage of 3-year graft survival was calculated for each group, and the observed graft survival was compared to the expected survival. Since there was only one patient in the >10-20% group, that group was combined with the >20-30% group to produce a >10-30% group. The midpoint of each group's probability range was used as the expected percent survival. As shown in Figure 2, the prediction of the probability of

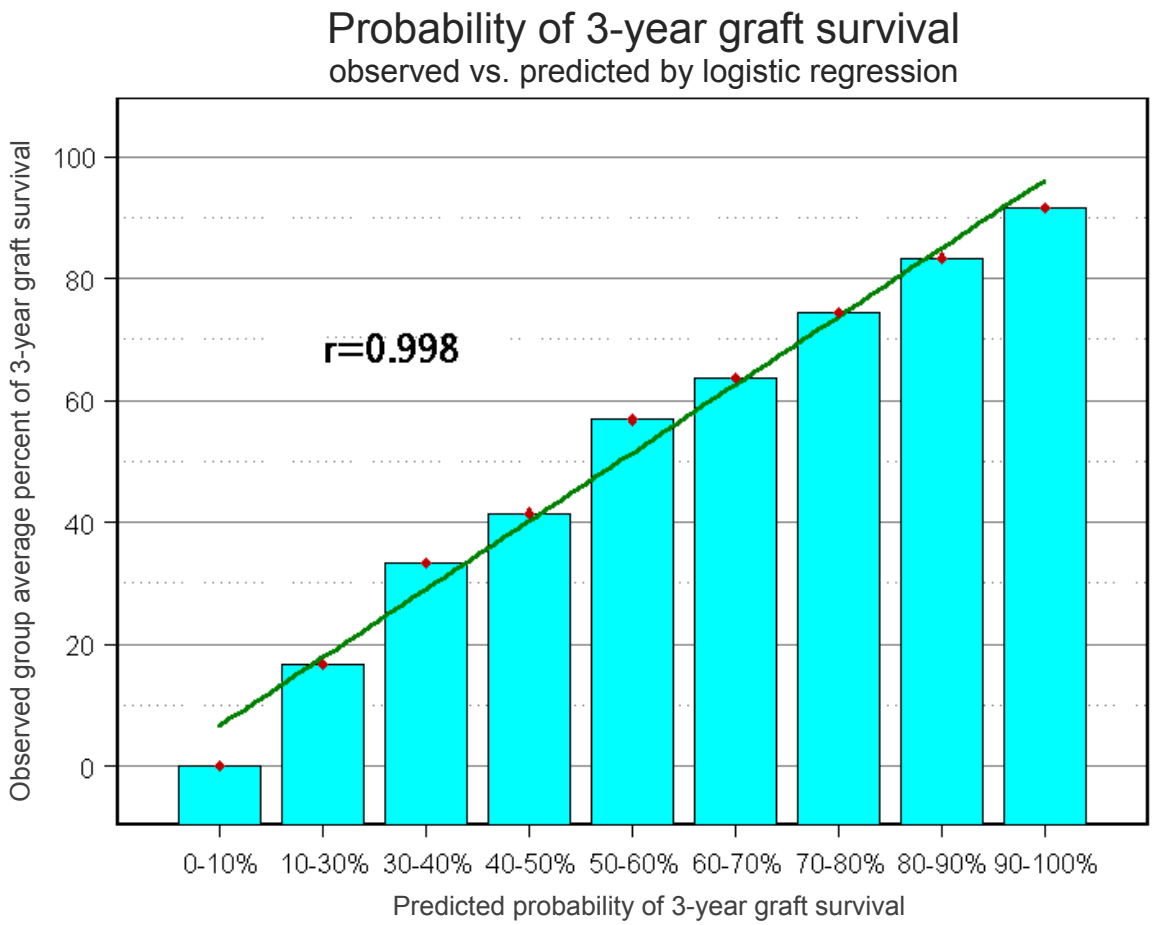


Figure 2. Results of the prediction of 3-year graft survival using a logistic regression model on the testing dataset. All patients were divided in ten groups based on predicted probability of graft survival. The observed group averaged graft survival is compared to the predicted probability.

graft survival from the training model achieved a very good match with the observed survival of the testing set, with a Chi-square value of 6.15 and p=0.63, which shows no significant difference between observed and predicted category, and a correlation of r=0.998.

We converted predicted allograft failure probability into a binary variable (graft survival = “yes” or “no”) using a cut-point of 50% probability. The results were compared by means of a 2x2 contingency table. The positive predictive value of allograft survival with the model was 76.0%, and the negative predictive value was 63%.

3.3.4.1. Tree-based model

We used a tree-based model to identify predictors of 3-year graft survival and to develop a prediction model. The outcome of a cross-validation procedure in the form of deviance plotted against number of terminal nodes (tree size) was analyzed, and the optimal size of the tree was determined to be equal to 54 terminal nodes. To identify predictors of the outcome, the initial tree was constructed on the entire dataset and pruned to 54 terminal nodes. The following 17 predictors of outcome (in order from the root of the tree to the terminal nodes) were identified by the tree-based model: recipient race, donor age, recipient weight, cold ischemia time, recipient height, previous number of transplants, recipient age, number of matched HLA antigens, donor race, cause of end-stage renal disease, recipient gender, number of mismatched HLA antigens, recipient BMI, recipient weight, presence of diabetes and/or hypertension, donor height, and donor/recipient BMI. The residual mean deviance of the model was 1.03 and the misclassification error rate was 0.23.

The new tree-based model was built upon a training set and validated on the testing set. Using the model generated with the training set, we calculated the probability of 3-year graft survival in the testing set. All records were divided into 10 groups based on deciles of predicted probability of graft survival (0-10%, >10-20%, >20-30%, etc.). The observed percentage of 3-year graft survival was calculated for each group. The observed graft survival was compared to the expected survival. Since there were only six patients in the 0-10% and >10-20% groups taken together, those groups were combined with the >20-30% group to produce a 0-30% group. For the same reason groups >30-40% and >40-50% were combined to produce a >30-50% group. The midpoint of each group's probability range was used as the observed percent survival (Figure 3). The prediction of the probability of graft survival from the training model achieved a good correlation with the observed survival of the testing set

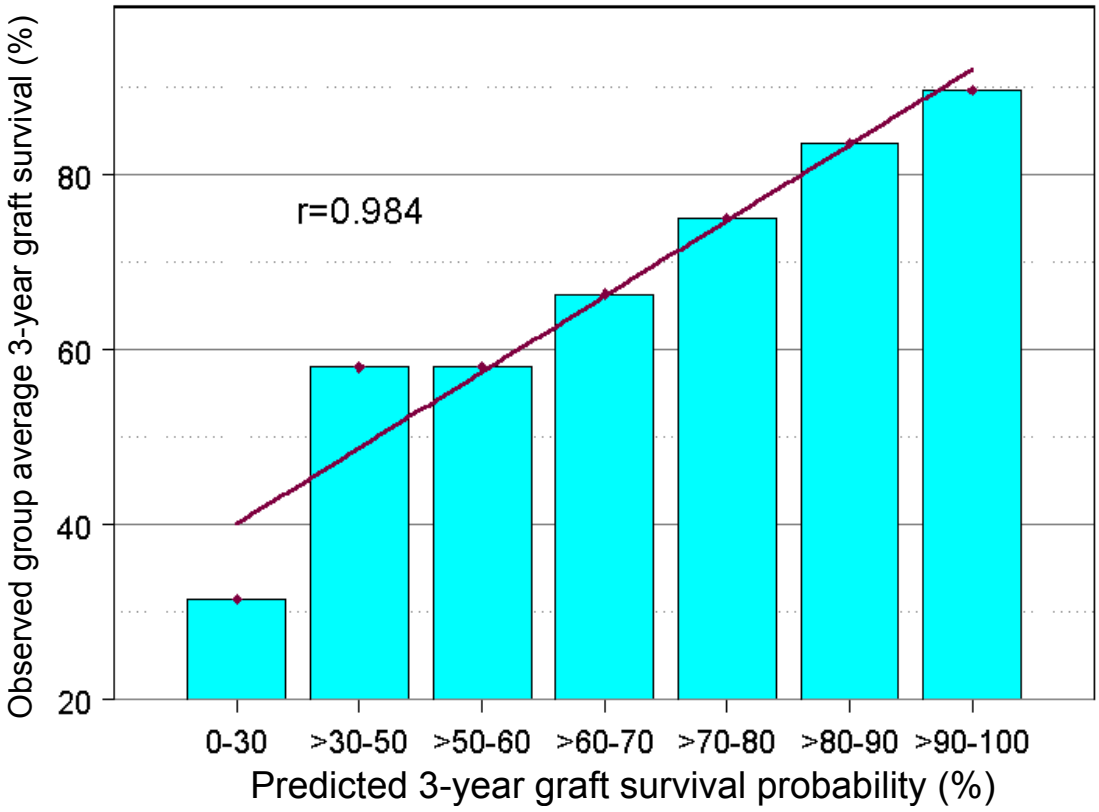


Figure 3. Results of the prediction of 3-year graft survival using a tree-based model on the testing dataset. All patients are divided into seven groups based on predicted probability of graft survival. The observed group-averaged graft survival is compared to the predicted probability.

(r=0.984). We converted predicted allograft failure probability into a binary variable (graft survival = “yes” or “no”) using a cut-point of 50% probability (Figure 4). The graph represents the model in a form of a dichotomized tree, where each node presents a question regarding the value of a single independent variable. If the answer to the question is “yes,” users move to the next node by way of the left branch (or right branch, if the answer is “no”) until it reaches the terminal node, which predicts 3-year graft survival (Y or N). The results were compared by means of a 2x2 contingency table. The positive predictive value of the allograft survival with the model was 76.0% and the negative predictive value was 53.8%.

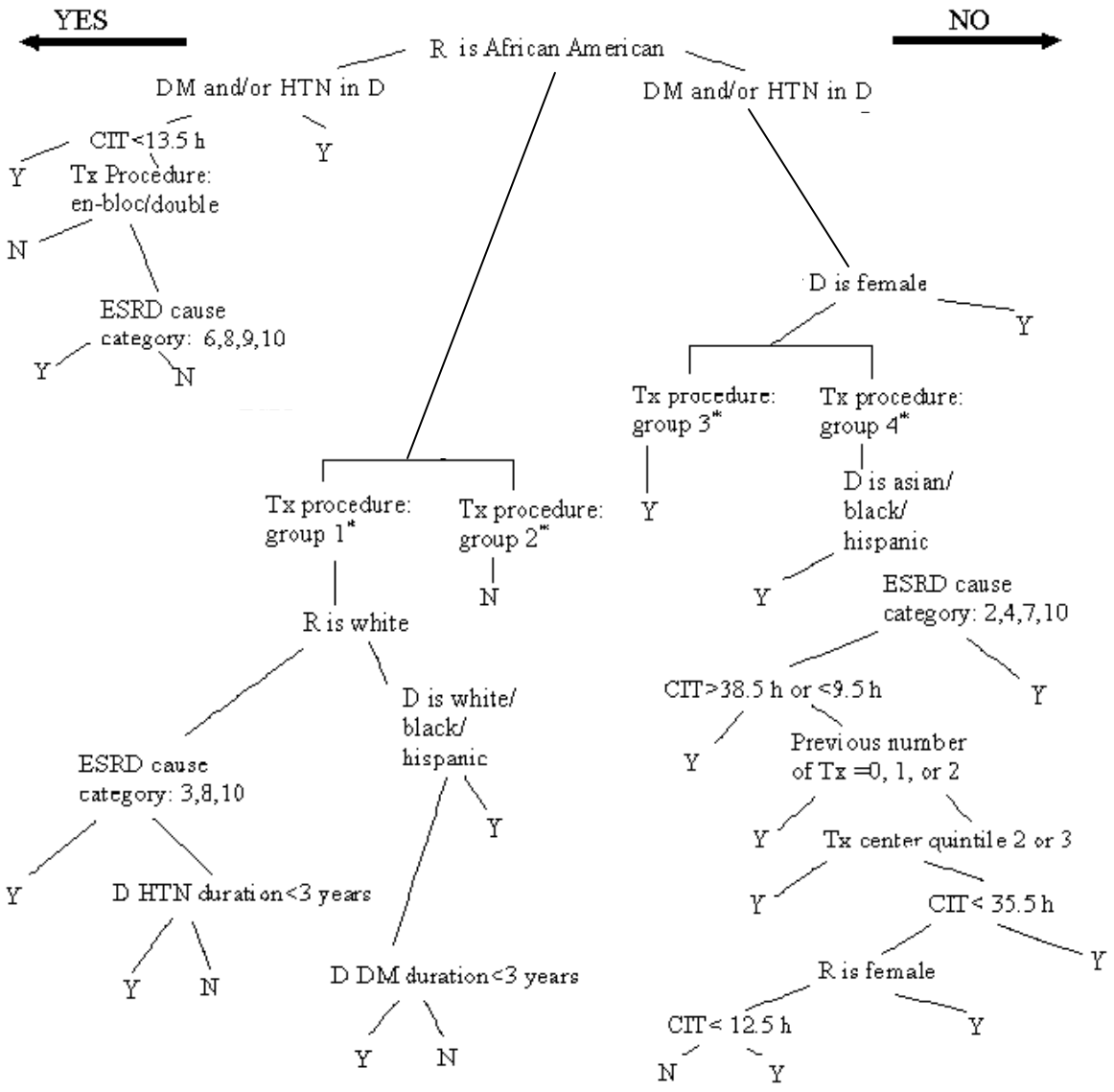


Figure 4. Tree-based model built on the training dataset. D- donor, R – recipient, Tx – transplant, CIT – cold ischemia time, "Y" and "N" at the terminal nodes of the tree correspond to predicted 3-year graft survival (yes or no).
Transplant procedure group 1: left /right, or en-bloc kidney with or without the whole pancreas with duodenum or whole pancreas with duodenal patch / left kidney
Transplant procedure group 2: double kidneys, pancreas segment with left kidney, whole pancreas with duodenum and double kidneys, whole pancreas with right kidney
Transplant procedure group 3: pancreas segment and left kidney, whole pancreas with duodenum and right or en-bloc kidney, whole pancreas and left kidney
Transplant procedure group 4: left /right / en-bloc kidney, whole pancreas with duodenum and left kidney, whole pancreas with duodenal patch and left kidney, whole pancreas and right kidney.

3.4. Discussion of the results and deficiencies of the present study

Factors affecting kidney allograft survival were evaluated previously, based on local datasets and national databases. In this project, we evaluated a large national dataset which includes a relatively new collection of data covering all renal and kidney-pancreas transplants between 1990 and 1998. Using strict criteria, we eliminated records with incomplete information and made careful imputation of some variables.

3.4.1. Discussion on dealing with missing information in UNOS dataset

While cleaning the data, we encountered certain problems with missing and poorly reported values. The amount of misreported or missing information in the1990-1998 UNOS dataset can be explained by several factors that need to be considered by researchers analyzing the data. As mentioned above, certain variables may not have been collected over the entire time period of the cohort. For example, donor history and duration of diabetes and hypertension, and recipient most recent serum creatinine and donor terminal creatinine were collected only since April of 1994. Additionally, voluntary data submission via paper form (with some fields not mandatory) account for much of the missing information. It has been speculated that this is the reason that height and weight are not populated well (e.g., recipient height is missing in approximately 90% of the values). In some cases, the field may not be relevant in that particular instance, so the member may have chosen to leave it blank (e.g., data for PRA tends to be entered only if the patient is sensitized [PRA 80 or above]; otherwise, it is left blank). One may expect improved quality of data in the future. The number of outstanding forms has been steadily declining in recent years For example, there were almost 150,000 outstanding forms in April of 2000 and 56,000 in September 2002 (UNOS, personal communications). UNet, the online transplant data entry system, was implemented in

October 1999. The new system of on-line data entry employed real-time data quality control, forcing the user to enter the data in a correct and unified format. Therefore, the quality of information should substantially improve. Thus far, the effect of the new system on the individual variables over time has not been studied closely. In this study, missing categorical variables were coded as a new category and missing continuous variables were replaced using appropriate data imputation methods. In particular, a tree-based algorithm was used for height and weight imputation. The algorithm that we developed has been shown to have good precision when validated on a separate database derived from USRDS Wave 3 and 4 study patients. Tree-based imputation can be a useful tool for the researchers analyzing the datasets with missing values for the anthropometric characteristics. After careful imputation, the results and conclusion of our analysis should not be affected by various causes of missing data (UNOS not collecting it vs. poor reporting). During cleaning of the initial dataset, we tried to preserve as much useful information as possible and at the same time eliminate potentially erroneous, incomplete, or unreliable information. A significant number of records had to be eliminated as some critical information was missing or deemed unreliable.

3.4.2. Individual predictors of the transplant outcome

Our bivariate and multivariate analyses demonstrated the importance of several pretransplant donor, recipient, and procedure variables in predicting 3-year graft survival; in particular, we found that the number of previous kidney transplants in recipients has a direct relationship to the transplant failure rate, and that diabetes and hypertension worsen the outcome. The relationship between donor and recipient age, race, gender, and 3-year graft survival previously reported [27, 34] proved to be nonlinear. The number of HLA matched/mismatched antigens has a very strong linear

relationship with the percent 3-year graft survival. On the other hand, the effect of cold ischemia time is much less dramatic by bivariate analysis than we initially expected and that was previously reported [102]. The transplant center effect was studied before [103] and showed only a very slight difference between the large and small centers. In our study, centers with higher number of transplants have more similar outcomes, while the outcomes of the smaller centers exhibited considerable variability. This may represent either a regression to the mean or a true phenomenon of more uniform outcome that comes with greater experience. The logistic regression model selected transplant center volume as a predictor of the outcome, with centers having less experience increasing the risk of 3-year allograft failure. Some of the causes of end-stage renal disease in a recipient as a predictor of the outcome were described before [104]. In addition, we evaluated all the diagnoses with known 3-year outcome that we could derive from UNOS database. We confirmed previously reported beneficial effects of preemptive transplantation [105-107]. Body mass index (BMI) of donor and recipient as well as recipient obesity in relation to outcome has been discussed in the literature and has been found to have an important role in the prediction of the kidney allograft outcome in some studies [108, 109], while in others obese (high BMI) transplant recipients have similar outcomes to nonobese patients [110]. In our study, both donor and recipient BMIs were found to be good predictors of outcome by means of bivariate and multivariate analysis. Since successful transplantation of adult living donor kidneys into infants and small children with good long-term outcome has been shown in a small study [111], the unexpected, almost bell-shaped curve (Figure 3) describing the relationship between donor-to-recipient BMI and graft survival is surprising. This may represent either the deleterious effect of donor obesity [108] or the impact of poor recipient nutritional status. This relationship needs to be further evaluated in prospective studies and may be an important factor affecting the selection of the donor.

3.4.3. Predictive model issues

The novel part of this study is the predictive model. The time period of interest covers the “postcyclosporine era”; however, the 1990s were associated with changes in immunosupression protocols and surgical techniques and therefore, the database represents a very heterogenous population. This heterogeneity may potentially affect the performance of the prediction models, especially since we included in the analysis only a limited number (26) of pretransplant independent variables. In designing the study, our intent was to develop a prediction model for use prior to transplantation; therefore, we excluded posttransplant variables that were not available until after the transplant procedure. We did not analyze the impact of immunosuppressive therapy, immediate posttransplant graft function, and episodes of acute rejection, since this information was not available prior to transplant. Along with the conventional logistic regression model, we used a tree-based model never before used to analyze transplant outcome. This model represents a relatively new approach compared to conventional regression analysis of the data. Interest in this statistical approach has been increasing over the last 10 years. Several features make tree-based models a powerful tool for building a prediction algorithm that can be successfully used in practice. The tree-based model works when the regression variables are a mixture of categorical and continuous variables, and it is often able to uncover complex interactions between predictors which may be difficult or impossible to uncover using traditional multivariate techniques. The algorithm is nonparametric, so no assumptions are made regarding the underlying distribution of values of the predictor variables. The tree-based model identifies "splitting" variables based on an exhaustive search of all possibilities, even in problems with many hundreds of possible predictors. Simultaneously, it requires relatively little input from the analyst. This graphical algorithm, presented as a collection of simple binary rules, is much simpler to interpret by a nonstatistician than the multivariate logistic

regression. Thus, it can be used in the decision-making process without doing any additional calculations, and therefore is more likely to be followed in clinical practice.

Prediction models using logistic regression and tree-based algorithms are developed in this study on the large set of data, and can potentially be used in recipient counseling and decision-making regarding cadaveric renal transplants. The relatively low area under the ROC curves of the initial models suggests that a longer list of the potential predictors should be evaluated. However, the prediction algorithms generated on the training dataset can be successfully used in practice to identify the probability of 3-year kidney allograft survival, since both models achieved good precision in predicting the probability of the graft survival on the separate set of data. There is an experience of using similar data derived from univariate and multivariate analyses in a smaller study in a cadaveric kidney allocation decision-making study in a northern Italy transplant program [112]. The identification of factors that play an important role in graft survival helps to focus efforts of transplant programs on certain individual aspects of patient care. The implementation of the models that were generated in this study in the form of software to make it available for transplant programs and prospective transplant recipients may be a subject of future projects.

3.5. Significant deficiencies of this project

A very important deficiency of this project is a limited number of predictors. In particular, none of the factors associated with the pretransplant dialysis course were included in the model. Similarly, socioeconomic factors and comorbid conditions were left out of the model, since the information is not available in UNOS database. Furthermore, it is not clear in the existing literature which of the factors have a significant association with the outcome and therefore need to be included in the modified model. Furthermore, the model presented above predicted the probability of 3-year graft

survival, but not at any other time points. Finally, only deceased donor transplant recipients were included in the reported study, while the recipients of living donor grafts were left out [23].

Based on these deficiencies, the decision was made to proceed as follows.

1. Evaluate the association between specific variables and the transplant outcome in order to make a decision whether or not to include them in the final model.

2. Build a more sophisticated model based on a more complete list of predictors available in other datasets.

4. STUDIES OF THE ADDITIONAL PREDICTORS OF ALLOGRAFT SURVIVAL

4.1. Project goal

The goal of this series of projects was to establish the association between previously unexplored potential predictors and transplant outcome in order to improve the performance of the predictive model.

4.2. Dataset and methods

4.2.1. Dataset

Using the USRDS database, we collected data on all kidney allograft recipients (both pediatric and adults) who underwent kidney or kidney-pancreas transplantation during the period of January 1, 1990 through December 31, 1999. The follow-up data were collected through December 31, 2000.

For recipients of multiple transplants, the most recent one was considered the target transplant (transplant of interest). Patient records with missing information regarding graft or patient survival were excluded from the study. A total of 92,844 patients with kidney transplant were identified. Records of patients with prior kidney transplants (n= 11,714) were also identified and analyzed separately.

4.2.2. Study outcomes

There were two outcomes in this study. The first outcome was the time between the most recent kidney transplant and the failure of the graft. The second outcome was

the time between most recent kidney transplant and the patient's death. Both outcomes were modeled using continuous survival time variables.

Graft failure definition did not include patient death with a functioning graft, the latter determined in the USRDS as a single binary variable. In case the value of this variable was missing and the patient's death date was found to be equal to the graft failure date, we assumed that patient died with a functioning graft, unless the cause of death was coded as one of the following: 3200 (graft failure: primary failure), 3201 (graft failure: rejection), 3202 (graft failure: technical), 3299 (graft failure: other), or 3903 (miscellaneous: renal failure).

Allograft outcome was censored at the earliest of the following events: loss to follow-up, patient death, or the study completion date (12/31/2000) and was analyzed as days-to-graft-failure or censor. Patient follow-up was censored at the earliest of loss to follow-up or study completion date, and was analyzed as day-to-recipient death or censor.

4.2.3. Covariates

The following independent variables were collected:

1. recipient variables: recipient age, gender, race, height, weight, history of hypertension (HTN) and diabetes, history of prior transplant, total duration of ESRD, total number of transplants, mean and peak panel reactive antibody (PRA) levels, education level, primary source of pay, citizenship (the combination of the last three variables was used as a surrogate for socioeconomic status);
2. donor variables: type of donor (cadaveric or living), heartbeating donor or not, donor age, gender, race, height, weight;
3. transplant procedure variables: day of the week the transplant was done, the year of the transplant, number of matched HLA antigens, and cold storage time.

To adjust the multivariate models for recipient comorbidities, we calculated a comorbidity score similar to one proposed by Davis, which has been shown to be strongly associated with the survival in a prospective study of 97 peritoneal dialysis (PD) patients [113]. The comorbidity score used in this study was calculated based on the following coexisting conditions, each of them contributing one point to the score: cardiovascular disease (defined in USRDS as symptomatic cardiovascular disease or angina/coronary artery disease), symptomatic peripheral vascular disease, diabetes mellitus, and hypertension. Information about coexisting conditions was obtained from the TXUNOS file (that file's data come from the Transplant Candidate Registration Form); therefore, the comorbidities used for this study are those that patient had at the time of listing for the study transplant. We did not use data from the CMS-2728 form (that also has comorbidity information at the time of onset of ESRD) in order not to exclude patients who were not Medicare eligible prior to 1995 (prior to 1995 dialysis units and transplant centers were required to fill the Medicare Evidence form only for Medicareeligible patients). To reduce lead time bias, the models were also adjusted for total duration of ESRD prior to the follow-up time included in the Cox models. Unrealistic values of the independent variables used in the study were eliminated. In particular, for donors and recipients younger than 13 years of age, the United States CDC Growth charts were used as a guide for determining valid ranges. The heights and weights of recipients and donors age 13 and older were based on the acceptable ranges: height (122 to 274 cm), weight (23 to 180 kg).

Other variables, delayed graft function, episodes of acute rejection, and type of immunosuppressive medications were not included in the models. Delayed graft function and acute rejection may represent intermediate outcome rather than the confounding factor and therefore, we speculated that adjusting for it might yield false negative results (type 2 error: failure to reject null hypothesis).

Patients with a prior history of kidney transplant in some subprojects described below were analyzed separately and for this subgroup, the following variables were added to the analysis: donor type for the transplant immediately prior to the current transplant, age at the first transplant, age at the first graft failure, age at transplant immediately prior to the current transplant and at graft failure immediately prior to the current transplant, time period between last transplant failure and current transplant. To reduce lead time bias, the models were also adjusted for total duration of ESRD.

4.2.4. Statistical analysis

Categorical variables in the subgroups were compared using cross-tabulation. Continuous variables were summarized using means and standard deviations. Kaplan-Meier graphs and Cox regression models were used for survival analysis. To avoid colinearity between the primary variables of interest, we analyzed these variables in separate Cox models. SAS (SAS Institute, Cary, NC) was used for survival analysis (Kaplan-Meier and Cox proportional hazards models), while S-Plus (Insightful, Seattle, WA) was used for descriptive statistics and tree-based modeling for data imputation.

4.3. Baseline characteristics

The characteristics of the study population are presented in Table 2. The recipients were 60% male, 70% White, and 27% diabetic, with an average age of 43 years at the time of the study transplant. Roughly one-in-eight (12.6%) had at least one prior transplant. The subset of patients had more than one transplant (retransplants, n=11,714). These recipients were 59% male, 78% White, and 16% diabetic, with an average age of 38.5 years at the time of the study transplant. The median time between last graft failure and current transplant surgery was 21.9 months; 13.7% had preemptive retransplants (n=1,609).

Table 2. Baseline characteristics of the of kidney transplant recipients (n=92,844) at the time of the most recent transplantation[1]

Recipient characteristics	
Age (yrs)	43.3±14.2
Gender (males)	60.3%
Race (White, African American, Asian, Native American)	70.2%, 23.0%, 3.4%, 0.9%
Weight (kg)	72.6±17.2
Height (cm)	169.0±13.7
Primary cause of end-stage renal disease	
DM	25.2%
HTN	17.2%
Glomerulonephritis	25.8%
Cystic disease	7.6%
Other	24.2%
Comorbidity score[2]	0.8±0.8
History of diabetes	27.2%
History of hypertension	52.5%
Total duration of end-stage renal disease (yrs)	3.1±3.6
Percent of end-stage renal disease duration time on peritoneal dialysis[3]	22.8±38.0
Percent of end-stage renal disease duration time on hemodialysis[3]	67.3±41.5
Percent of total end-stage renal disease duration with transplant[3]	6.1±20.1
Renal replacement therapy modality immediately prior to transplant	
Hemodialysis	71.3%
Peritoneal dialysis	21.8%
Transplant (dialysis free retransplant)	1.1%

Table 2 Continued

Recipient characteristics	
Unknown	5.8%
Predominant renal replacement therapy modality[4]	
Hemodialysis	67.3%
Peritoneal dialysis	22.6%
Transplant	6.4%
None	3.6%
Total number of transplants (including the current one)	1.2±0.4
Time on the transplant list (yrs)	1.3±1.1
Peak reactive antibody level (%)	12.1±21.5
Mean reactive antibody level (%)	5.3±14.7
Number of matched HLA antibodies	1.8±1.5
Cold ischemia time (hr)	15.5±8.7
Transplant day of the week[5]	4.0±1.8
History of previous kidney transplant(s)	12.6%

Table 2 Continued

Donor characteristics	
Age (yrs)	34.4±15.5
Gender (males)	56.2%
Race (White, African American, Asian, Native American)	82.5%, 11.5%, 1.3%, 0.4%
Weight (kg)	72.8±19.0
Height (cm)	164.3±21.9
Terminal serum creatinine level (mg/dL)	0.9±0.3
Terminal blood urea nitrogen level (mg/dL)	12.1±6.1
Living donors	24.8%

[1]Continuous variables presented as mean ± standard deviation
[2] The comorbidity score used in our study was calculated based on the following coexisting conditions, each of them contributing one point: cardiovascular disease (defined in USRDS as symptomatic cardiovascular disease or angina/coronary artery disease), symptomatic peripheral vascular disease, diabetes mellitus, and hypertension.
[3] Information obtained from USRDS RXHIST file; due to missing/unknown data and "60 days rule" convention adopted by USRDS (see text) the total is less than 100%
[4]Predominant renal replacement therapy modality defined as a modality used for >50% of the duration of end-stage renal disease
[5]Transplant day of the week expressed in numbers starting with Sunday (1=Sunday, 2=Monday, etc.)

4.4. The role of pretransplant renal replacement therapy modality

4.4.1. Introduction

The ESRD course itself (e.g., the modality of renal replacement therapy [RRT], alone or in combination) as a predictor of graft and patient outcomes has not been well studied. Several studies suggest that this pretransplant dialysis modality has an impact on patient outcome [114-117]. However, some reports have not shown that long-term graft survival is affected by the modality of dialysis treatment [118, 119]. What is established is that increased time on dialysis is associated with decreased survival of transplant recipients [119].

The goal of this project was to perform a retrospective analysis of United States Renal Data System (USRDS) data to evaluate the role of renal replacement modalities, including number of modalities used and their combinations in allograft and recipient survival.

4.4.2. Primary variables of interest

The primary variables of interest were those pertinent to RRT from the USRDS database: RRT modality immediately prior to current transplant; predominant RRT modality during the ESRD course (defined as modality used for >50% of the ESRD period; if none of the modalities were used for more than 50%, then predominant modality was labeled as “None”); number of different RRTs used; the combination of RRT modalities used (e.g., peritoneal dialysis [PD] and hemodialysis [HD] and transplant); and the time course during the pretransplant period that the patient was treated with a specific RRT modality. We defined the use of a specific dialysis modality using the “60 day rule,” (the convention adopted by USRDS), stating that a dialysis modality must continue for at least 60 days in order to be considered stable, and therefore constitute a change in modality.

4.4.3. Results

4.4.3.1. Baseline characteristics

The dataset comprised 92,844 records of patients receiving kidney or kidney-pancreas transplants starting January 1, 1990 and through December 31, 1999. The study population characteristics are presented in Table 2.

4.4.3.2. RRT modality immediately prior to transplant

A Cox model using HD as a reference demonstrated the following results. Having a transplant immediately prior to the transplant of interest without dialysis in between was associated with increased risk of graft failure (Hazard Ratio [HR] 1.65, $p<0.001$). PD as a modality immediately prior to transplant predicts a better graft outcome compared to HD (HR 0.97 $p<0.05$). See Table 3. A similar association was found in the subgroup of patients with a previous history of kidney transplant: having the transplant as an RRT modality prior to the last transplant without going on dialysis in between posed a greater risk of graft failure (HR 1.99, $p<0.001$) in this subgroup of patients. The protective effect of PD is not significant in this patient subgroup.

In the analysis of recipient survival in the Cox model using HD as a reference, both prior transplant (0.80 $p<0.005$) and PD (0.94 $p<0.001$) had protective effects on recipient survival compared to HD. This association was confirmed again in the subgroup of patients who had prior transplants, though the difference between PD and reference (HD) was not statistically significant (Table 3).

Table 3. Results of Cox proportional hazard model analyzing the role of renal replacement therapy in the allograft and recipient survival [1].

	Graft survival				Recipient survival			
	Hazard ratio	95% CI		p	Hazard ratio	95% CI		p
Renal replacement therapy modality immediately prior to current transplant[2]								
Peritoneal dialysis	0.97	0.94	1	<0.05	0.94	0.91	0.97	<0.001
Transplant	1.65	1.51	1.8	<0.001	0.8	0.68	0.93	<0.005
Unknown	0.92	0.85	1	<0.05	0.87	0.77	0.97	<0.05
Lost to follow-up	1.07	1	1.15	0.069	0.9	0.81	0.99	<0.05
Predominant renal replacement therapy modality[2]								
Peritoneal dialysis	0.97	0.94	1	<0.05	0.96	0.92	0.99	<0.05
Transplant	0.86	0.81	0.9	<0.001	0.82	0.76	0.89	<0.001
None	0.9	0.84	0.95	<0.001	0.92	0.85	1	0.063
Time spent on hemodialysis (years)	1.02	1.01	1.02	<0.001	1.05	1.04	1.05	<0.001
>0 to 1 year	1.05	1.01	1.09	<0.05	1.18	1.12	1.24	<0.001
>1 to 3 years	1.18	1.13	1.23	<0.001	1.42	1.34	1.5	<0.001
>3 years to 10 years	1.18	1.12	1.23	<0.001	1.59	1.5	1.7	<0.001
>10 years to 33 years	1.27	1.16	1.39	<0.001	1.77	1.57	2	<0.001
Time spent on PD (years)	1.02	1.01	1.03	<0.005	1.04	1.03	1.06	<0.001
>0 to 1 year	1.04	1.01	1.08	<0.05	1.12	1.07	1.17	<0.001
>1 to 3 years	1.08	1.04	1.12	<0.001	1.21	1.16	1.27	<0.001
>3 years to 10 years	1.13	1.06	1.2	<0.001	1.33	1.23	1.44	<0.001
>10 years to 33 years	1.28	0.99	1.64	0.057	1.43	1	2.04	0.053
Time spent with prior transplant (years)	0.98	0.97	0.99	<0.001	1	0.99	1.01	0.525
>0 to 1 year	0.84	0.78	0.9	<0.001	1.06	0.95	1.19	0.319
>1 to 3 years	0.82	0.75	0.9	<0.001	1.08	0.94	1.23	0.291
>3 years to 10 years	0.72	0.67	0.78	<0.001	1.08	0.95	1.22	0.24
>10 years to 33 years	0.67	0.6	0.75	<0.001	1.12	0.94	1.33	0.217
Number of different renal replacement therapy modalities[3]	1.04	1.02	1.07	<0.005	1.11	1.08	1.15	<0.001

Table 3 Continued

	Graft survival				Recipient survival			
	Hazard ratio	95% CI		p	Hazard ratio	95% CI		p
Combinations of renal replacement therapy modalities[2]								
PD only	0.93	0.9	0.96	<0.001	0.9	0.86	0.94	<0.001
PD+transplant	0.87	0.78	0.97	<0.05	0.98	0.83	1.17	0.86
PD+HD	1.09	1.05	1.12	<0.001	1.1	1.06	1.15	<0.001
HD+transplant	0.74	0.69	0.8	<0.001	0.96	0.86	1.08	0.508
Transplant only	0.94	0.85	1.05	0.269	0.89	0.75	1.06	0.196
PD+HD+transplant	0.73	0.67	0.8	<0.001	1.11	0.98	1.27	0.106
None	0.75	0.69	0.81	<0.001	0.81	0.73	0.89	<0.001

[1] The Cox model represents a multivariate analysis of graft and recipient survival. To avoid colinearity between the primary variables of interest they were analyzed in separate Cox models. Only primary variables of interest are presented in the table. All models were also adjusted for the following covariates: recipient age, gender, race, height, weight, history of hypertension, diabetes, recipient comorbidity score, history of prior transplant, total duration of ESRD, and total number of transplants, panel reactive antibody levels (mean and peak), recipient education level, primary source of renal care payment, and citizenship; donor variables: heartbeating donor or not, age, gender, race, height, weight, number of matched HLA antigens, and citizenship; and transplant procedure variables (day of the week for the procedure, the season and year of the transplant, and cold storage time).
[2]Hemodialysis is a reference
[3]Sixty days rule applied

4.4.3.3. Predominant RRT modality

Predominant RRT modality, defined as RRT modality (used for more than 50% of the whole ESRD period) was analyzed in a Cox model in relation to the graft survival. Both PD (HR 0.97 $p<0.05$) and transplant (HR 0.86 $p<0.001$) had a protective effect for the graft survival compared to HD.

The absence of the predominant modality (each of the modalities were used for less than 50% of the duration of ESRD, or no RRT was used) was also associated with a lower risk of graft failure (HR 0.90 $p<0.001$). These results were illustrated by Kaplan-Meier plots (Figure 5, Panel A). In the Cox model, better recipient survival was also associated with both PD (0.96 $p<0.05$) and transplant (0.82 $p<0.001$) as predominant pretransplant RRT modalities. Those patients who had no predominant modality during ESRD course also had better survival compared to HD, though the difference was not statistically significant (HR 0.921, $p=0.063$). The worst patient outcome associated with HD is illustrated by Kaplan-Meier plots (Figure 5, Panel B). Same trends for graft and recipient survival were found in the subgroup of patients with prior transplants.

4.4.3.4. Number of different modalities used

We calculated the number of different RRT modalities that the patient was exposed to during ESRD course using the “60-day rule,” where the change in dialysis technique is considered stable, if the patient remained on a new modality for 60 or more days (“60-day rule” does not apply to transplant). We analyzed the Cox model and demonstrated that the number of RRT modalities is a significant predictor of graft failure (HR 1.04 per additional modality $p<0.001$) and recipient death (HR 1.11 per additional modality $p<0.001$). In the separate model in the subgroup of patients with prior transplants, the number of modalities was not a significant risk for graft failure, while it was for recipient death (HR 1.09 $p<0.005$).

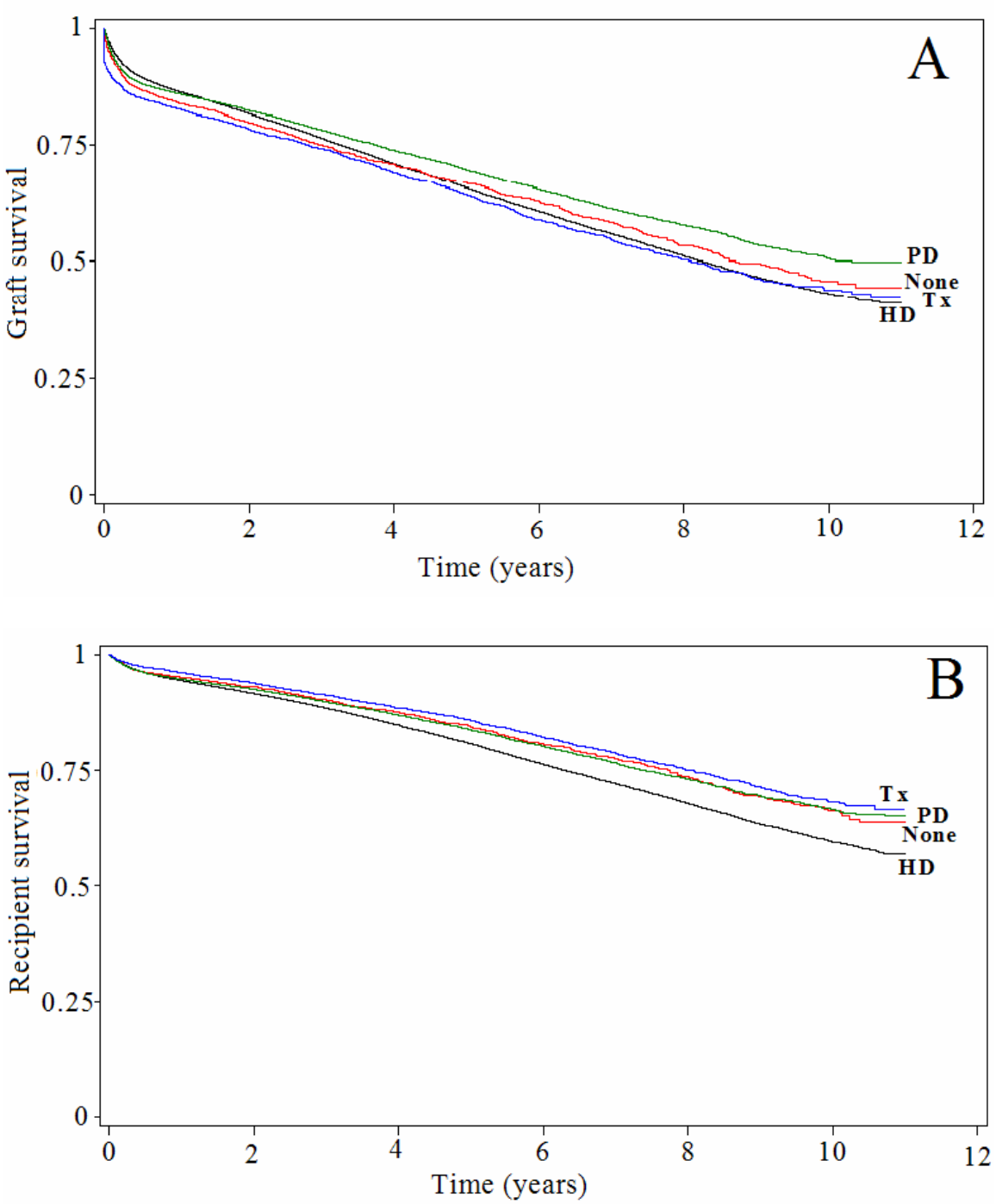


Figure 5. Predominant renal replacement therapy modality and graft (Panel A) and recipient (panel B) survival. The worst graft and recipient outcome is associated with HD.

These associations are illustrated by the Kaplan-Meier plots: the increased number of modalities is associated with the worsening of graft survival (Figure 6, Panel A), the best graft survival being associated with zero pretransplant RRT modalities. Similarly, zero modalities used before transplant were associated with the best recipient survival, but an increased number of modalities above 1 does not affect recipient survival (Figure 6, Panel B).

4.4.3.5. Combination of different RRT modalities

We considered 8 different combinations of RRT modalities during the ESRD course independent of the sequence and number of times patient would return to a particular modality: PD only, HD only, transplant only, PD + HD, PD + transplant, HD + transplant, all three modalities, and None. We defined combinations of RRT modalities using the “60 days rule” described above. In the Cox model (“HD only” was used as a reference group), any combination or single modality (except for transplant only, PD + HD, and None) were better than HD only (Table 2). In particular, “PD only” was associated with HR 0.93 ($p<0.001$). PD + HD and None were associated with nonsignificantly higher risk. When patient survival was evaluated, modality combinations showing the significant difference with the reference group (HD only) were: PD only (HR 0.90 $p<0.001$) and None (HR 0.81, $p<0.001$) and also PD and HD (1.10 $p<0.001$). When patients with prior transplants were analyzed separately compared to HD alone, PD alone was associated with the lower risk of graft failure (HR 0.60 $p<0.05$), PD + HD + transplant was also beneficial (HR 0.79 $p<0.005$), as well as HD + transplant (HR 0.791 $p<0.005$). When recipient survival was used as an outcome, PD + transplant (HR 0.73 $p<0.05$), HD + transplant (HR 0.74 $p<0.005$), and transplant only (HR 0.62 $p<0.0005$) were associated with the lower mortality risk.

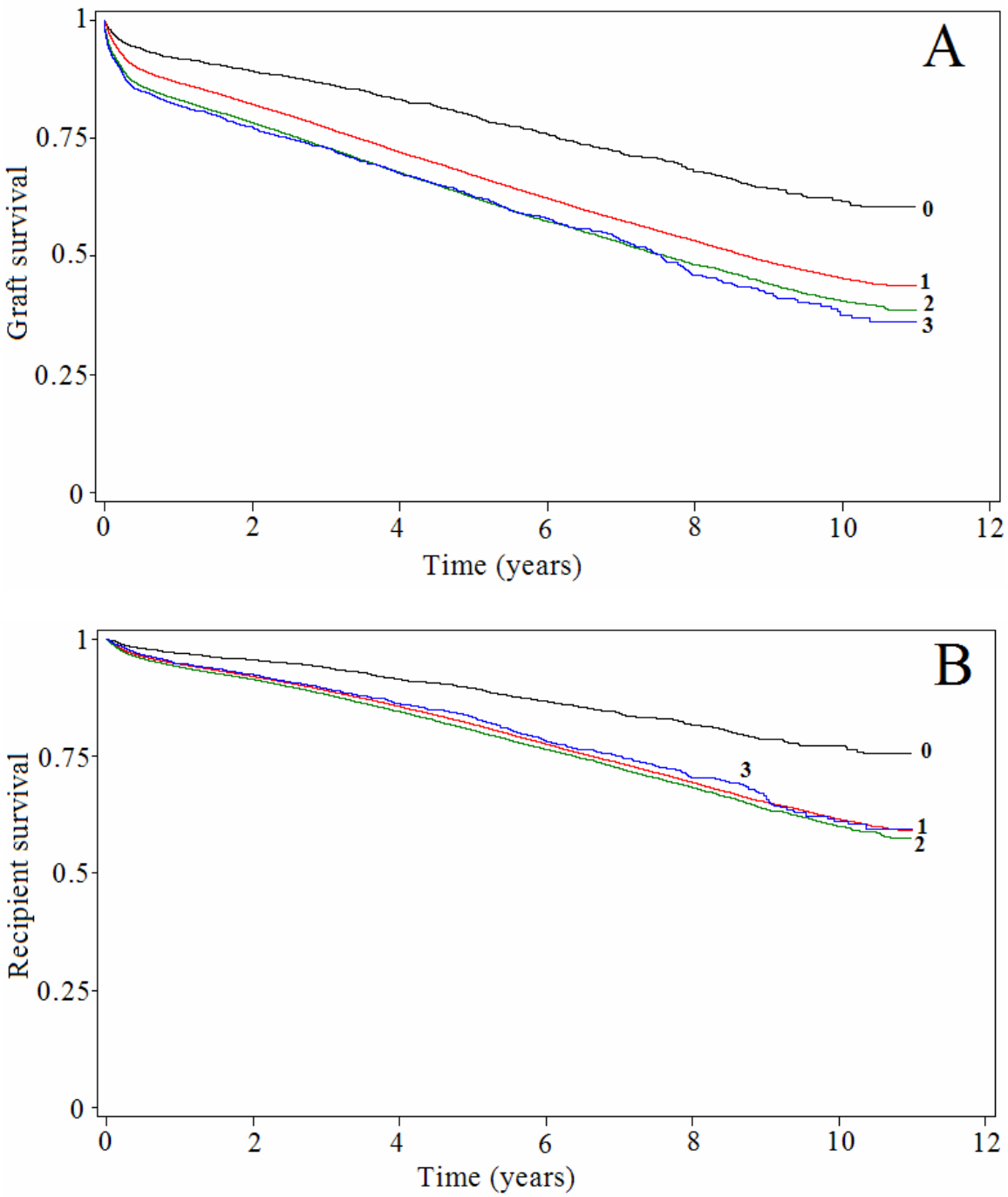


Figure 6. Number of different renal replacement therapy modalities and graft (Panel A) and recipient (panel B) survival. The increased number of modalities is associated with the worsening of graft survival, with the best graft and recipient survival associated with zero RRT modalities (preemptive kidney transplant).

4.4.3.6. Number of years on specific dialysis modality

The Cox model discussed in this section was not adjusted for total duration of ESRD to avoid colinearity with the primary variables of interest. The duration of both dialysis modalities was associated with a higher risk of graft failure. Each year of PD is associated with HR of 1.02 ($p<0.005$), while each year of HD is associated with HR of 1.02 ($p<0.001$). On the other hand, the number of years with functioning graft in the past had a protective effect on a current graft survival (HR 0.98 $p<0.001$). In the subgroup of patients with prior transplant, the same trend is true, but the association between the duration of PD and graft failure is not statistically significant. We performed the same analysis for the recipient survival and demonstrated similar associations. The longer the patient was on HD (HR 1.05 $p<0.0001$) or PD (HR 1.04 $p<0.005$), the higher the risk of dying, while number of years with prior transplant did not make a significant difference. Recipient survival in the subgroup of patients with prior transplant was also analyzed. The number of years on PD (HR 1.05 $p<0.005$) or HD (1.04 $p<0.001$) was associated with greater risk of recipient mortality, while the number of years with a functioning graft was not associated with any significant change.

4.4.4. Discussion

In general, prior studies comparing different renal replacement modalities in relation to the transplant outcome were based on the small datasets [115, 120], evaluated short-term rather than long-term outcome [115, 117, 121, 122], have not studied combination of the RRT modalities, or were done 10-20 years ago, before significant changes in the immunosuppressive regimens [120-124]. Most of the studies examined the graft outcome only, and not patient survival. In addition, most of the authors evaluated the role of RRT modality immediately prior to the transplant rather than predominant modality as a primary variable of interest. Patients who were on PD

for a number of years and were switched to HD immediately prior to transplant would be classified as a HD in these studies, which introduces a significant degree of misclassification bias.

Previous studies on short-term transplant outcome have yielded somewhat conflicting results. Higher rates of early graft failure were associated with PD as demonstrated by [125]. In the report by Bleyer et al. [117], the authors evaluated delayed graft function after deceased donor transplant based on dialysis modality immediately prior to transplantation and found an association between HD and delayed graft function. Similar results were demonstrated by other authors [115, 116, 125-127]. Vanholder et al. also demonstrated the advantage of PD for short-term outcome: patients on PD have reduced incidence of acute renal failure [115]. PD is recommended as an initial modality in patients who plan a kidney transplant within 2-3 years [128].

Though in one report there was no association between dialysis modality and graft thrombosis [129], in several other studies, increased incidence of graft thrombosis associated with PD compared to HD was reported [33, 125, 130-132]. Higher rates of graft thrombosis in PD patients might be because hypercoagulable states are not so readily detected in PD patients as in HD patients. Higher rates of acute rejection were associated with PD [115]; however, in other reports, the rate of acute rejection was not found to be different between patients on PD vs. those on HD before the transplant [117, 124, 127, 132]. Peritoneal dialysis was associated with a higher rate of posttransplant infection compared to patients on HD in some reports [133], but in other ones, the rate of infection between PD and HD was found to be similar [115, 134] or lower in patients with pretransplant PD [135].

When long-term outcome (1 and 5 years) was studied, no difference between dialysis modalities was reported [124]. Similarly, PD and HD showed similar 1-year outcome in a report by Donelly in the mid-80s [122]. In a small case-control analysis, 1-

year outcome of transplantation in patients on continuous ambulatory peritoneal dialysis is not significantly different from that in HD patients with similar clinical characteristics [120]. Similar long-term graft and patient survival is achieved independent of the modality of dialysis prior to transplantation in a retrospective analysis of the first cadaveric graft. Graft and patient survival cases were identical in HD and continuous ambulatory peritoneal dialysis groups (5-year graft survival: continuous ambulatory peritoneal dialysis 67%, HD 66%; 5-year patient survival: continuous ambulatory peritoneal dialysis 88%, HD 87%) [123]. No difference in long-term outcome between patients treated with PD compared to those on HD was demonstrated in other studies [121, 127, 136, 137]. Snyder et al. [125] compared long-term transplant outcome between PD and HD and demonstrated that compared to pretransplant HD, death censored long-term graft failure was 15% higher in patients on PD and short-term graft failure was 33% higher. Their analysis was based on 22,776 Medicare beneficiaries with kidney transplant. Compared to our analysis, the Snyder et al. study [125] used a smaller number of patients, shorter follow-up (3 years), and some baseline characteristics of the study population were different from ours (pediatric patients and those with prior history of transplant were excluded). These authors studied pretransplant dialysis modality (based on UNOS form) adjusted for the dialysis modality change as a binary variable, while we evaluated the role of both pretransplant and predominant dialysis modality as well as the number of modalities used and their combinations.

Our study, when compared to HD and/or PD immediately prior to transplant, demonstrated a protective effect on the graft and recipient survival. Even though the effect size associated with PD is modest, we disprove previous reports claiming a higher long-term risk associated with PD. We evaluated the role of the predominant RRT modality during the ESRD course. Peritoneal dialysis, transplant, and preemptive or

very short course dialysis had a protective effect for the graft and recipient survival. This approach again confirmed an advantage for allograft and recipient survival of PD over HD as a modality immediately prior to transplant and as a predominant modality during the ESRD course. Though statistically significant, the effect of the size of the dialysis modality is quite limited (HR 0.97 and 0.94 for graft and recipient survival, respectively, for PD as an RRT modality immediately before transplant; and HR 0.97 and 0.96 for graft and recipient survival, respectively, for PD as a predominant RRT modality compared to HD). For comparison, the effects of size of other predictors of the graft and recipient survival evaluated in our analysis were as followed: recipient age (HR 1.01 p <0.001; HR 1.04 p<0.001 per year of life for graft and recipient survival, respectively); recipient history of diabetes (HR 0.96 p=0.48; HR 1.11 p=0.107 for graft and recipient survival, respectively); recipient comorbidity score (HR 1.1 p <0.001; HR 1.26 p <0.001 per unit increase in score for graft and recipient survival, respectively); living donor as compared to deceased donor (HR 0.68 p <0.001; HR 0.67 p <0.001 for graft and recipient survival, respectively); donor age (HR 1.01 p<0.001; HR 1.01 p <0.001 per year of life for graft and recipient survival, respectively); and number of HLA matched antigens (HR 0.94 p<0.001; HR 0.96 p <0.001 per antigen matched for graft and recipient survival, respectively).

The number of RRT modalities used during ESRD course is a significant predictor of graft failure and recipient death. Almost any single RRT modality or their combinations were associated with better graft and recipient outcome than with HD only.

The mechanism of the outcome observed in our analysis is not completely clear. Residual renal function that might be better preserved in patients on PD may contribute to better preservation of kidney function after transplant [138]. One can hypothesize that the degree of residual renal function is more important for the graft and recipient outcome than either PD or HD modality. Unfortunately, we did not have information

about the residual renal function for the whole study population. Answering this question could be a subject of another research project. Furthermore, body mass index and degree of hypervolemia might be different in the PD and HD patients and therefore confound the results. The rate of posttransplant infections associated with HD might be higher as compared to PD [135]. In addition, there are some indications that HD membranes and vascular access might cause sensitization in transplant candidates [139]. It has been shown that HD patients demonstrate the elevation of natural killer cells [140] and production of cytokines [141]. Other immunological differences might exist between HD and PD patients. It was postulated that PD modifies the population of T-helper (Th) cells with an increase in the percentage of Th2 cells and by a normal percentage of Th1 cells [142]. Th2 cells produce inteleukin-4 and inteleukin-10, which inhibit interferon-gamma secretion and cell immunity [143], while increased Th2 cell fraction may provide additional immunosupression.

Potential selection bias should be considered when interpreting the results of this study. We speculated that the decision regarding dialysis modality is made based on patient's age, diabetic status, comorbidity, ability to learn the technique, prior history of abdominal surgeries, the distance to dialysis center, and the status of vascular access. Adjusting our multivariate models for recipient age, diabetic status, comorbidity index, socioeconomic status (indicated by educational level, primary source of pay for renal care, and citizenship), and duration of ESRD should considerably reduce the selection bias. We recognize that some factors not included in the models (e.g., exhausted vascular access) might force the selection of the dialysis modality and confound the results. Though our models were carefully adjusted for pertinent covariates, HD and PD populations are different in our study as well as in other reports. For example, it was demonstrated that PD patients are more likely to be transplanted than HD patients both in the group of adult patients [125], and to a lesser extent in the group of pediatric

patients [144]. One can speculate regarding the causes of this discrepancy, that certain demographic characteristics and potentially the more assertive personality of the PD patient versus the HD patient might make the former more aggressive in pursuing transplantation. Indeed, in our study population, PD was a pretransplant RRT modality in 21.8% and predominant RRT modality in 22.6% of patients, while in the dialysis population, PD patients comprised less than 15% [145]. To explain this phenomenon, Snyder et al. [125] proposed that there is a perception among physicians that PD patients may be better candidates for transplant [115, 128] and therefore, there exists a selection bias, where potential transplant candidates are more likely to be placed on PD rather than on HD. Other potential shortcomings should be considered in interpreting results of this retrospective data analysis. Retrospective analysis of data registry demonstrates the association (but not necessarily the causative relationships) between the primary variables of interest and the outcome. The sequence of PD and HD for those patients receiving both has not been evaluated in this study and might be a subject of future research.

In conclusion, our results suggest that compared to PD, hemodialysis as a RRT modality immediately prior to transplant or as a predominant RRT modality during ESRD course, used alone or in combination with other RRT modalities, is associated with increased risk of graft failure and recipient death. An increased number of RRT modalities used during ESRD course is associated with worsening of the graft and recipient survival. Peritoneal dialysis is a reasonable choice of renal replacement therapy and should not be avoided in the transplant candidates [66].

4.5. The role of previous history of kidney transplant

4.5.1. Introduction

In general, preemptive transplant (i.e., without exposing the patient to dialysis) seems to be advantageous for graft survival [32, 64, 146]. The length of time on dialysis prior to the first transplant is a predictor of the graft and recipient survival. However, a relatively short duration of dialysis does not change either graft or recipient outcome [64]. It is unclear if the general advantage associated with preemptive transplantation holds for patients with a prior kidney transplant. There is no clear evidence in the literature whether patients who failed a previous transplant should be retransplanted preemptively or be allowed to "cool down" on dialysis before the next transplant. Since the role of renal replacement therapy in the period between graft failure and a follow-on transplant is understudied in this important and growing set of patients, the aim of this project was to evaluate the effect of preemptive retransplantation on graft and recipient survival.

4.5.2. Methods

The following independent variables were collected: history of transplants prior to the study transplant, total number of transplants, renal replacement therapy immediately prior to the study transplant, and time between the last allograft failure and the study transplant surgery.

Our definition for preemptive retransplant included all patients with dialysis-free retransplant (n=788) or those who had <7 days between a graft failure and a retransplant (the data to calculate this variable were complete for the subset of patients with prior kidney transplants) (n=1,609). The latter group was broader and in fact included all 788 patients with dialysis-free retransplant; therefore, the number of patients with preemptive transplant was 1,609. Dialysis-free retransplant was assumed for any

case where the renal replacement therapy (RRT) immediately prior to transplant was reported itself as “transplant.” RRT modality prior to transplant was derived from the RXHIST USRDS file. We considered this source more reliable than the PRTXDIAL variable from the UNOS file (the latter had > 30% missing values, where the RXHIST file only had about 6% missing or unknown values). The time between the last graft failure and the most recent transplant was calculated as a difference between the most recent transplant surgery date and the failure date of the graft prior to the most recent one. This variable was complete for the subset of patients with prior kidney transplants.

Separate Cox models were used to correct for colinearity between the primary variables. In particular, these pairs of variables were considered to have high degree of possible colinearity and were evaluated in a separate Cox model: history of prior transplant as a binary variable and total number of transplants; time after last graft failure and preemptive transplant as a binary variable; time after last graft failure and duration of ESRD course; and duration of ESRD course and duration of previous graft function. Use of Mycophenolate Mofetil (MMF) in the maintenance antirejection regimen was used as an indicator of transplant era.

4.5.3. Results

4.5.3.1 The role of prior transplants

The role of previous transplants was analyzed for the entire dataset (n=92,844), and a total of 11,714 patients had been retransplanted. The Kaplan-Meier curves representing the role of prior transplant in the graft and recipient survival are presented in Figure 7 for any transplant history (Panels A and B) and for the total number of prior transplants (Panels C and D). The analysis represented by Kaplan-Meier graphs is not adjusted for confounding factors and suggests that patients with prior transplants do significantly better than those with the first transplant, and that patients with a total of 2

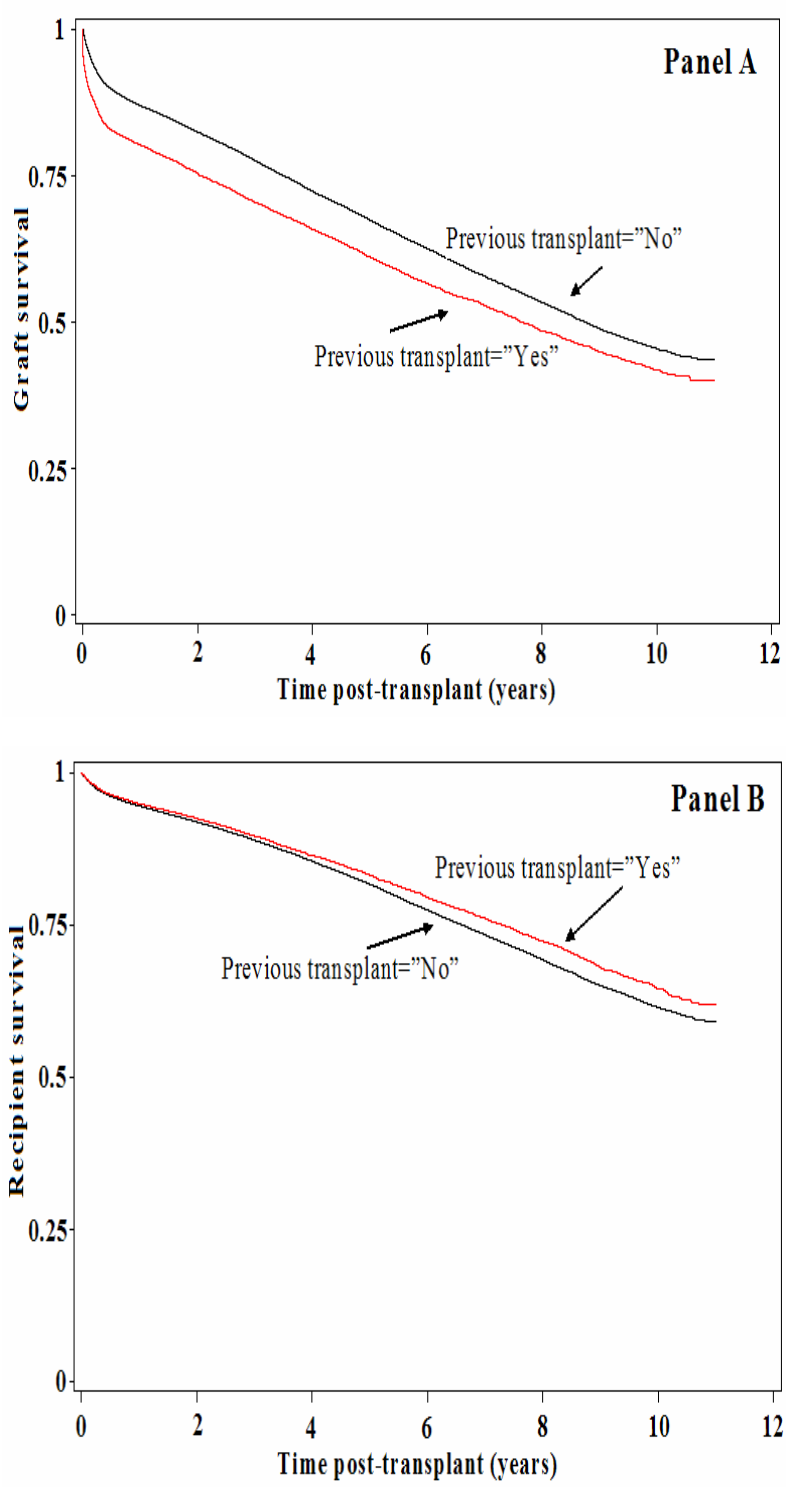


Figure 7. Kaplan-Meier analysis of the graft (Panel A, χ^2=218.4, p<0.001) and recipient (Panel B, χ^2=22.5, p<0.001) survival in patients with and without prior kidney transplant and association of the graft (Panel C, χ^2=525.1, p<0.001) and recipient (Panel D, χ^2=57.4, p<0.001) survival with total number of transplants. Log-Rank test was used to test strata homogeneity.

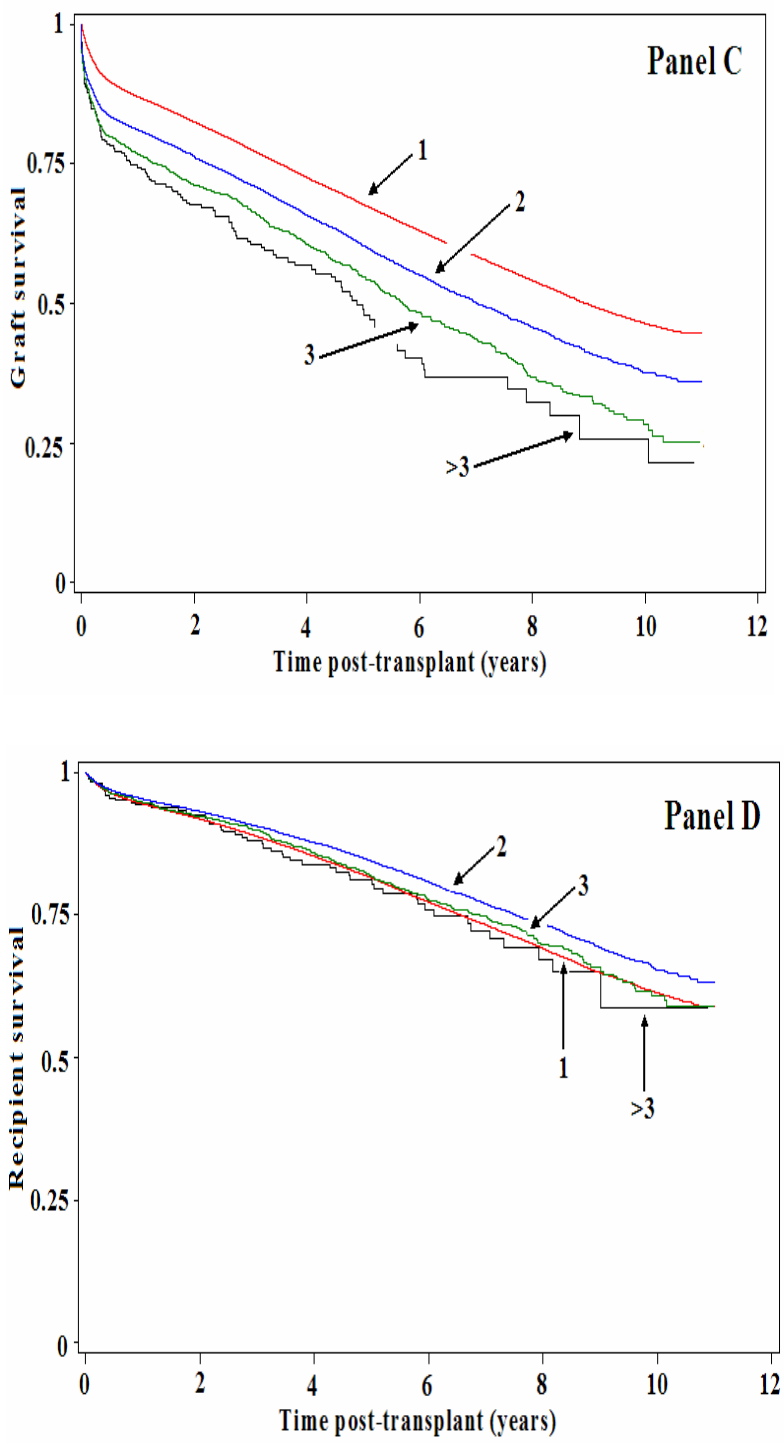


Figure 7 continued

transplants might survive longer than the recipients of a single transplant. However, when the analysis is adjusted for confounding factors in the Cox model (described below) the association between prior transplant and recipient survival loses its statistical significance.

In the Cox model, any history of prior transplant was associated with a significant increased risk of failure of the study graft (Hazard Ratio [HR] 1.24, $p<0.001$) but not the risk of recipient death; and the risk of graft failure (but not the recipient mortality) increases as the number of past transplants increases (increase in HR of 1.35 per transplant, $p<0.001$). The longer duration of prior graft survival but not the type of the graft (living vs. deceased) had a protective effect on the consecutive graft and recipient survival.

4.5.3.2. Preemptive retransplant

Altogether, 1,609 or 13.7% of all retransplanted patients had preemptive retransplants. Using the Cox model presented in Table 4, preemptive retransplant was associated with an increased risk of graft failure (HR 1.36, $p<0.001$) but not of recipient mortality (HR 1.02, $p=0.77$). The shape of the Kaplan-Meier curves suggests early graft failure as contributing to the poor graft survival in the recipients of preemptive retransplants. Therefore, we repeated the Cox analysis after eliminating the recipients in whom graft survived 0 days (primary nonfunctioning graft) (n=555) and demonstrated similar results. The risk of preemptive retransplant for graft failure had a HR of 1.29 ($p<0.001$, 95% CI 1.13 - 1.46), and the risk of recipient mortality had a HR of 1.12 ($p=0.084$, 95% CI 0.984 - 1.283). Furthermore, we analyzed the subgroup of patients with previous graft survival of ≥90 days after excluding recipients with previous graft survival of <90 days. In the remaining dataset (n=10,053), the risk of preemptive

Table 4. Results of a Cox proportional hazard model to evaluate the role of variables describing prior transplant characteristics. Variables analyzed in all recipients of retransplant (n=11,714) and in the subset of patients with a single prior transplant (n=10,070).

	All retransplant patients		**Recipient of single retransplant**	
Model number and predictor variable(s) [1]	Hazard Ratio (95% Confidence Limits)	p	Hazard Ratio (95% Confidence Limits)	p
Graft failure				
1. Preemptive retransplant = "yes"[2]	1.36 (1.21-1.54)	<0.001	1.59 (1.23-2.04)	<0.001
2. Time between last graft failure and current transplant (per month)	1.001 (1.00-1.002)	0.194	1.001 (1.00-1.003)	0.025
3. Donor type for prior transplant				
Living[3]	0.99 (0.93-1.07)	0.8488	0.99 (0.91-1.06)	0.684
Missing[3]	1.05 (0.94-1.17)	0.432	0.87 (0.71-1.08)	0.202
4. Duration of ESRD and fraction of time with transplant				
Total duration of ESRD (years)	0.99 (0.98-1.00)	0.012	0.99 (0.98-1.00)	0.019
Percent of ESRD time with prior transplants	0.999 (0.998-1.00)	0.1252	1.00 (0.999-1.001)	0.435
5. Duration of previous graft (years)	0.983 (0.98-0.99)	<0.001	0.98 (0.97-0.99)	<0.001
Recipient mortality				
1. Preemptive retransplant = "yes"[2]	1.02 (0.90-1.15)	0.77	0.83 (0.69-0.99)	0.037
2. Time between last graft failure and current transplant (per month)	1.003 (1.001-1.004)	<0.001	1.004 (1.002-1.006)	<0.001
3. Donor type for prior transplant				
Living[3]	0.90 (0.81-1.00)	0.055	0.92 (0.82-1.03)	0.143
Missing[3]	1.11 (0.95-1.29)	0.185	0.92 (0.69-1.23)	0.576
4. Duration of ESRD and fraction of time with transplant				
Total duration of ESRD (years)	1.02 (1.01-1.03)	<0.005	1.01 (1.00-1.03)	<0.01

Table 4 continued

	All retransplant patients		Recipient of single retransplant	
Model number and predictor variable(s) [1]	Hazard Ratio (95% Confidence Limits)	p	Hazard Ratio (95% Confidence Limits)	p
Percent of ESRD time with prior transplants	0.997 (0.996-0.998)	<0.001	0.997 (0.995-0.998)	<0.001
5. Duration of previous graft (years)	0.988 (0.98-1.00)	0.035	0.99 (0.98-1.00)	0.037

[1]Separate models were fitted for co-linearity-related factors. Each model shown in the table is adjusted for the following list of covariates: recipient age, gender, race, height, weight, history of hypertension (HTN), diabetes, comorbidity index, total duration of ESRD prior to the follow-up time included in the Cox models, education level, primary source of pay, citizenship, history of prior transplant, total duration of ESRD, and total number of transplants, type of donor (cadaveric or living), heartbeating donor or not, donor age, gender, race, height, weight, and citizenship, day of the week the transplant was done, year of the transplant, number of matched HLA antigens, and cold storage time.

[2]Preemptive retransplant define as “Yes” if renal replacement modality immediately prior to the study transplant was “transplant” or the time between last graft failure and the study transplant was <7 days.

[3] Deceased donor is the reference.

retransplant for the graft survival (HR 1.26, p<0.005, 95% CI 1.09-1.46) and recipient survival (HR 1.24, p=0.027, 95% CI 1.03 – 1.50) was substantially increased.

Analysis of the subgroup of patients with only one retransplant (history of single graft failure in the past, n= 10,070) yielded similar results for the graft survival (HR 1.59, p<0.001), while the recipient survival associated with preemptive retransplant was significantly better (HR 0.83, p<0.05).

4.5.3.3. The effect of waiting time for retransplant

To examine the effect of the waiting time for the retransplant, we examined the role of the time between last graft failure and the most recent transplant (median time was 21.9 months). Increasing this time interval had significant association with the adverse outcome of the most recent graft (only in patients with a single retransplant), and the risk of patient death (Table 4).

4.5.3.4. Stratification by the transplant era

Major changes in immunosuppressive medications were unveiled in the mid-1990s (e.g., tacrolimus was approved for liver transplantation in 1994 and was used "off-label" in kidney transplant soon after its release; Mycophenolate Mofetil and Neoral were introduced in 1995). Therefore, we report a stratified survival analysis by the use or nonuse of Mycophenolate Mofetil (MMF) as a surrogate for a transplant era. In 5.6% of the population, the information about use of MMF was missing, and the remaining dataset was used for analysis. In the remaining dataset of single and multiple kidney transplants (n=87,652), 28,360 (32.4%) patients were on MMF, while 59,292 (67.6%) were not. In the dataset of patients with retransplant(s) with information of MMF use nonmissing (n=11,565), 3,693 (31.9%) patients were on MMF, while 7,872 (68.1%) were not (Tables 2 and 4). Most of the associations observed in the entire dataset were also present in both the MMF(+) and MMF(-) strata.

4.5.3.5. Characteristics of the patients who received preemptive retransplants

We evaluated the subgroups of preemptive retransplant patients and nonpreemptive retransplant patients to assess their potential distinguishing characteristics. We evaluated the percent of the whole ESRD course prior to the study transplant spent on dialysis or with another transplant. Patients with preemptive retransplants had a greater percentage of their pretransplant ESRD course up to the time of the study transplant spent with transplant (50.6%±43.6% vs. 42.0%±32.6% in nonpreemptively retransplanted patients, $p<0.001$), but a lower percentage time spent on hemodialysis (34.6%±38.1% vs. 38.0%±31.9% $p<0.001$) and peritoneal dialysis (9.4%±21.8% vs. 11.5%±21.5% $p=0.083$). The duration of the ESRD was longer in patients without preemptive retransplant. Thirty percent of the preemptive retransplant patients had living donors, while only 17.6% of those without preemptive retransplant had living donors.

4.5.4. Discussion

The prediction of renal transplant recipient and graft survival is an important clinical issue, especially in view of the growing shortage of donor organs[147]. Traditionally, ESRD patients would take a course of hemodialysis (HD) or peritoneal dialysis (PD), or both, possibly followed by one or more transplants. Increasingly, patients are opting for transplantation as the very first ESRD treatment modality, a choice labeled “preemptive transplant.” Much of the enthusiasm for preemptive transplantation stems from reports that they are advantageous for graft and recipient survival [22, 32, 146, 148], while increased time on dialysis prior to a transplant is a predictor of negative short-term graft outcome [32, 64].

More specific to this study, factors that influence retransplant graft survival have been identified as well. Notable roles have been identified for the period of survival of

the previous graft, the use of cyclosporin A, the level of preformed antibodies, the ESRD cause (in particular diabetes and analgesic nephropathy), and the patient's gender [149]. Gjertson recently delineated the top five factors affecting 1-year regraft survival rates (transplant center, duration of first graft function, donor age, recipient's body mass index, and year of transplant) [150]. He also showed that long-term allograft outcome depended on donor age, transplant center, recipient age and race, and donor relationship.

In this project, we demonstrated a better graft outcome, but not recipient survival, with the first transplant compared to the patients with prior history of transplants; the latter had a 24% higher risk of graft failure. Each additional transplant in the past incrementally increased the risk of graft failure. Since retransplantation patients occupy an ever-increasing portion of the transplant waiting list, it is reasonable to ask whether preemptive retransplantation should be added to these lists of important predictors. While numerous studies, including one by our group [64], demonstrated the positive association between preemptive first kidney transplant and graft and recipient survival, the effect of preemptive retransplantation on the graft and recipient outcome has not been established.

Our data suggest that the risk of graft failure is actually higher in preemptive retransplant patients by 36%. We did not find any association between the recipient survival and preemptive retransplant, except for the subgroup of patients with a single retransplant, where the risk of death decreased by 17%. The result that preemptive retransplant decreases graft survival but increases recipient survival in the subgroup of patients with single retransplant is somewhat counterintuitive; better allograft outcome should translate into better patient survival. One can imagine that lead time bias, which favors healthier recipients at the outset, may play a role here. This effect would represent a true bias rather than true improvement in the survival.

Interestingly, the recipients of the nonpreemptive transplant in our study on average had significantly more kidney transplants in the past compared to recipients of the preemptive retransplant. Also, there is a greater proportion of the deceased donors in the recipients of nonpreemptive retransplant. Furthermore, the comorbidity score is higher and the total duration of ESRD is significantly greater in the recipients of the nonpreemptive retransplant, which should also adversely affect their outcome. The comparison between the groups does indicate that the recipients of the nonpreemptive retransplant are at a disadvantage in regards to the classic predictors of the clinical outcome. Despite that, however, the multivariate model, when adjusted for such variables, demonstrated a better outcome in nonpreemptively transplanted patients with respect to the graft survival. Although apparently counterintuitive, this discrepancy is fairly common when the results of simple group comparison are considered separately from multivariate modeling. The multivariate model takes the disparity that exists between the study groups into account and makes an adjustment for it, so these differences become irrelevant to the final outcome of the modeling. The results of the Cox model therefore should be interpreted as if the study populations were equal in regard to the baseline characteristics included in the model.

We also found that waiting time after the previous graft failure has an association with the worse graft survival in the recipient of single retransplant and with recipient survival in the whole patient population. However, the effect size of this association is relatively small, and since the recipient survival is calculated as a time period starting at the transplant event; latter association might be confounded by the lead time bias (i.e., patients with preemptive retransplant might have an advantage over those waiting for retransplant simply because their clock started earlier).

Also, to reconcile the better graft survival associated with shorter waiting time and worse survival associated with preemptive retransplant, one might imagine that a

relatively short period of dialysis between the transplants might be beneficial in comparison to preemptive retransplant, while longer time on dialysis might in fact be somewhat detrimental. However, the optimal time on dialysis before retransplant was not evaluated in this study.

Our findings that suggest that preemptive retransplantation is associated with worse graft outcome seem to contradict the prior reports of a beneficial effect of the first transplant on the graft survival [32, 64, 146]. The question is why preemptive transplant is good for the first kidney transplant, but negatively affects the outcome of the consecutive transplants. We hypothesized that this phenomenon could be explained by at least several mechanisms based on the difference between the first and subsequent transplants. Recipients of retransplant have been exposed to immunosuppressive medications for a period of time, and might have accumulated additional comorbidities, as well as experienced side effects of the medical treatments. The effect of dialysis on T-cell activity [140-143] and also the withdrawal of immunosuppressive medications with subsequent recovery of the immune system may be the mechanisms of the positive effect of the dialysis on subsequent graft outcome. Hypothetically, the discontinuation of the immunosuppressive medications and recovery of the immune system in between transplantations might be an important factor in reducing the risk of viral infections and malignancies.

Furthermore, to explain the negative role of preemptive retransplantation, we hypothesized that better clearance of toxic products and drug metabolites might be achieved with dialysis as compared to the failing kidney allograft, so that patients with failed graft receiving the preemptive retransplant might be more “uremic” at the time of transplantation than those who were dialyzed prior to retransplantation. It is also possible that patients with failing graft might try to hold on to the poorly functional kidney and delay the initiation of dialysis. By the same token, patients with failing graft might be

in general more “uremic” than those with native kidney failure, which would explain the opposite effect of the preemptive transplantation on the graft survival in recipients of the first vs. subsequent transplantations.

It is worth mentioning that since using the year of the transplant as an indicator of transplant era may introduce bias in the statistical analysis, we selected the use of MMF, that came on the market in the mid-90s, as a surrogate of the transplant era. Evaluating particular immunosuppressive medications was not the focus of our investigation. Since MMF is only an indicator of the transplant era, we do not necessarily think that it has direct effect on the outcome. However, the question remains, why is it that in patients transplanted in the late era (on MMF) the negative effect of the preemptive retransplant is not statistically significant? Since the hazard ratio between the groups is very similar, the nonsignificant effect in patients on MMF may simply be a reflection of the smaller sample size (among patients with retransplant, 3,693 were on MMF and 7,872 patients were not on MMF).

Finally, since this study was based on the analysis of the large dataset, there are some issues in interpreting the results that need to be pointed out. The power of the large amount of data leads to the small and clinically nonsignificant associations still demonstrating statistical significance in the analysis. Therefore, the associations with the borderline p value (<0.05), while technically significant, should be interpreted with caution.

Also, in this analysis, only patients who survived from the graft failure to the next transplant were included in the nonpreemptively transplanted group, which potentially introduces a survivor bias. In other words, the study excludes those patients who were transplanted once, failed the graft and died while being on the waiting list, before getting the next graft. That potentially may allow for selection of the healthiest recipients in the group with nonpreemptive retransplants. Multivariate models adjusted for the specific

covariates such as comorbidity index may reduce this bias, but it is certainly problematic to exclude patients who died on the waiting list from the analysis altogether. We considered including patients with failed graft who were on the waiting list for retransplant into the analysis and classifying them as nonpreemptive retransplant. However, that would introduce additional problems: some of the patients on the waiting list might have never been transplanted for the reason other than death; also, the analysis of the graft outcome for this subpopulation would have been impossible because the retransplants have never happened. Therefore, the analysis was done based only on the patients who received the retransplant, while those who could potentially receive it, but did not survive, were excluded. Therefore, the results of the study should be interpreted with caution due to the potential survivor bias, where only patients who survived from the last graft failure to the next transplant were included in the study. In other words, regarding the recipient survival, the results of the study should be interpreted as applicable only to those patients who survived to retransplant. One should also keep in mind the potential residual survivor bias (even after adjusting for comorbidity index) while interpreting the results of the graft survival.

With the potential caveats associated with retrospective data analysis, these results suggest that preemptive retransplantation is associated with increased risk of graft failure, while longer time on dialysis in between transplants is associated with negative effect upon graft and recipient survival in most patient subgroups. The optimal time in between graft failure and retransplant was not evaluated in this study. This knowledge is important for future construction of the predictive model of long-term graft outcome [65].

4.6. The role of duration of pretransplant dialysis

4.6.1. Introduction

While preemptive transplant would appear to have an advantage over traditional therapy, it is unclear if this represents a negative effect intrinsically associated with dialysis or the fact that patients who had a transplant after dialysis generally have a longer history of ESRD or have accumulated more comorbid conditions. Aside from prolonging the ESRD course, suggested mechanisms that may account for the worsening outcome by exposure to dialysis include increased rate of acute rejection, delayed graft function, vascular access complications, and various immunological mechanisms[148, 151].

This study addresses several factors that confounded earlier comparisons of dialysis duration to preemptive transplant. Lead-time bias, which occurs because candidates for preemptive transplants have better residual kidney function than patients already on dialysis, is a variable rarely accounted for in previous work. Categorical dialysis modeling strategies, where dialysis is modeled as a categorical variable (e.g., the patient was on dialysis or not, or the patient had dialysis for 0-175 days, 176-365 days, etc.) can obscure subtle or moderate factors influencing outcomes that cannot be resolved when patients are lumped together in a few, large groups. Lastly, socioeconomic variables are often ignored in previous studies, even though it has been shown that educational level and ethnicity are predictors of receiving a preemptive transplant in the first place[146]. An important question remains: are there subgroups of patients who might have better outcomes if they received short-course dialysis before transplant (e.g., patients with renal failure awaiting transplant, for whom the graft is not yet available or those with overt uremic complications where dialysis prior to transplant might improve their pretransplant health status)?

4.6.2. Results

4.6.2.1. Baseline characteristics

In this study, recipients were 44.1±14.3 years old, 60.5% male, 69% White/24% African American, 29% diabetic, 49% hypertensive, and had ESRD an average 2.2±2.2 years prior to transplantation. Kidney donors were 34.6±15.6 years old, 56% were males, 82% White/11.9% African American, and 25.7% living donors.

4.6.2.2. Duration of ESRD and graft survival

The Kaplan-Meier plot shows that graft outcome worsens as the duration of ESRD increases, supporting the results of earlier studies. The Cox models also demonstrated a modest overall increase in graft failure as ESRD duration is prolonged: a 2% increase in risk per year overall (hazard ratio[HR], 1.02 per year, $p<0.001$). Analysis stratified by the donor type demonstrated the same results for cadaveric and living donors.

An important pattern in the relationship between short-tem ESRD and transplant outcome emerges when pretransplant ESRD duration is analyzed with a fine time granularity (i.e., 0-14 days, 15-60 days, 61-180 days, 181-365 days, 1-2 years, 2-3 years, 3-5 years, and >5 years). A longer course of ESRD was indeed associated with a higher risk of graft failure, although the difference became statistically significant only after 180 days. The hazard ratio of graft failure increases from this point in a nearly linear fashion, until ESRD duration reaches 3-years, when there is no further increase (Figure 8). Analysis stratified by the donor type yielded similar results for both cadaveric and living donors. To evaluate a potential difference in the association of ESRD duration with graft outcome between different dialysis modalities, we stratified the Cox model by the predominant dialysis modality. We found that the association between ESRD

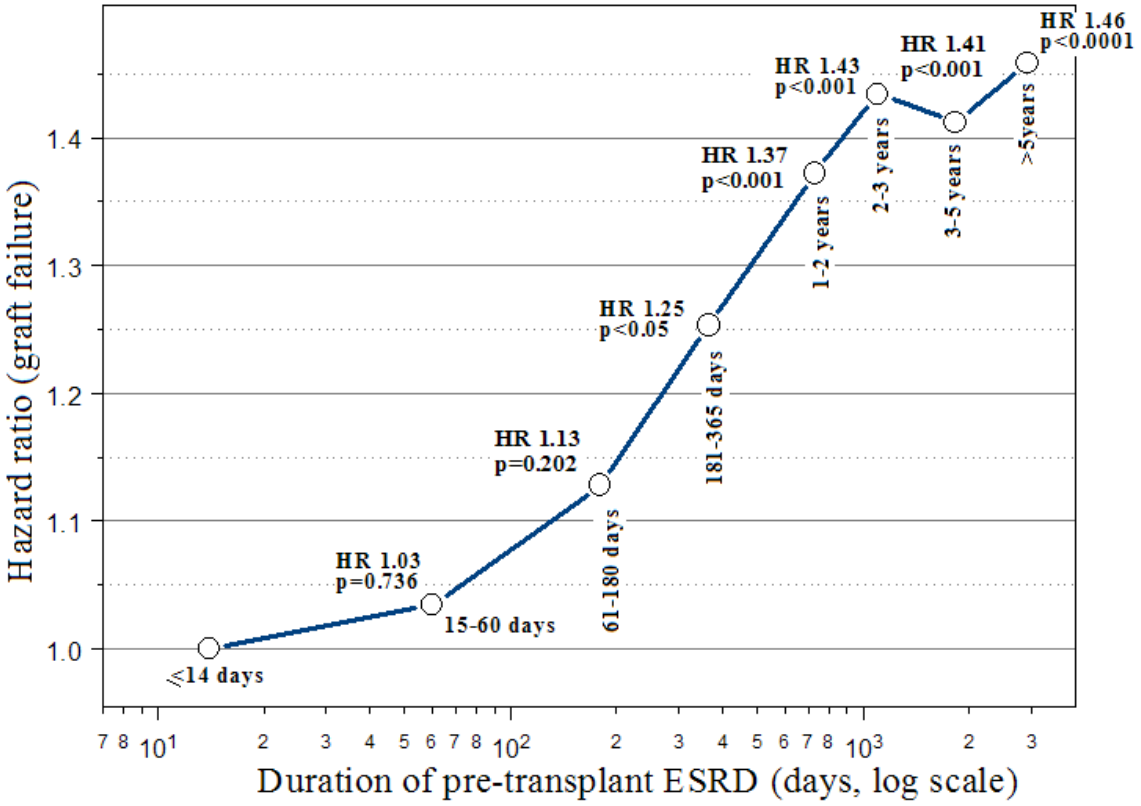


Figure 8. Hazard ratio of the graft failure in different categories of the pretransplant ESRD duration. Compared to the reference (ESRD duration ≤14 days), the hazard ratio of graft failure became significant only after 180 days of pretransplant ESRD. The hazard increased from this point in a linear fashion, until the ESRD duration reached 3 years, when there was no further increase in the risk of graft failure.

duration and graft survival were similar between HD (HR 1.02 per year, p<0.001) and PD (HR 1.03 per year, p<0.001).

4.6.2.3. Duration of ESRD and recipient survival
(calculated from the time of transplant)

The Kaplan-Meier plot shows that a longer duration of ESRD was also associated with poorer recipient survival. In the Cox models, overall recipient survival decreased with increased duration of ESRD for all patients (HR 1.04 per year, p<0.001) as well as recipients of cadaveric (HR 1.04 p<0.001) and living kidneys (HR 1.06 p<0.001) analyzed separately. When ESRD duration was categorized into finer time

blocks, the higher risk of recipient mortality only became significant when ESRD duration reached 1-year (HR 1.35, $p<0.05$). From that point, the hazard increased linearly (Figure 9). Separate analysis of the cadaveric kidney recipients yielded similar results; in the recipients of living kidney, the effect of ESRD duration on survival became significant at 181-365 days (HR 1.98 $p<0.05$). When Cox analysis was stratified by the predominant ESRD modality, the overall results were similar between HD (HR 1.04, $p<0.001$) and PD (HR 1.07 $p<0.001$).

4.6.2.4 Duration of ESRD and recipient survival (calculated from the time of onset of ESRD)

To avoid lead time bias, analysis was also performed with recipient survival calculated from the time of ESRD onset rather than from the time of transplant surgery.

Kaplan-Meier curves are flat for the time that the patient remained on dialysis pretransplant, since only patients who survived until transplant are evaluated. The curves represent different durations of the follow-up, where the longest duration was in the group which was on pretransplant dialysis for the longest time. On visual examination, the slopes of the Kaplan-Meier curves seem to be similar in those patients who received a kidney transplant after ≤14 days, 15-60 days, or 61-181 days of dialysis. Patients who received the kidney 181-365 days after being on dialysis had a faster rate of decline, and those who were on dialysis for more than a year had the fastest rate of graft loss (including those who received a kidney after being on dialysis for >5 years). In the Cox models, when the duration of ESRD was analyzed as a continuous variable, longer ESRD duration was associated with a better recipient survival (HR 0.85 per year, $p<0.001$). There was no significant advantage in recipient survival with increased duration of ESRD when the latter is analyzed as a categorical variable until the ESRD duration reached 3 years and greater. This better outcome was likely to be at least partly attributed to survival bias.

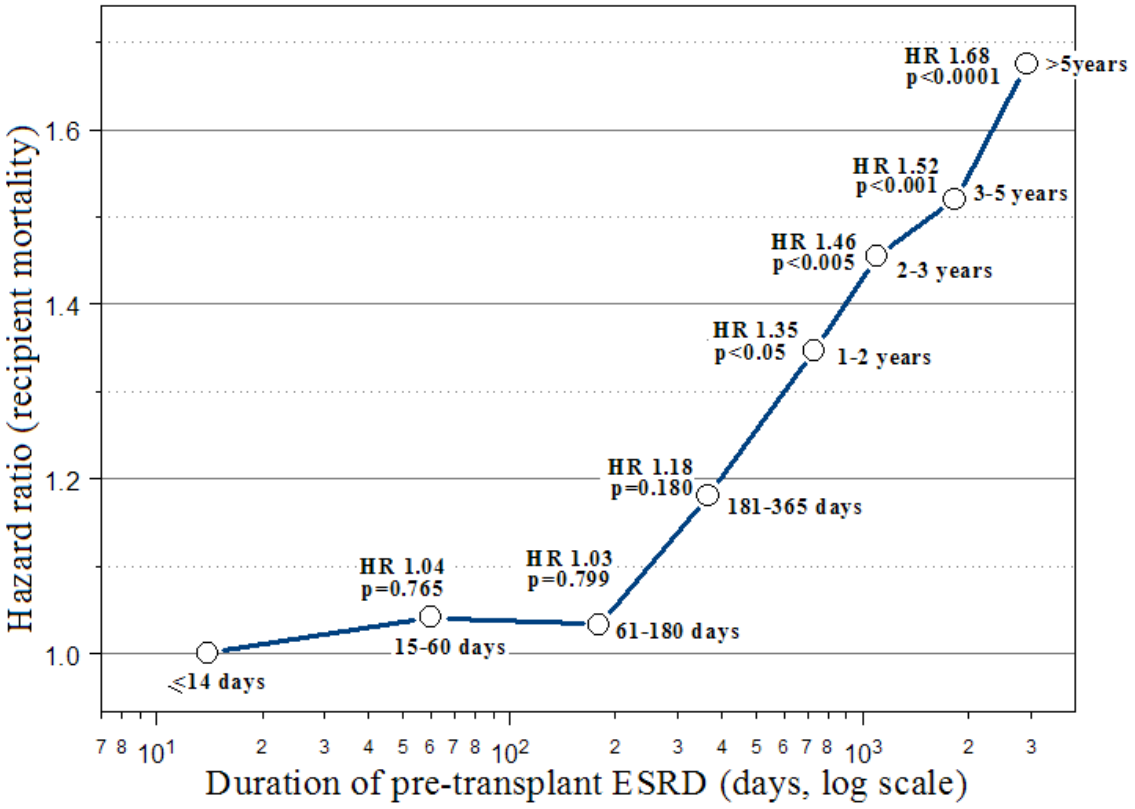


Figure 9. Hazard ratio of the recipient mortality in different categories of the pretransplant ESRD duration. Compared to the reference (ESRD duration ≤14 days), the hazard ratio of the recipient death became significant only after 1 year of pretransplant ESRD and from that point increased in a linear fashion.

4.6.3. Discussion

The literature on the association between preemptive transplantation and ESRD duration versus survival is rich and at times inconsistent. Recent reports have suggested that increased duration of pretransplant ESRD is associated with poor graft and recipient outcome [117, 137]. While preemptive transplant without the patient going on dialysis at all has been shown to be advantageous to the graft survival in several studies[32, 146, 148], some of these studies examined the time on dialysis only as a binary variable[146, 148].

Meier-Krische [32] reported that longer waiting time on dialysis was found to be a significant risk factor for death-censored graft survival and patient death for those subjects with a functioning graft after renal transplantation. However, the smallest category of dialysis duration authors analyzed was 0-6 mos. This particular duration of dialysis worsened graft survival, but has not worsened patient survival.

Previous studies have usually calculated recipient survival from the time of transplant to the time of patient death. This type of analysis may introduce a lead time bias, in which patients with shorter ESRD duration have a starting time advantage; in effect they are healthier by definition. Additionally, residual kidney function may confound the result of these studies, as those with shorter duration of ESRD are likely to have better preserved kidney function[152].

To address the lead time bias, we also calculated recipient outcome based on the time of onset of ESRD, instead of the time of transplant. When the recipient survival was calculated from the time of ESRD onset, the survival had a sharper rate of decline only when the pretransplant ESRD duration was over 180 days. In addition, in our Cox models, the duration of ESRD was analyzed as a continuous variable, and longer duration was associated with a better recipient survival. We recognize that this outcome may potentially be explained by survivor bias, where only those patients with long duration of dialysis, who survived to transplant, were included in the study. In the present study, the duration of dialysis was analyzed as both a continuous and a categorical variable, rather than simply as a binary variable describing preemptive versus nonpreemptive transplant. The 60-day rule (a convention adopted by USRDS, that a dialysis modality must continue for at least 60 days in order to be considered stable, and therefore dialysis duration for less than 60 days may not be reflected by the binary variable describing pretransplant dialysis) was not applied. Instead, the actual number of days for which the patient was dialyzed prior to transplant was analyzed.

There are many potentially confounding variables in renal transplant outcome studies, such as socioeconomic status, age, race, citizenship, and primary payer. Kasiske et al. demonstrated that some of these factors (race, ethnicity, education) are associated with receiving a preemptive transplant [146]. In the study by Meier-Krische et al. [32], the authors have not adjusted for socioeconomic status and education level. In the study by Mange [148], authors have not adjusted for socioeconomic status or education. Instead, their model was adjusted for race and median household income for the ZIP code of recipient. We adjusted our Cox models for recipient education level, primary source of payment, and citizenship as a surrogate for differences in the socioeconomic status.

Finally, it is unclear from the existing literature if both HD and PD used prior to transplant affect the outcome of the transplant to the same extent. We stratified the Cox models by predominant dialysis modality and demonstrated that the association between duration of dialysis and the graft and recipient survival for patients on HD and PD are essentially the same. This study did not address other factors associated with dialysis prior to transplantation either in a negative (e.g., loss of job) or positive (e.g., potentially better compliance after exposure to dialysis) way.

We confirmed that a longer duration of ESRD is associated with a worsening graft outcome; however, the association only becomes significant after 6 months of dialysis therapy, and after 3 years, no significant change in risk was evident. Similarly, a longer duration of ESRD was also associated with a worsening recipient survival as well when calculated from the time of transplant. However, it only becomes significant after 1 year of ESRD duration.

This retrospective study did not address the mechanism of association described above. However, we speculate that clinically significant accumulation of ESRD related comorbidities and loss of residual kidney function occurs only after 6 months of exposure

to dialysis. The negative effect of dialysis therapy and/or ESRD on the graft survival (but not recipient survival) plateaus at 1 year after initiation of dialysis. This can potentially be explained by the fact that predictors of the graft survival (e.g., oxidative stress, loss of residual renal function, aberrant T-, B-cell, and cytokine production[153]) might be peaking at 1 year. Additional factors affecting recipient survival (e.g., cardiovascular calcification) continue to accumulate after 1 year of dialysis therapy.

Since dialysis for up to 6 months does not appear to adversely affect graft survival, these results suggest that patients who have uremic symptoms should not defer dialysis while waiting for kidney transplant [64].

4.7. The role of recipient socioeconomic status

4.7.1. Introduction

The role of socioeconomic status of the donor and recipient in the graft and recipient survival remains controversial and poorly understood. We and other authors previously demonstrated that donor and recipient race plays an important role in allograft survival [23, 154], and that long-term transplant outcomes in African American patients remain significantly lower than all other ethnic groups, independent of genetic matching [155]. However, it is not clear what impact genetic and environmental factors have on these racial disparities in allograft survival. Furthermore, it has been demonstrated that racial differences affect the access to specific transplant procedures: in particular, kidney-pancreas transplant [156] are associated with different levels of compliance [157]. In addition, there are apparent disparities in chronic kidney disease care provided to ethnic minorities. Disparities exist in wait-list time and kidney transplant rates for Native Americans and African American patients, independent of insurance status [155]. African American patients were less likely than White patients to want a transplant and less likely to be referred for evaluation at a transplantation center and placed on a

waiting list. These differences, however, explain only a small fraction of the substantial racial differences in access to transplantation [158]. While certain genetic factors associated with race might potentially play a role, literature reports suggest the presence of poorly understood social aspects contributing to the survival differences. We hypothesized that certain socioeconomic factors, such as education level, citizenship/immigration status, and source of payment for medical service, play an important role in graft and recipient outcome. The goal of this project was to evaluate the role of the above factors in kidney allograft and recipient outcome.

4.7.2. Results

4.7.2.1. Baseline characteristics

The recipients (n=92,844) were 60% male, 70% Euro American, 23% African American, 3% Asian; and 27% diabetic, with an average age of 43 years at the time of the study transplant. Roughly one-in-eight (12.6%) had at least one prior transplant. These recipients were 59% male, 78% White, and 16% diabetic, with an average age of 38.5 years at the time of the study transplant.

4.7.2.2. Survival analysis

While the models described here were not adjusted for the year of the transplantation due to a relatively short study period, we realize that the time of the transplant might still confound the results. Therefore, additional analysis was performed after adjusting the model for the year of the transplant. Also, since using the year of the transplant as an indicator of transplant era may introduce bias in the statistical analysis, we selected the use of mycophenolate mofetil, that came on the market in the mid-90s, as a surrogate for the transplant era. Using both approaches revealed results very similar to our original analysis and are not presented here.

4.7.2.3. Role of education level

Kaplan-Meier plots suggested incremental improvement in the outcome with increased education level. The proportional hazard model demonstrated improved outcome associated with more advanced education. Compared with patients who receive grade to high school (0-12) education, those with some college to bachelor degree had significantly better graft (HR 0.93, $p<0.005$) and recipient (HR 0.90, $p<0.005$) survival. Furthermore, recipients with postcollege graduate degrees had even better outcomes with HR 0.85 ($p<0.005$) for the graft and HR 0.88 ($p=0.09$) for recipient failure (Table 5). When different racial groups were analyzed separately, African Americans and White patients (but not Asians) had a similar trend for graft survival. Similar trends for recipient survival was observed only in White patients.

4.7.2.4. Primary source of pay

Based on Kaplan-Meier plots, recipients with private insurance had better outcomes than those with Medicare, Medicaid, or other sources of payment. As far as recipient survival, patients on Medicare seem to have worse outcome than other groups, which could be confounded by older age. In the entire patient population, using Medicare as a reference group, the proportional hazard model demonstrated statistically significant benefits to graft survival from having private insurance (HR 0.87, $p<0.001$). This effect was not observed in Asian recipients, but remained in African Americans (HR 0.8, $p<0.001$) and Whites (HR 0.89, $p<0.001$). Private insurance in comparison with Medicare also had an advantage for recipient survival in the entire group of patients (HR 0.8, $p<0.001$) as well as in Asians (HR 0.66, $p<0.05$), African Americans (HR 0.71, $p<0.001$), and Whites (HR 0.83, $p<0.001$), when analyzed separately. Health maintenance Organizations (HMO) and Preferred Provider Organizations (PPO) were associated with a significantly higher risk of graft failure (HR 1.2, $p<0.05$) but

Table 5. Proportional hazard model evaluating the role of socioeconomic status in graft and recipient survival[1]

	Graft Survival		Recipient Survival	
Variables	HR (95%CI)	p	HR (95%CI)	p
Recipient education level				
Missing or Unknown	1.07 (1.03-1.12)	<0.001	1.101 (1.04-1.17)	<0.001
N/A: <5 yrs old	1.26 (0.98-1.62)	0.076	2.36 (1.5-3.72)	<0.001
None	1.05 (0.83-1.31)	0.7	1.17 (0.87-1.59)	0.298
Grade to High School: grades 0-12	reference			
Some College to Bachelor Degree	0.93 (0.89-0.97)	<0.005	0.9 (0.84-0.96)	<0.005
Postcollege Graduate Degree	0.85 (0.76-0.95)	<0.005	0.88 (0.76-1.02)	0.09
Primary Source of Payment				
Medicare	reference			
Missing or Unknown	1.00 (0.96-1.05)	0.865	1.12 (1.05-1.19)	<0.001
Medicaid	1.00 (0.91-1.09)	0.916	0.92 (0.80-1.05)	0.214
US/State Government Agency	1.00 (0.87-1.15)	0.957	0.84 (0.69-1.04)	0.108
Private Insurance	0.87 (0.83-0.90)	<0.001	0.80 (0.76-0.85)	<0.001
HMO/PPO	1.20 (1.02-1.42)	<0.05	0.52 (0.36-0.74)	<0.001
Other: Self, Donation, Free Care, VA, Pending, Foreign Government	1.08 (0.85-1.38)	0.515	0.91 (0.63-1.32)	0.608
Recipient Citizenship				
U.S. Citizen	reference			
Missing or Unknown	1.03 (0.97-1.10)	0.357	0.99 (0.91-1.08)	0.849
Resident alien	0.81 (0.74-0.88)	<0.001	0.70 (0.62-0.80)	<0.001
Nonresident alien	0.78 (0.54-1.13)	0.190	0.64 (0.35-1.15)	0.134

[1] Only primary variables of interest are presented in the table. The model was adjusted for the following covariates: recipient age, gender, race, BMI, history of DM, history of HTN, total duration of ESRD, cause of ESRD, mean and peak PRA levels, number of pretransplant transfusions, total number of transplants, number of different RRT modalities used, donor type, donor age, gender, race, BMI, heartbeating or not, donor history of DM, cold ischemia time, number of matched antigens.

4.7.2.5. Role of citizenship.

improved patient survival (HR 0.52, p<0.001). Having Medicaid, U.S./State Government agency, or other sources of payment for medical services did not show any significant association with outcome as compared with Medicare either in the whole patient population or in the subgroups divided by race.

Kaplan-Meier plots suggested that resident and nonresident alien recipients had the best graft outcome and patient survival as compared to U.S. citizens. Using the Cox model in the entire patient group with U.S. Citizens as the reference group, resident aliens had significantly better graft outcomes (HR 0.81, p<0.001). When analysis was stratified by race, only in White patients did this association reach statistical significance (HR 0.823, p<0.001). Similar results were observed for recipient survival, so where compared to U.S. citizens, legal aliens had a survival advantage (HR 0.7, p<0.001). This effect was observed in Asian patients (HR 0.66, p<0.05) and Whites (HR 0.7, p<0.001), but not in African Americans. In addition, similar to resident aliens, nonresident aliens have better outcome than the U.S. citizens, but this finding did not reach statistical significance, likely due to the very small sample size of this group.

4.7.2.5. Subgroup analysis: Adult patients with the first transplant

We reanalyzed the subset of patients older than 18 when the first transplant occurred (n=78,181). In this subset of the data, we found associations similar to those in the entire dataset. Compared to patients with high school attendance, those with college education had a trend towards better graft (HR 0.96, p=0.0965, 95% CI 0.91-1.01) and recipient (HR 0.90, p<0.01, 95% CI 0.84-0.97) outcome. Those with more advanced education had even better outcomes for the graft (HR 0.88, p<0.05, 95% CI 0.78-1.00) and recipient (HR 0.90, p=0.173, 95% CI 0.77-1.05) survival. Compared to patients with Medicare (n=28,882), recipients who had private insurance (n=15,339) had a lower risk for the long-term graft failure (HR 0.86, p<0.001, 95% CI 0.82-0.90) and recipient death

(HR 0.80 p<0.001, 95% CI 0.76-0.85). Having HMO/PPO (n=618) was associated with worse graft survival (HR 1.27, p<0.01, 95% CI 1.07-1.51) but better recipient survival (HR 0.54, p<0.005, 95% CI 0.37-0.78). Also, resident aliens (n=1,739) had an advantage over the U.S. citizens for graft (HR 0.81 p<0.005, 95% CI 0.74-0.90) and recipient (HR 0.70, p<0.001, 95% CI 0.62-0.81) survival.

4.7.3. Discussion

Socioeconomic factors have been shown to affect health care outcomes. Poverty, unemployment, and low education levels have been listed among the factors adversely affecting health [159]. Socioeconomic status has been suggested to play a significant role in kidney transplant outcome. Among others, the following socioeconomic factors have been listed as risk factors for posttransplant noncompliance: occupational status, educational level, language or cultural barriers, and ethnic background [160]. Race and income have substantial effects on mortality and use of services among Medicare beneficiaries [161]. Poor individuals are less likely than wealthy individuals to be medically suitable, to be interested in transplant, and to complete the pretransplant workup [162].

In a study similar in design to our project and based on UNOS data, in patients with liver transplant, it has been shown that neighborhood income had no effect on graft or patient survival; education had only marginal influence on the outcome (survival was lower in those with a high school education than in those with graduate education); and patients with Medicaid and Medicare had lower survival when compared to those with private insurance [163]. The results of our study done in kidney transplant recipients are similar. In the entire patient group, there is a statistically significant benefit to graft and patient survival from having private insurance compared to Medicare. This effect was observed across almost all racial groups (except for Asians, where there was no

significant association between private insurance and graft survival). HMO/PPO was associated with significantly higher risk of graft failure but improved patient survival. These results are similar to those reported in liver transplant recipients [163].

Compliance with regards to immunosuppressive medication use is one of the key factors in prolonging graft survival. Until 1993, Medicare regulations allowed for coverage of immunosuppressive medications for only 1 year posttransplantation unless the recipients maintain their Medicare beneficiary status through disability or age. Between 1993 and 1995, that duration was gradually extended to 3 years posttransplantation, which was further extended by 8 months in 2000. Woodward et al. [164] have shown that extending the coverage from 1 year to 3 years posttransplantation has eliminated the 4.5% difference in graft survival between low income and high income recipients. In a follow-up analysis [165], the same authors estimated that if Medicare provided life-long immunosuppressive medications to all the recipients, graft failure would be reduced by 1.2% annually beginning in the fourth year posttransplantation. Furthermore, Medicare beneficiaries who are eligible to receive the immunosuppressive medication coverage must still pay 20% of the cost of these medications, as Medicare covers only 80% of the total cost. With many HMO/PPO or private insurances, carrier subscribers may be required to pay substantially lower co-payments. This could also contribute to better compliance with immunosuppressive medications and subsequently, better graft outcome among HMO/PPO or private insurance subscribers compared with Medicare beneficiaries. Medicare beneficiaries who underwent kidney transplantation do not have coverage for nonimmunosuppressive prescription drugs. This could explain the poor recipient survival seen in our analysis. Medicare beneficiaries were shown to be more likely to take required prescription medications if they had prescription drug coverage [166]. Finally, even though we included age as an independent variable in our analysis, there may be a residual

confounding effect of age on the outcome. As Medicare patients tend to be older compared to HMO/PPO or private insurance patients, Medicare beneficiaries may have poor outcome compared to non-Medicare recipients.

A possible reason for inferior outcomes in Medicaid beneficiaries is as follows: Previous studies have shown that Medicaid beneficiaries are less likely to receive optimal treatment, and their outcome is worse compared with privately insured patients for common conditions such as myocardial infarction and bronchial asthma [167, 168]. Restricted access to medical care because of lower reimbursement by Medicaid and highly variable coverage benefits between different states are some of the possible explanations for such poor outcomes. Low income and poverty indicated by Medicaid may directly or indirectly contribute to worse health outcomes in general. Indeed, cost-related skipping of medications has been shown to be associated with the level of drug coverage and the income level [169]. A potential explanation for better outcomes among those with private insurance could be better quality of care. Furthermore, these patients might be either healthy enough to be employed or have high enough personal incomes to be able to afford private insurance, both of which may potentially influence the outcomes.

Our study demonstrated that better recipient but worse graft survival is associated with HMO/PPO coverage. Better graft survival does not always translate into improved recipient survival. In this particular case, we hypothesize that the HMO population is likely to consist of relatively young employed patients. The residual confounding effect of age might explain longer recipient survival as compared to Medicare beneficiaries. Poor graft survival among HMO/PPO recipients is intriguing and difficult to explain. Interestingly, in another study, no difference in clinical outcome was demonstrated between HMO and fee-for-service patients [170]. We speculate that higher co-pays and deductibles in these plans for specialist physician visits and

expensive immunosuppressive medications compared either to private insurance plans or Medicare/Medicaid may be a hindrance for the patients to comply with required posttransplant treatment. Indeed, the HMO membership was associated with higher degrees of cost-related skipping of medications as compared to Medicare beneficiaries [169].

Also, in our analysis, recipients with higher education level have better graft and patient survival. There is a clear trend in incremental lowering of the hazard ratio for both graft failure and recipient survival with advanced education level. Theoretically, people with higher level of education are more likely to be well-informed and have better awareness of posttransplant care, which could potentially improve outcomes. The correlation between the better education status and compliance is arguable. We also contemplated the possibility of the association between education level and insurance status, so that the effect of these variables on the outcome is not independent. It seems logical that the insurance status would be associated with education level of the recipients. To address this question, we evaluated the potential association between these variables in a bivariate (Chi-square) analysis. We found a significant association between education level and insurance status ($p<0.001$). In general, people with higher level of education tend to earn higher income. For example, according to the US Census Bureau data [171], annual average earnings of workers with a bachelor's degree was $45,678 in 1999 compared with $24,572 for those with only a high school diploma. Higher income may translate into better medical care, greater ability to pay for medication, which in turn may translate in to better graft and recipient survival. This effect of the higher education on the outcome might or might not be independent of the insurance status. To address this potential confounding effect of the education level on the insurance status, we constructed two separate models with each one having either the level of education or the type of insurance coverage and found that the results were

very similar to the main analysis that included both the variables. This similarity suggests an independent association between the outcomes and the level of education and the type of insurance coverage.

Finally, in our analysis, resident aliens seem to have a significantly better outcome than U.S. citizens in terms of both graft and recipient survival. This effect was observed in Whites, but not in African Americans, and may be explained by a number of factors. These results are somewhat counterintuitive, as previously, the negative association between foreign immigration status and the health outcome has been suggested [159]. Low income, unemployment, low level of education, lack of health insurance and access to quality health care along with anti-immigrant sentiment and discrimination in health care [159], as well as language barrier [172] have been listed as potential reasons. However, due to the selection process, the transplant population might not reflect the general trends described in the immigrants. Also, it is conceivable that people who recently arrived to the US might have certain differences in environmental factors compared to the people born in the US. In a recent study, women from Poland and more recent migrants had generally more nutritious intakes, compared to US-born women, or earlier migrants [173]. In the year 2000, persons born outside the United States comprised an estimated 11.1% of the U.S. population [174]. In the report published by the Centers for Disease Control, women born outside the United States had better birth outcomes than their racial/ethnic US-born counterparts [175]. In addition, we speculate that the fraction of the foreign population immigrating to the US might not be simply a random slice of the foreign society, but rather the motivated and active part of it. Therefore, one can hypothesize that there is a degree of selection bias when the outcome of the American citizens is compared to the foreign nationals living in the US. The attitude towards medical care (e.g., commodity rather than active involved process), such as the physician authority and subsequent compliance with

recommendations might be different between Americans and foreigners. While most of these potential reasons are merely speculative, some cultural differences in regard to specific aspects of medical care between Americans and foreign nationals have indeed been described in the literature [176].

In general, based on our results, it seems that some of the socioeconomic factors are significant predictors of the outcome across racial groups. This supports the independent role of these factors from the racial characteristics. Also, in the studies analyzing the role of race in the transplant outcome, potentially uneven distributions of the socioeconomic factors in the different racial groups may confound the results of the analysis and hypothetically explain some of the differences in the outcome between the races.

This study is a retrospective analysis utilizing data reported to the United States Renal Data System. There are limitations as well advantages to large renal transplant database analyses. Database analyses can show long-term differences in outcomes, and provide the statistical power to help determine the differences between the primary variables of interest. However, the quality of data is always a concern due to a significant amount of missing and potentially erroneous information (misclassification bias). In particular, socioeconomic status is difficult to quantify and subjects might be unwilling to share certain information (e.g., immigration status, education level). For example, in our dataset, the education level variable is missing in 61% of the data. Therefore, the analysis of the role of the education status is based on the remaining 39% percent of the data (over 32,000 subjects). It would be optimal not to have any missing values, but due to very large sample size of the remaining observations, the results are still valid. One can assume a random pattern of missing elements in the data and analyze only records with nonmissing information. While the random distribution of the missing values is likely, we decided not to discard the records with values missing, but

rather code and analyze them separately, as reported above. Misclassification bias is difficult to address in the retrospective study and remains one of the shortcomings of the data registry analyses.

Other potential problems with retrospective data analysis should be considered. As in other retrospective studies, while establishing the association between independent variables and the outcome, this analysis cannot ascertain causative relationships. In addition, as in most retrospective studies, the results could be distorted by reverse causality described elsewhere [177]. Finally, as our multivariate models depend on the variables available in the dataset, certain potential confounders may not be included in the analysis (e.g., annual income, employment status, geographic location, IQ level, marital status). Analysis of the role of these variables may present a new and exciting opportunity for future research.

In conclusion, recipients with higher education level, resident aliens (as compared to US citizens), and patients with private insurance have an advantage over graft and recipient outcomes independent of racial differences [95].

4.8. The role of posttransplant immunosuppressive medications

4.8.1. Introduction

In the last decade, the immunosuppressive armamentarium has increased substantially, and several choices are now available for immunosuppression in kidney transplant recipients. Improvement in patient and graft survival over time has correlated best with the introduction of new more effective immunosuppressive agents. These newer immunosuppressant medications have shown equal or superior short-term (1 year) outcomes in comparison with the established immunosuppressive medications [178-180]. We have seen improvement in short-term graft survival, due in part to the reduction in the incidence of acute rejection episodes or potentially a better use of

existing medications [181]. Unfortunately, these improvements in immunosuppression and reduced incidence of acute rejection episodes have had only minimal effects on chronic allograft nephropathy and late graft loss [147, 182].

There is a continuing shift in the calcineurin inhibitor used from cyclosporine to tacrolimus and in antimetabolites from azathioprine to mycophenolate mofetil. Both tacrolimus and mycophenolate mofetil were introduced for kidney transplantation in the mid-90s. Since then (in 2003), according to the Scientific Registry of Transplant Recipients, 67% of kidney transplant recipients received tacrolimus and 81% of kidney received mycophenolate mofetil at the time of discharge [183].

There have been numerous clinical trials comparing the different immunosuppressive agents. These trials have historically evaluated the short 1 year outcomes of graft and patient survival and have contained a relatively small number of patients. The results from clinical trials utilizing tacrolimus and /or mycophenolate have varied in their outcomes.

Clinical trials have shown superior graft survival with tacrolimus when compared to cyclosporine [184], while others have failed to show any significant differences in either graft or patient survival [178, 185]. Other trials have shown improved renal function for tacrolimus-based regimens when compared to cyclosporine-containing regimens but showed no significant differences in graft or patient survival [186]. On the other hand, in the brief report based on the UNOS Scientific Renal Transplant Registry analysis by Bunnapradist and Takemoto, the authors demonstrated better 3-year graft outcome in patients on cyclosporine + mycophenolate mofetil than in those on tacrolimus + mycophenolate mofetil regimen [187]. Similar data for clinical trials comparing mycophenolate mofetil to azathioprine can be found. Although mycophenolate mofetil has been shown to decrease the incidence of acute rejections when compared to azathioprine in renal transplant recipients, the 3-year follow-up of the United States and

the Tricontinental studies did not show an increase in graft survival [3, 188]. Ojo et al. have subsequently shown an improved 4-year graft survival in patients treated with mycophenolate mofetil when compared to azathioprine treated patients [189]. To date, long-term outcome studies of different immunosuppressive regimens are lacking. The goal of this project was to analyze retrospective data provided by the United States Renal Data System and compare the graft and recipient outcome of kidney transplants managed with the three most common maintenance immunosuppressive protocols over the last 5 years of last century.

In this project, the primary variable of interest was the type of maintenance immunosuppressive regimen at the time of discharge from the hospital. Three regimens that were considered the most common maintenance protocols in the 1990s were selected for this analysis: prednisone + cyclosporine + mycophenolate mofetil (PCM); prednisone + tacrolimus + mycophenolate mofetil (PTM); and prednisone + cyclosporine + azathyoprine (PCA).

4.8.2. Results

4.8.2.1. Baseline characteristics

Among recipients (n=31,012), average age was 44.2±14.3 years, 39.6% were females, 68.7% were White, and 23.3% were African Americans. Patients on maintenance PCM were 55.2% (n=17,108), PTM 23.3% (n=7,225), and PCA 21.5% (n=6,679). Since different immunosuppressive drugs were introduced at different time periods, we evaluated the prevalence of different immunosuppressive protocols in transplants performed in two different time periods during the study: prior to 1997 and during 1997 and later. Prior to 1997, 38.1% of the transplant recipient were placed on PCA maintenance at the time of discharge, 50.1% were placed on PCM, and 11.9% on PTM protocols. During and after 1997, 16.3% were placed on PCA maintenance, 56.8%

were palced on PCM, and 26.9% on PTM protocols. We compared baseline characteristics of the patients in the three study groups using ANOVA for continuous variables and Chi-squared for the categorical variables.

4.8.2.2. Survival analysis

Using the PCM group as a reference, the Cox model demonstrated the increased risk for allograft failure associated with PTM (HR 1.08 $p<0.05$) and PCA (HR 1.14 $p<0.001$) regimens (Table 6). PCA (HR 1.15 $p<0.005$) but not PTM (HR 0.99 $p=0.9$) regimen was associated with increased recipient mortality. This association is illustrated by Kaplan-Meier survival curves for donor and recipient survival.

4.8.2.3. Transplant era

Since clinical practice has evolved over the follow-up period of our study, we analyzed the outcomes of the transplants performed during two time periods as described above: (1) from January 1, 1995 and through December 31, 1996 (early period) and (2) from January 1, 1997 and through December 31, 1999 (late period). Among patients transplanted in the early period, 11.7% (7,448) were on PTM, 38.1% on PCA, and 50.2% on PCM. Among those transplanted in the late time period, 26.9 % (n=23,564) were on PTM, 16.3% on PCA, and 56.8% on PCM. Among the transplants performed in the early time period, using PCM as a reference group, PTM was associated with the significantly greater risk for graft failure (HR 1.16, $p<0.05$ 95% CI 1.01 - 1.33). PCA was associated with nonsignificantly increased risk of graft failure (HR 1.06, $p=0.244$, 95% CI 0.96 - 1.17). Among the late time period, both PTM and PCA regimens were associated with significantly greater risk of graft failure (HR 1.10, $p<0.05$, 95% CI 1.01 - 1.19 and HR 1.14, $p<0.01$, 95% CI 1.04 - 1.25, respectively). Recipient

Table 6. Cox model: graft and recipient survival in recipients on different immunosuppressive regimens

	Graft survival		Recipient survival	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Recipient age (per year)	1.01 (1.01 - 1.01)	<0.001	1.04 (1.03 - 1.04)	<0.001
Recipient gender female	0.96 (0.90 - 1.02)	0.169	0.93 (0.84 - 1.03)	0.140
Recipient race				
White	reference			
African American	1.25 (1.16 - 1.33)	<.0001	1.04 (0.94 - 1.15)	0.429
Asian	0.72 (0.61 - 0.86)	<0.001	0.66 (0.51 - 0.84)	<0.005
Other	0.98 (0.85 - 1.13)	0.781	1.15 (0.94 - 1.39)	0.175
Recipient history of diabetes	0.96 (0.82 - 1.13)	0.626	1.14 (0.94 - 1.39)	0.197
Recipient history of hypertension	0.86 (0.78 - 0.95)	<0.005	0.71 (0.63 - 0.81)	<0.001
Recipient height (cm)	1.00 ()0.99 - 1.00	<0.01	1.00 (0.99 - 1.00)	0.06
Recipient weight (kg)	1.00 (1.00 - 1.01)	<0.005	1.00 (1.00 - 1.00)	0.63
Recipient comorbidity score	1.07 (1.00 - 1.15)	<0.05	1.29 (1.19 - 1.40)	<0.001
Total duration of pretransplant end-stage renal disease (per year)	1.00 (0.99 - 1.01)	0.474	1.04 (1.03 - 1.06)	<0.001
Total number of transplants	1.40 (1.30 - 1.52)	<0.001	0.93 (0.81 - 1.07)	0.322
Cause of ESRD				
diabetes	reference			
hypertension	0.99 (0.85 - 1.15)	0.848	0.96 (0.79 - 1.16)	0.679
glomerulonephritis	0.89 (0.76 – 1.03)	0.122	0.79 (0.65 - 0.95)	<0.05
other	0.91 (0.79 - 1.05)	0.207	0.88 (0.74 - 1.06)	0.186

Table 6 continued

	Graft survival		Recipient survival	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Mean PRA level (%)	1.00 (1.00 – 1.01)	<0.05	1.00 (1.00 – 1.01)	0.13
Peak PRA level (%)	1.00 (1.00 – 1.00)	0.741	1.00 (1.00 – 1.00)	0.267
Number of HLA matched antigens	0.94 (0.92 – 0.96)	<0.001	0.93 (0.91 – 0.96)	<0.001
Deceased donor	Reference			
Living donor	0.72 (0.65 – 0.80)	<0.001	0.61 (0.53 – 0.71)	<0.001
Donor age (per year)	1.01 (1.01 – 1.01)	<0.001	1.01 (1.01 – 1.02)	<0.001
Donor gender female	1.03 (0.97 – 1.09)	0.298	1.00 (0.92 – 1.09)	0.984
Donor race White	Reference			
African American	1.24 (1.14 – 1.34)	<0.001	1.25 (1.11 – 1.41)	<0.001
Other	1.20 (1.07 – 1.33)	<0.005	0.96 (0.81 – 1.15)	0.676
Donor height (cm)	1.00 (1.00 – 1.00)	<0.001	1.00 (1.00 – 1.00)	<0.05
Donor weight (kg)	1.00 (1.00 – 1.00)	<0.005	1.00 (0.99 – 1.00)	<0.005
Cold ischemia time ≤6 hours	Reference			
>6 and ≤14 hours	0.83 (0.73 – 0.94)	<0.005	0.86 (0.72 – 1.04)	0.117
>14 and ≤19 hours	0.93 (0.82 – 1.05)	0.248	0.98 (0.81 – 1.17)	0.791

Table 6 continued

	Graft survival		Recipient survival	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
>19 and ≤24 hours	0.99 (0.88 - 1.12)	0.906	1.01 (0.84 - 1.21)	0.920
>24 and ≤30 hours	0.94 (0.83 - 1.07)	0.354	0.98 (0.81 - 1.18)	0.823
Number of pretransplant transfusions: 0	reference			
1-5	1.08 (1.02 - 1.15)	<0.05	1.29 (1.18 - 1.41)	<0.001
6-10	1.07 (0.94 - 1.22)	0.328	1.31 (1.10 - 1.57)	<0.005
>10	1.28 (1.11 - 1.47)	<0.005	1.59 (1.31 - 1.94)	<0.001
Percent of ESRD time on HD	1.00 (1.00 - 1.00)	0.069	1.00 (1.00 - 1.01)	<0.05
Percent of ESRD time on PD	1.00 (1.00 - 1.00)	<0.05	1.00 (1.00 - 1.00)	0.283
Maintenance immunosuppressive regimen: Prednisone + Cyclosporine + MMF	reference			
Prednisone + Tacrolimus + MMF	1.08 (1.01 - 1.15)	<0.05	0.99 (0.90 - 1.10)	0.901
Prednisone + Cyclosporine + Azathioprine	1.14 (1.07 - 1.22)	<0.001	1.15 (1.04 - 1.26)	<0.005

survival had no significant association either with PTM or PCA regimens in the early or late time periods. For the early period, HR was 1.04 (p=0.693) and 1.10 (p=0.15) for the PTM and PCA regimens, respectively. In the late time period, HR was 1.003 (p=0.96) and 1.14 (p=0.057) for the PTM and PCA regimens, respectively (Figure 10).

4.8.2.4. Year of transplant

To evaluate the outcome in patient cohorts with the same or similar duration of follow-up period, we stratified the analysis by the year of transplant, evaluating the patients who were transplanted in 1995 (n=997), 1996 (n=6,451), 1997 (n=8,160), 1998 (n=8,379), and 1999 (n=7,025) separately. Patients transplanted in 1995 would have had 5 to 6 years follow-up during the study; those transplanted in 1996 - 4 to 5 years of follow-up; those transplanted in 1997 – 3 to 4 years follow-up; etc. For the graft survival, using PCM as a reference group, the results were as follows: in the recipients transplanted in 1995, the PTM regimen was associated with an increased risk of graft failure (HR 1.49, $p<0.05$), while the PCA regimen did not have any significant association. In the recipients transplanted in 1996, no significant associations between the graft survival and maintenance immunosuppressive regimen were found. For the recipients transplanted in 1997 and 1998, only PCA was associated with shorter graft survival (HR 1.14 and 1.25, respectively, $p<0.05$). Finally, recipients of the kidney transplant in 1999 had an increased risk of graft failure associated with PTM (HR 1.17, $p<0.05$), while PCA did not have any significant association with graft survival. We did not find any significant association between the maintenance immunosuppressive regimen and the recipient survival in the cohorts of patients stratified by the transplant year.

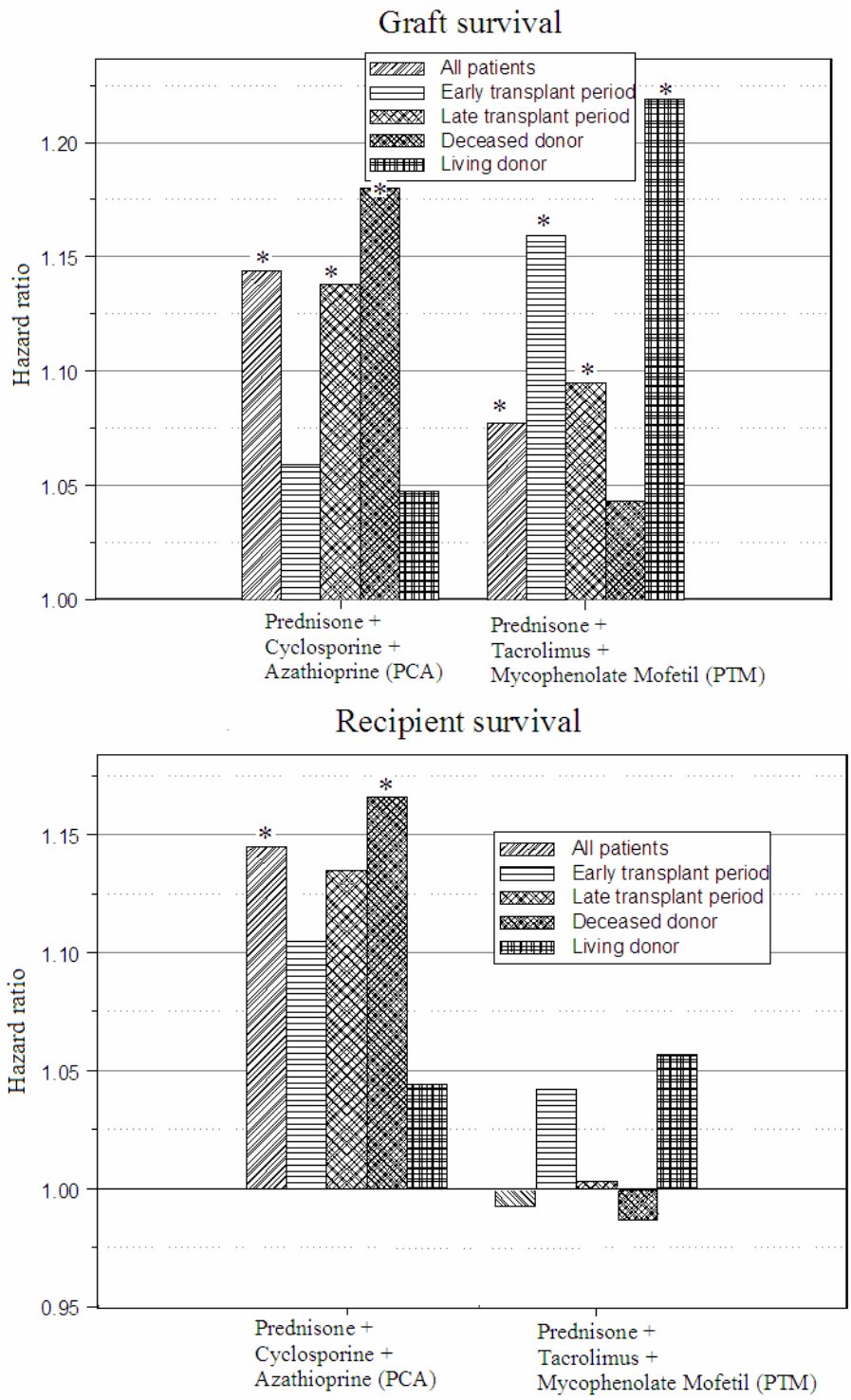


Figure 10. Illustration of the results of Cox proportional hazard model evaluating the role of immunosuppressive regimen. Hazard ratio of the graft failure and recipient death in the entire group of patients and in the subgroups based on the transplant period (early vs. late), and donor type (deceased vs. living). Patients on the Prednisone + Cyclosporine + Mycophenolate Mofetil used as a comparison/reference group (HR 1.0), significant associations (p values <0.05) indicated by *.

4.8.2.5. Living vs. deceased donor

A separate analysis was performed for the recipients of living and deceased donor transplants. Among the recipients of living donor kidney (n=8,924), 19.6% were on PTM, 23.4% on PCA, and the remaining 57% were on PCM regimen. Among the recipients of the deceased donor kidney (n=22,088), 24.8% were on PTM, 20.8% were on PCA, and the remaining 54.4% were on the PCM regimen.

In the recipients of the deceased donor graft using PCM as a reference group, PTM had no significant association with the allograft outcome (HR 1.04 p=0.284), while the PCA regimen was associated with 18% increased risk (HR 1.18, p<0.001, 95% CI 1.1-1.27). In the recipient of the living donor kidney, PTM (HR 1.22, p<0.01, 95% CI 1.06 – 1.41) but not PCA (HR 1.05, p=0.51) was associated with the higher risk of graft failure as compared to PCM. Furthermore, since the analysis is somewhat suggestive of a potential superiority of PCA over PTM regimen in the recipient of living kidneys, we repeated the Cox analysis in living donors with PTM group as a reference. That provides direct comparison between PCA and PTM regimens. While, as expected, the PCM regimen had an advantage over the PTM (HR 0.820, p<0.01, 95% CI 0.71 - 0.95), the PCA regimen was not significantly different from the PTM. Therefore, we concluded that the PCM, but not the PCA maintenance regimen, is superior to PTM regimen in living donors.

In the recipients of the deceased donor kidneys, the recipient survival had no significant association with the PTM regimen, but was significantly associated with the PCA regimen (HR 1.17, p<0.001, 95% CI 1.05 – 1.29). In the recipient of the living donor kidney, the recipient survival had no significant association with either one of the maintenance immunosuppressive regimens (Figure 10).

4.8.2.6. Adult vs. pediatric recipients

Separate analysis was performed for the recipients younger than 18 years of age (pediatric) and those 18 years and older (adult). In pediatric patients (n=1,227), 18.3% were on PTM, 35.0% on PCA, and the remaining 11.7% were on PCM maintenance immunosuppressive regimen. In adult recipients (n=29,785), 23.5% were on PTM, 21.0% were on PCA, and 55.5% were on PCM regimen. Among pediatric patients, we did not find any significant association between the drug regimen and the graft or recipient outcome. In adults, the results were similar to those in the entire study population: PTM was associated with increased risk of graft failure (HR 1.08, $p<0.05$), but not recipient survival, while PCA was associated with increased risk for both graft failure (HR 1.14, $p<0.001$) and recipient death (HR 1.14, $p<0.01$).

4.7.2.7. Kidney-only vs. simultaneous kidney pancreas (SPK) transplant

We performed separate analyses of the recipients of kidney-only and recipients of SPK. The information about SPK was missing in 542 patients; therefore, 28,404 patients with kidney-only and 2,066 patients with SPK were included in the analysis. In patients with kidney-only transplant, 20.9% were on PTM, 22.5% on PCA, and the remaining 56.6% were on PCM regimen. In SPK recipients, 55% were on PTM, 7.6% were on PCA, and 37.4% were on PCM. In SPK recipients, we did not detect any significant association between the drug regimen and either graft or patient survival. In the recipients of kidney-only transplants, results were similar to those in the entire patient population: in comparison to PCM regimen, PTM was associated with increased risk of graft failure (HR 1.10, $p<0.01$) but not recipient death, while PCA was associated with both increased risk of graft loss (HR 1.15, $p<0.001$) and recipient death (1.16, $p<0.005$).

4.8.2.8. Effect of the induction therapy

Since the results of the survival analysis potentially could be confounded by the induction therapy, we collected the data describing induction regimen divided into the following groups: muromonab-CD3 (OKT3), antithymocyte globulin (ATG), interleukin-2 receptor monoclonal antibodies (IL-2R mAb): daclizumab or basiliximab, and "Other or Missing." The latter category included patients with no induction, those in whom induction therapy information was missing, and those in whom regimens other than OKT3, ATG, or IL-2R mAb induction were used. Of the total patient population, ATG was used for induction in 5,152 patients, OKT3 in 3,904 patients, and IL-2R mAb in 3,337 patients. The remaining recipients (n=18,619) were either on other induction therapy, or information was missing. We included the information regarding the induction therapy into the Cox model and reanalyzed the data. The results were similar to those reported above. Using the PCM group as a reference, graft survival in the recipients on PTM and PCA regimens was associated with increased risk of graft failure (HR 1.07 $p<0.05$ and HR 1.15 $p<0.001$, respectively). For recipient survival, only PCA regimen was associated with significant risk (HR 1.14 $p<0.01$).

4.8.3. Discussion

Multiple factors have been shown to affect the outcome of renal transplantation. These include demographic characteristics [190] such as race and ethnicity [154], pretransplant dialysis course [66], and the timing of the transplant [64]. Patient response to the transplantation procedure (e.g., delayed graft function, acute rejection, acute tubular necrosis) is strongly associated with the long-term prognosis [191]. The selection of the appropriate immunosuppressive regimen (including induction and maintenance) is without doubt one of the most important modifiable factors that might affect the short-term events, as well as long-term results of the transplantation.

Determining the optimal maintenance immunosuppressive regimen in kidney transplantation is an area of continued research. The immunosuppressive regimen that provides the best long-term outcome has yet to be defined. There are multiple factors to consider when choosing a maintenance immunosuppressive regimen, including the side effect profile, cost, potency, and effect on allograft function [192]. Due to the short term outcomes and the lack of power of trials for new immunosuppressants, there is little information about the long-term graft outcomes associated with the different maintenance immunosuppressant regimens [193].

The short-term outcome of the kidney transplant, mostly expressed as an incidence of acute rejection, has been shown to be better with tacrolimus than with cyclosporine in both pediatric [194] and adult [195, 196] kidney transplant patients as well as in heart transplant recipients [197]. In lung transplant recipients, the episodes of acute rejections were similar in patients receiving cyclosporine and those receiving tacrolimus in combination with steroids and mycophenolate mofetil [198]. The data regarding long-term outcome are controversial. In the recipients of living donor kidney transplants, cyclosporine + mycophenolate mofetil had better long-term outcome in terms of all-cause graft failure and death-censored graft failure than tacrolimus + mycophenolate mofetil protocol [187]. However, other authors report better 3-year outcome with tacrolimus-based regimens as compared to cyclosporine-based regimens [199, 200] or no significant difference between the protocols [201, 202]. In a recent study based on 2-year follow-up comparing tacrolimus and cyclosporine-based regimens, the authors demonstrated no difference in the graft loss between the regimens; however, renal function was better in patients receiving tacrolimus [195]. Using the annualized change in glomerular filtration rate as an outcome, the superiority of the tacrolimus plus mycophenolate mofetil regimen in preserving renal function has been demonstrated in a study by Gill et al. [193]. The latter study, however, was

criticized for potential biases, including the nonuniform measurements of renal function between immunosuppressive regimens and between transplant centers [203]. Despite the lack of long-term outcome data, the trend in recent years has been towards a shift from cyclosporine-based to tacrolimus-based and from azathioprine to mycophenolate mofetil regimens [204].

We attempted the analysis of the kidney transplants performed during the last 5 years of the last century to compare the long-term outcomes of the patients receiving three most frequently used drug protocols. Since the data are available, we considered extending the study period into the earlier years of the 1990s but decided against it. Our study period covers the use of all three immunosuppressive regimens of interest, while comparing the early 90s (where azathioprine and cyclosporine were mostly used) to the latter years (where tacrolimus and mycophenolate mofetil started to dominate) would not be a fair comparison, since major changes in practice took place during the 1990s. Stratifying analysis by the transplant era, as well as analyzing patient cohorts transplanted in the same year, to some extent should eliminate the factor of time and related issue of evolving clinical practice confounding the outcome.

This study demonstrates that the use of PTM and PCA as maintenance immunosuppression between 1995 and 1999 was associated with increased risk of graft failure by 9% ($p<0.05$) and 15% ($p<0.001$), respectively, as compared to the PCM protocol. Using the PCA regimen was associated with recipient survival worsening by 15% ($p<0.005$) as compared to PCM. Similar results were reported by other investigators analyzing long-term outcome on the large kidney transplant datasets [187], where, using data from the UNOS Scientific Renal Transplant Registry, authors demonstrated that the death-censored graft failure is 25% higher in the tacrolimus + mycophenolate mofetil group as compared to cyclosporine + mycophenolate mofetil. Woodward et al. at the recent American Transplant Congress presented results of the

analysis, where graft survival in patients on PCM regimen was superior to those on PTM regimen in living [205] and deceased [206] donor kidney transplant recipients. In the analysis of the secondary outcomes, the results seemingly are pointing in another direction. Serum creatinine concentration values were consistently lower in the PTM group, except for the 7-year follow-up time point (Figure 11). Results of this analysis should be interpreted cautiously. Serum creatinine has been used in numerous studies as a surrogate outcome, when the longer follow-up period needed to observe graft failure is not feasible. In this project, however, we feel that we have long enough follow-up to adequately observe the "hard" outcomes (i.e., graft failure and recipient death) to make a conclusion. In a way, it is probably less important what a patient's serum creatinine value is at a given point in time, as long as his or her graft is surviving longer. In addition, while interpreting these results, one must realize one very important potential flaw of this type of analysis.

Comparing serum creatinine values among the groups at a given time point may be misleading since only those patients who survived to that time point are included in this analysis. Therefore, if the PTM group were to have a higher graft failure rate, creatinine might be artificially lower in the surviving patients as compared to the PCM group, where fewer patients failed the transplant, and therefore average creatinine values might be artificially higher (survivor bias). For example, it is conceivable that if two cohorts of patients were compared, and in the first one that graft failure rate is greater than in the second one, the average creatinine might also be lower in the first cohort, since only the "healthiest" patients remain in the study. In the second cohort, where the graft failure rate is slower, more patients with dysfunctional grafts, which have not failed yet, would remain in the study, and therefore, the average creatinine might be higher. This would still mean the better outcome (lower rate of graft failure) in the second cohort despite higher average creatinine concentration.

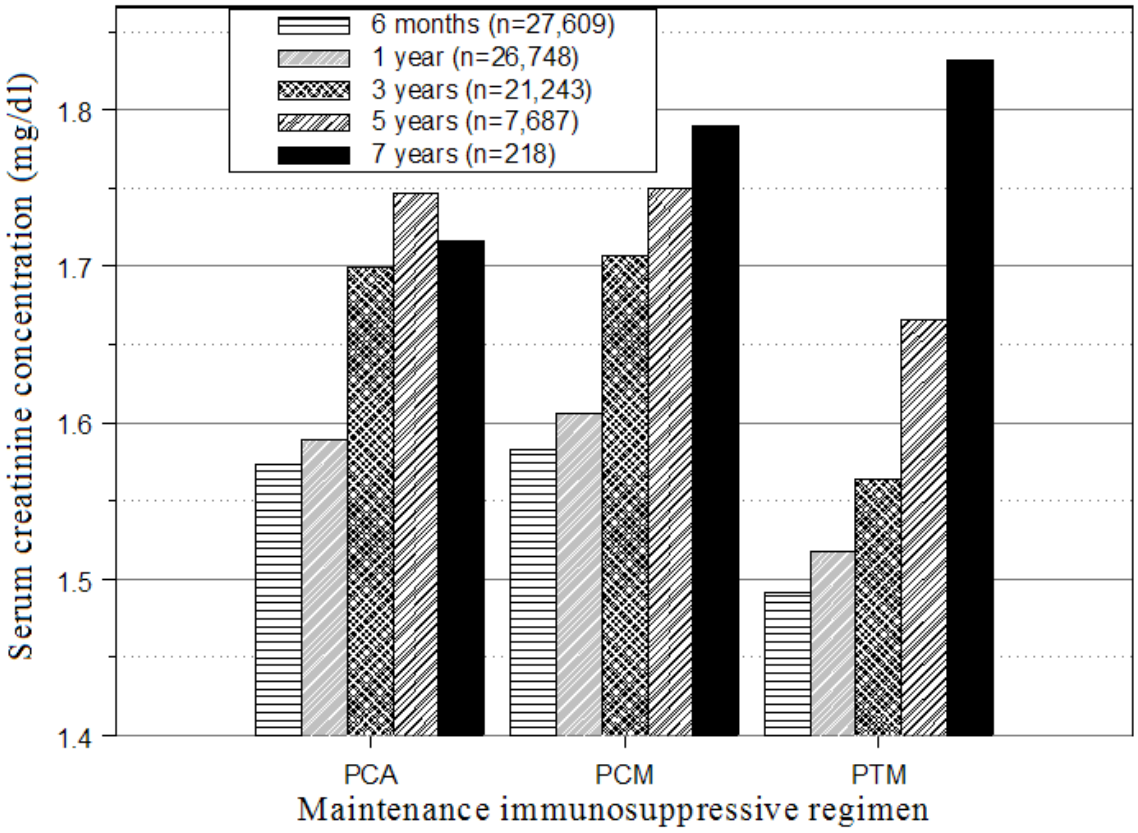


Figure 11. Results of mean serum creatinine concentration in the study groups at 6 months, 1 year, 3 years, 5 years, and 7 years posttransplant associated with different immunosuppressive regimens. Differences between the groups are significant by ANOVA ($p<0.001$) for 6-month, 1-year, and 3-year, ($p<0.01$) for 5-year follow-up. Differences are not significant for 7-year follow-up.

Another interesting finding of this study is a significantly lower rate of posttransplant malignancies in the PTM compared to PCM and PCA groups. This phenomenon, however, did not translate into improved patient survival in the PTM group as compared to PCM group. Contrary to our results, in a recent meta-analysis, no difference has been demonstrated between tacrolimus-based and cyclosporine-based regimens [207]. It has been suggested by other authors that induction therapy might be equally or even more important than the maintenance immunosuppression in developing posttransplant malignancies [208]. Adjusting our model for the induction therapy

demonstrated results similar to those which we detected in the model not adjusted for induction, suggesting lower risk of posttransplant malignancies with the PTM regimen.

This study is a retrospective analysis utilizing data reported to the United States Renal Data System. There are limitations as well advantages to large renal transplant database analyses. Database analyses can show long-term differences in outcomes, but the results must be evaluated with caution. Using a database such as the USRDS provides the statistical power to help determine the differences between current maintenance immunosuppressive regimens. However, because the database does not contain information about the dose or duration of therapy, caution must be taken when making conclusions from the data. Certain limitations should be considered when interpreting the results of this study. Selection bias is a common flaw of a retrospective analysis. Based on our results, the outcome of the cyclosporine-based regimen is superior to that of the tacrolimus-based protocol. We recognize that during the early use of tacrolimus, there was a tendency to use it mostly in the higher risk population (e.g., those with higher PRA levels, retransplants, and African Americans), and hence the selection bias. Indeed, we compared subgroups of patients on three immunosuppressive regimens of interest and found that there is a very small, though statistically significant, difference in the baseline characteristics between the study groups (Table 2). To reduce this potential bias, we adjusted the Cox model for the risk factors of premature graft failure (e.g., recipient race, PRA levels, number of previous blood transfusions, number of previous transplants, and comorbidity index). Including these potential confounding factors in the multivariate model should considerably reduce the bias. In addition, we tried to reduce the selection bias by stratifying the analysis by the transplant era, as tacrolimus became more of a “mainstream” medication (as opposed to be used in high risk patients only) in the later 1990s. Also, since living donors might have been considered at lower risk and thus affect the choice of

immunosuppression, we stratified the analysis by donor type. Finally, we analyzed pediatric and adult recipients and kidney and SPK recipients separately. The negative association between the PTM regimen and graft survival was observed in the entire patient population. Importantly, the observed negative association between the PTM regimen and the graft outcome was observed not only in the early period, but in the late period as well, when the use of tacrolimus was supposedly not limited only to the high-risk patient population. The negative association between the PCA regimen and graft survival was observed in the entire patient population and only in late, but not in early transplant periods, and only in deceased, but not in living donor transplants. The described associations were also revealed in adult recipients and kidney-only recipients (but not in to pediatric and SPK recipients). Specifically, there is no superiority of PTM as compared to PCM in SPK recipients. Subgroup analysis of the recipient survival did not demonstrate any association between PTM regimen and the recipient survival either in the whole patient population, or in any of the subgroups. As kidney transplant recipients survival is relatively long, it is conceivable that longer follow-up period is needed to observe enough events to demonstrate a difference between the PTM and PCM regimens. The negative association between the PCA regimen and recipient survival was demonstrated in the whole patient population, but in the subgroup analysis, only patients transplanted with a deceased donor kidney, adult recipients, and those receiving kidney-only (as opposed to SPK) transplant had increased risk of death on this regimen.

Unfortunately, any study evaluating the long-term outcome has to deal with the fact that the practice evolves during the time of the study. We partially addressed this issue by performing analysis separately for early and late transplant eras. However, clinical practice, even during the late era of the study (late 1990s), is different compared to the current practice in the early 2000s. In particular, the proportion of various

immunosuppressive regimens during the study is different from that in the modern days. We tried to address that by performing additional analysis comparing centers that use particular regimen (PCM, PCA, or PTM) exclusively or predominantly. However, the amount of missing data related to the immunosuppressive regimen evaluated separately by the transplant center prevented us from performing this analysis. We did, in fact, identify the centers leaning towards one regimen or another; however, in every case we encountered a high amount of missing information that made the classification of the [illegible] potentially misleading and thus are not presented here. Our study was performed in a retrospective fashion and unfortunately does not provide the explanations for the mechanism of the observed associations. Future studies are needed to confirm this association and establish the mechanism of it. In general, the difference in graft survival between two regimens may be explained by the difference in nephrotoxicity, associated comorbidity, different side effect profile, or better follow-up due to censoring. Our study period included all transplants done since 1995 with the duration of follow-up through the end of 2000. Of all patients included in the study, 997 were transplanted in 1995 and therefore had 5-6 years of follow-up; 6,451 were transplanted in 1996 and had 4-5 years of the follow-up; 8,160 were transplanted in 1997 and had 3-4 years of the follow-up; while patients transplanted in 1998 (n=8,379) and 1999 (n=7,025) had relatively short follow-up (1-3 years).

In summary, our data suggest that prednisone + cyclosporine + mycophenolate mofetil regimen is associated with lower risk of graft failure compared to prednisone + tacrolimus + mycophenolate mofetil, and lower risk of graft failure and recipient death compared to prednisone + cyclosporine + azathioprine regimen [96].

5. REVISED MODEL OF KIDNEY ALLOGRAFT PREDICTION SURVIVAL

5.1. Introduction

Several significant predictors of suboptimal transplant outcome were previously identified in adults [102, 109, 114, 209, 210] and children [38, 62, 211] based on data from the United Network of Organ Sharing (UNOS) and the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Donor and recipient age [212], preexisting donor hypertension and diabetes [213, 214], nonheartbeating donor [215], prolonged cold storage time [102], retransplantation [216], pretransplant renal replacement therapy modality [66], duration of pretransplant end-stage renal disease [64], body mass index of donor and recipient [109], and recipient marital status [71], along with other factors, play important roles in the outcome. However, the probable interaction of these factors, plus their potential to act in various combinations, make it difficult to predict the outcome in individual patients without using mathematical tools. Mathematical models would accurately predict graft survival duration as well as identify patients at risk and locate potentially modifiable risk factors. We previously described mathematical models predicting 3-year deceased graft survival [23]. However, that report was limited only to deceased donor kidney recipients, and the mathematical model was designed only to predict 3-year allograft survival. The attempt herein described is undertaken to develop a tree-based model predicting the probability of graft survival at posttransplant years 1, 3, 5, 7, and 10.

5.2. Methods

5.2.1. Dataset

As described above, we used the data collected by the United States Renal Data System (USRDS) and UNOS which described all kidney allograft recipients (both pediatric and adults) who underwent kidney or kidney-pancreas transplantation during the period of January 1, 1990, through December 31, 1999. The follow-up period was extended through December 31, 2000. Censored data used for multivariate analysis to identify factors that have an association with the outcome were excluded from the prediction analysis, as described below. Separate datasets were generated for each of the five prediction models. These datasets included only uncensored records which had specific information of graft survival at a given time period (i.e., 1, 3, 5, 7, and 10 posttransplant years in the respective datasets). For example, for the 1-year prediction model, only patients with a known 1-year outcome were selected, while those who were censored due to insufficient duration of follow-up or other reasons were excluded. From each of the datasets, 2/3 of the data were randomly selected into the training dataset and the remaining 1/3 into the testing dataset. The training set was used for knowledge acquisition (to generate the model), while validation was performed using the records from the testing set.

5.2.2. Outcome

The outcome was the time between the most recent kidney transplant and the failure of the graft. For the purpose of the prediction model, the outcome was converted into 1, 2, 3, 5, 7, and 10-year transplant recipients and graft survivals as a binary variable. The graft failure definition did not include patient death with a functioning graft (i.e., death censored graft survival). In the event that the information regarding death with a functioning graft was missing in the dataset, and the patient death date has been

found to be equal to the graft failure date, we assumed that the patient died with a functioning graft unless the cause of death specified in the UNOS file was coded (ICD-9) as one of the following: 3200, graft failure: primary failure; 3201 graft failure: rejection; 3202 graft failure: technical; 3299 graft failure; other; or 3903 miscellaneous: renal failure.

5.2.3. Independent variables

The following independent variables were considered and evaluated for inclusion in the prediction models.

5.2.3.1. Recipient demographic and anthropometric data

Recipient demographic and anthropometric data: age, race, gender, height, and weight. Information was obtained from USRDS files SAF.PATIENT and SAF.TXUNOS.

5.2.3.2. Variables describing recipient ESRD course

Variables describing recipient ESRD course were obtained from SAF.PATIENT and SAF.RXHIST60 files: age of onset of ESRD; total duration of pretransplant ESRD period (time between the first ESRD service and most recent transplant date); renal replacement therapy (RRT) modality immediately prior to current transplant; predominant RRT modality during ESRD course (defined as modality used for >50% of the ESRD period as previously described [66]); number of different RRT modalities used; the specific combination of RRT modalities; absolute time and percent time of the whole ESRD period that the patient was treated with specific RRT modality; history of transplants prior to the current one (yes/no); and total number of transplants (including the current one). Since preemptive transplantation was reported to be advantageous in terms of graft survival [146, 148, 217], the binary variable defining preemptive transplant was considered for inclusion in the models. The definition of preemptive transplantation

was based on the variable PRTXDIAL from the SAF.TXUNOS file, as was done by other researchers [146]. In addition, since the PRTXDIAL variable was not collected prior to 1995, we defined preemptive transplant from the SAF.RXHIST60 file, based on duration of ESRD and use of dialysis prior to the transplant of interest, as described before [64]. The recipient's dialysis network was used as a proxy for geographic location.

5.2.3.3. Recipient comorbidity status

Recipient comorbidity status was described by a composite comorbidity index similar to the one proposed by Davies, which has been shown to be strongly associated with the outcome in ESRD patients [113]. Other comorbidity indices have been proposed in literature, and since it has been demonstrated that Khan, Davies, and Charlson scores are appropriate for expressing the prognostic impact of comorbidity on mortality risk in patients with ESRD [218, 219], Davies' approach was selected for its simplicity. Also, the specific comorbid conditions used as separate variables were considered for the model: presence and duration of HTN and DM; history of coronary artery disease; symptomatic cerebrovascular disease; symptomatic peripheral vascular disease; history of malignant tumors; recipient medical conditions at listing; and functional status prior to transplant. Information about coexisting conditions was obtained from the SAF.TXUNOS file, which was collected from the Transplant Candidate Registration Form prior to transplant (at the time of listing for the most recent transplant).

5.2.3.4. Donor variables

Donor variables: type of donor (deceased or living), age, race, gender, height, weight, and donor health conditions prior to donation (i.e., presence and duration of comorbidities: DM, HTN, CAD; smoking history; heart beating or not; donor cause/mechanism of death) were obtained from SAF.TXUNOS file.

5.2.3.5. Transplant procedure variables

Transplant procedure variables were also obtained from SAF.TXUNOS file: cold ischemia time, transplant procedure type (e.g., single kidney, kidney-pancreas, double kidney transplant), transplant center where surgery was done, donor and recipient HLA match, maintenance immunosuppressive therapy at the time of discharge from the hospital (latter was obtained from the SAF.TXIRUNOS file).

5.2.4. Variables selection

We used several strategies to select the optimal combination of predictors for the model. The selection criteria were based on the predictive value of the variable weighted against the practicality of including it in the model. Even though the longer list of the predictors may potentially improve the outcome of the model, using too many variables may compromise the parsimony and practical usefulness of the model in the clinical setting. In particular, since the decision support tool might potentially be used in the pretransplant clinical environment, only variables available before transplantation were used in developing prediction algorithms.

5.2.4.1. Survival analysis

We performed the survival analysis using proportional hazards regression modeling for the purpose of identifying the set of statistically significant predictors of graft ($p<0.05$). For the survival analysis, where outcomes were analyzed as time to event, allograft outcome was censored at the earliest of the following events: loss to follow-up, patient death, or study completion date (12/31/2000) and was analyzed as days to graft failure or censor. For the purpose of variables selection, the survival analysis was supplemented by the logistic regression models, as described below.

5.2.4.2. Logistic regression modeling for variables selection

We generated 5 separate logistic regression models predicting the graft survival as a binary variable at 1, 3, 5, 7, and 10 years of the follow-up. We used a conservative approach to variable selection. Only variables that had significant association ($p<0.05$) with the outcome in all of the 5 models were included in the final tree-based analysis. In other words, variables that were not significant in at least one model were excluded.

5.2.4.3. Additional variables

In addition to the variables selected by the algorithms described above, we also included several variables that were originally excluded. These variables were considered to be important for the graft outcome prediction: recipient history of unstable angina, predominant renal replacement therapy modality in the pretransplant course and percent time on peritoneal dialysis [66], recipient history of hypertension, recipient gender, and donor gender.

5.2.4.4. Additional selection

Using the set of variables selected by these methods, we tested the tree-based model for convergence and demonstrated poor performance, which were thought to be due to potential collinearity in the data. To make the model more practical and parsimonious, we evaluated the performance of the model with the shorter list of variables, excluding the variables that were considered nonessential. The heartbeating donor variable was found to have significant missing information, while nonmissing data was collinear with donor type (living vs. deceased). Variables describing cardiovascular disease history were collinear with the variable describing peripheral vascular disease history, and therefore, the latter was removed. The variable describing the use of antihypertensive medications by the donor was largely homogenous and was also removed. RRT modality immediately prior to transplant was not used, and instead

predominant RRT modality during ESRD course was included in the model. We also excluded the variable describing dialysis network, since the model did not converge in its presence. Based on R-squared statistics, the model based on the shorter list of variables (below) performed not worse than the one less parsimonious based on the longer list of predictors.

5.2.4.5. Final list of predictors

The final list included the following recipient variables: recipient race, gender, age, height, weight, recipient having a transplant prior to the current one (yes/no), total number of transplants (including the current one), the time recipient has been on the list prior to transplant, predominant renal replacement therapy modality, percent time on peritoneal dialysis prior to transplant, number of renal replacement therapy modalities used prior to transplant, specific combination of renal replacement therapy modalities, recipient comorbidity score, history of cardiovascular disease, history of unstable angina, history of diabetes, history of hypertension, presence of hepatitis B core antibodies, presence of hepatitis C antibodies, peak and most recent level of panel reactive antibodies, and primary source of pay for medical services. In addition, the following donor variables were used in the final model: donor race, gender, age, height, weight, donor type (living or deceased).

Finally, we used the following transplant procedure variables: cold ischemia time, and number of matched HLA antigens, using MMF in the immunosuppressive regimen (as a proxy for the transplant era).

5.2.5. Statistical analysis and prediction models

Continuous variables were summarized using means and standard deviations. A tree-based model analysis has been extensively described elsewhere [101] and was previously used by our group in the prediction of renal function of diabetics [220] and in

the prediction of kidney allograft survival [23]. Briefly, tree-based modeling, also called classification and regression trees, or CART, is a form of binary recursive partitioning which systematically separates data into two groups using regression of a single factor on the outcome. Unlike traditional methods, tree-building techniques are ideally suited for the development of a reliable clinical decision rule, which can be used to classify new patients into categories according to predicted allograft outcomes, where traditional statistical methods are sometimes cumbersome to use, or of limited utility [101]. Tree-based modeling works well when the regression variables are a mixture of categorical and continuous variables. The algorithm is nonparametric, so no assumptions are made regarding the underlying distribution of values of the predictor variables. Tree-based modeling requires relatively little input from the analyst, as the outcome is presented in a form of binary trees is easy to interpret by a nonstatistician. However, the model is limited in that the partitioning method leads to the predicted value being presented in a discrete format, which may not make full use of the information that continuous variables can provide [101].

5.2.5.1. Validation and performance testing

To test the performance of the models, prediction algorithms were applied to the testing dataset, and the values of the predicted probability of graft failure were generated and compared to actual values of graft outcome.

Two measures were used for the validation of the prediction models. The probability of graft failure predicted on a testing set was categorized into deciles, and for each category, the rate of graft failure was calculated and compared with the predicted value [23]. We also used receiver operating characteristic (ROC) curve analysis to evaluate and compare the performance of the models. ROC (probability that for a randomly chosen pair of patients the predicted and observed graft survival are

concordant) analysis is a nonparametric method used to quantify the accuracy of the prediction. It is a plot of the true positive rate against the false positive rate for the different possible cut-points of a prediction algorithm. It shows the tradeoff between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity). The closer the curve follows the left-hand border and then the top border of the ROC space (resulting in large area under ROC curve: an area of 1 represents a perfect prediction), the more accurate the model. The closer the curve comes to the 45-degree diagonal of the ROC space (resulting in a smaller area under ROC curve: an area of 0.5 represents a worthless prediction), the less accurate the model. The procedure ROCCOM in the software package STATA (Stata Corporation, College Station, TX) was used to calculate and compare the area under the ROC curves.

5.2.6. Software

SAS (SAS Institute, Cary, NC) was used for descriptive statistics and survival analysis; S-Plus (Insightful, Seattle, WA) was used for logistic regression and tree-based modeling [23, 220]; and STATA (Stata Corporation, College Station, TX) was used for ROC analysis.

5.3. Results

5.3.1. Descriptive statistics

Data were collected from USRDS and included 92,844 records of patients receiving kidney or kidney-pancreas transplants starting January 1, 1990, and through December 31, 1999, with the follow-up period through December 31, 2000. The study population characteristics are presented in Table 1. The average age of patients was 43.3 years, of which 60.3% were male, 70.2% were White, 27.2% were diabetics, 77.1% were on HD prior to transplant, and 12.6% had another kidney transplant prior to the

current transplant. During the 11 years of the study, the graft failed in 34.9% of the patients. Cold ischemia time was on average 15.5 hours.

5.3.2. Prediction model generation

5.3.2.1. Selection of training and testing datasets

The same training and testing datasets were used for logistic regression and tree-based models. The training and testing datasets were derived from the full dataset after records were shuffled in the random order (S-Plus code: menuRandomSample(data = knownoutcome1, replace = F, save.name = " knownoutcome1", show.p = T)). As discussed above, roughly 2/3 of the data were used for the training dataset (for example the S-Plus procedure to select the training data for 1-year outcome prediction: knownoutcome1.training <- remove.row(target = knownoutcome1, start.row = 60001, count = 32844)), while 1/3 was used for the model testing (knownoutcome1.testing <- remove.row(target = knownoutcome1, start.row = 1, count = 60000)).

5.3.2.2. Comparison of the models with long and short list of Predictors

As indicated above, we aimed at finding the most parsimonious model, and in this particular exercise compared the outcome of the model based on the short list of predictors with the model based on longer list of predictors. We used R-squared to compare models (Rsquared.Model1.Short<-Rsquared(Model1.Short); Rsquared.Model1.Long<-Rsquared (Model1.Long)) and found no differences in the outcome.

5.3.2.3. Regression modeling

The Regression Model was based on the list of predictors described above. Five different logistic regression models predicting the probability of the allograft survival for 1, 3, 5, 7, and 10 years were generated using S-Plus software. As an example, the code for the model predicted 1-year outcome is presented here:

```
Final.model1.reg <- menuBinomialGlm(formula = AA.GS~ UNSANGR.Cat +
   Predom.Mod + htnnew1 + tx.sex + DSEX + height + PKPRA + prev.tx +
   PRIPAY.Cat + tx.months + weight + tx.race + CVASCR + HBCORE + HCSRN
   + DTYPE + DAGE + DRACE + Dheight + Dweight + match + MRPRA +
   C.COLDTIME + total.txs + RRage + time.onlist + MMF.Maint + RCITZ.Cat
   + PTXTFUS.Cat + Comorb.Score + Mod.Number60 + Mod.Comb60 + pd.months
   + hd.months + dmnew1, family = binomial, link = logit, variance =
   NULL, data = knownoutcome1.training, na.omit.p = T, trace = F, maxit
   = 50, epsilon = 0.0001, print.short.p = T, print.long.p = T,
   print.anova.p = F, print.correlation.p = F, save.fit.p = F,
   save.resid.working.p = F, save.resid.pearson.p = F,
   save.resid.deviance.p = F, save.resid.response.p = F,
   plotResidVsFit.p = F, plotSqrtAbsResid.p = F, plotResponseVsFit.p =
   F, plotQQ.p = F, smooths.p = T, rugplot.p = F, id.n = 3,
   plotPartialResid.p = F, plotPartialFit.p = F, rugplotPartialResid.p
   = F, scalePartialResid.p = T,
newdata = knownoutcome1.testing, predobj.name =
   "knownoutcome1.testing", predict.type = "response", predict.p = T,
   se.p = T)
pvalues1.final.reg <- anova(Final.model1.reg, test="Chi")
menuCreateCategories(xname = "knownoutcome1.testing", col = "fit",
numuse = "Cut Points", nbin = 10, numby = "Count", cutpoints =
"0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9",            newcol            =
"Predicted.Surv.Cutpoints")
```

Variables used in the models are presented in Table 7. Some variables had significant association with outcome in all or few of the five models. This probably has to do with the fact that different factors are predicting the outcome at different posttransplant time points. Few variables, however, were universally significant; in particular, higher degree of HLA match was associated with lower risk of graft failure, history of prior transplant increased the risk of graft failure in all but one models, while number of prior transplant was universally significant. The living donor dramatically and significantly decreases the risk of graft failure in all models as compared to the deceased donor. A more detailed description of the direction and significance of the associations is presented in Table 7.

Table 7. Variables used in logistic regression models predicting the risk of graft failure, their regression coefficients and p-values.

	1 year		3 years		5 years		7 years		10 years	
		p		p		p		p		p
Recipient race: Asian	1.0	0.97	0.8	<0.001	0.8	<0.001	0.7	<0.001	1.0	<0.001
Recipient race: Black	1.4	<0.001	1.4	<0.001	1.6	<0.001	1.7	<0.001	1.7	<0.001
Recipient race: White	1.3	<0.001	0.9	0.08	0.9	0.18	0.9	0.25	0.9	<0.001
Recipient sex: Female	1.0	0.65	1.0	0.60	0.9	0.30	0.9	0.17	0.9	<0.001
Recipient weight	1.0	<0.001	1.0	<0.001	1.0	<0.001	1.0	<0.001	1.0	<0.001
How long on the list (years)	1.0	<0.001	1.0	0.37	1.1	<0.001	1.1	0.01	2.4	<0.001
Recipient height	1.0	<0.001	1.0	<0.001	1.0	<0.001	1.0	0.06	1.0	<0.001
Number of HLA matched antigens	0.9	<0.001	0.9	<0.001	0.9	<0.001	0.9	<0.001	0.9	<0.001
History of prior transplant: Yes	1.5	<0.001	1.5	<0.001	1.2	0.06	0.9	0.56	0.9	<0.001
Total duration of ESRD (months)	1.0	0.02	1.0	0.12	1.0	0.77	1.0	0.25	1.0	<0.001
Total number of transplants	1.5	<0.001	1.6	<0.001	1.6	<0.001	1.9	<0.001	2.1	<0.001
Cause of ESRD: DM	1.1	0.52	1.2	0.05	1.5	<0.001	1.8	0.55	2.2	<0.001
Cause of ESRD: GN	0.9	0.01	1.0	0.58	1.0	0.37	1.1	<0.001	1.1	<0.001
Cause of ESRD: HTN	1.1	0.23	1.0	0.34	1.1	0.02	1.2	0.40	1.6	<0.001
Peak PRA level (%)	1.0	<0.001	1.0	0.02	1.0	0.14	1.0	0.05	1.0	<0.001
Mean PRA level (%)	1.0	0.06	1.0	0.06	1.0	0.34	1.0	0.08	1.0	<0.001
Comorbidity score	1.0	0.85	1.2	0.55	0.9	0.72	0.9	1.00	0.8	<0.001
History of cerebrovascular disease: No	0.9	0.78	0.9	0.66	0.6	0.13	0.0	0.84	1.0	0.24
History of cerebrovascular disease: Unknown	1.0	0.95	0.9	0.56	0.5	0.06	0.0	0.83	0.9	<0.001
History of peripheral vascular disease: No	0.9	0.84	1.2	0.42	1.0	0.38	1.0	0.85	1.1	<0.001
History of peripheral vascular disease: Unknown	0.9	0.75	1.0	0.29	1.0	0.96	0.1	0.06	1.2	<0.001
History of unstable angina: No	0.7	0.28	0.8	0.46	0.7	0.37	2.5	0.97	1.3	<0.001
History of unstable angina: Stability unknown	0.6	0.11	0.7	0.18	1.1	0.81	>999	0.72	1.2	<0.001
History of unstable angina: Stable angina	0.8	0.14	0.8	0.09	0.9	0.57	3.2	0.39	1.2	<0.001
History of unstable angina: Unknown	0.6	0.07	0.6	0.06	0.6	0.19	3.1	0.96	1.2	<0.001
Recipient history of HTN	0.9	0.57	0.9	0.64	1.2	0.61	1.3	0.99	1.3	<0.001
Recipient history of DM	1.0	0.99	0.9	0.62	1.1	0.74	1.2	0.99	1.2	<0.001
Donor age	1.0	<0.001	1.0	<0.001	1.0	<0.001	1.0	<0.001	1.0	<0.001

Table 7 continued

	1 year		3 years		5 years		7 years		10 years	
		p		p		p		p		p
Donor race: Black	1.4	<0.001	1.3	<0.001	1.3	<0.001	0.9	0.22	1.6	<0.001
Donor race: White	1.1	0.36	1.1	0.47	1.0	0.56	0.7	<0.001	1.1	<0.001
Donor sex: Female	1.0	0.38	1.0	0.45	1.0	0.06	0.9	<0.001	0.9	<0.001
Donor type: Living	0.5	<0.001	0.5	<0.001	0.5	0.01	<0.001	0.58	1.3	<0.001
Donor height	1.0	<0.001	1.0	0.42	1.0	<0.001	1.0	0.35	1.0	<0.001
Donor weight	1.0	<0.001	1.0	<0.001	1.0	0.11	1.0	0.04	1.0	<0.001
MMF-based maintenance therapy: missing	5.1	<0.001	2.3	<0.001	0.4	<0.001	0.5	0.02	4.9	<0.001
MMF-based maintenance therapy: No	1.5	<0.001	1.0	0.91	0.2	<0.001	0.2	<0.001	1.1	<0.001
Cold ischemia time <6 hours	1.0	0.35	1.1	0.18	1.1	0.09	1.1	0.04	1.1	<0.001
Cold ischemia time: >6 and <=14 hours	0.9	0.01	0.9	<0.001	0.9	<0.001	0.9	0.22	1.0	<0.001
Cold ischemia time: >14 and <=19 hours	0.9	<0.001	0.9	<0.001	0.9	0.07	0.9	0.24	1.1	<0.001
Cold ischemia time: >19 and <=24 hours	0.9	0.12	0.9	0.05	0.9	0.03	1.0	0.59	1.2	<0.001
Cold ischemia time: >24 and <=30 hours	1.0	0.28	0.9	0.02	1.0	0.25	1.0	0.98	1.1	<0.001
Pretransplant dialysis modality: HD	1.2	0.04	1.0	0.95	0.7	<0.001	0.8	0.38	2.5	<0.001
Pretransplant dialysis modality: no dialysis	1.7	<0.001	1.3	0.03	0.8	0.06	0.8	0.62	2.8	<0.001
Pretransplant dialysis modality: PD	1.2	0.06	1.0	0.73	0.7	<0.001	1.5	0.22	3.7	<0.001
RRT modality prior to transplant: HD	0.8	0.01	1.0	0.69	0.9	0.11	1.1	0.36	1.0	<0.001
RRT modality prior to transplant: lost to f/u	0.9	0.30	1.3	<0.001	1.0	0.77	1.2	0.28	0.9	<0.001
RRT modality prior to transplant: PD	0.9	0.20	1.1	0.38	0.9	0.16	1.2	0.32	1.0	<0.001
RRT modality prior to transplant: TX	3.2	<0.001	2.4	<0.001	1.8	<0.001	1.8	<0.001	1.0	<0.001
Predominant RRT modality: HD	1.0	0.76	1.2	0.30	1.2	0.16	1.1	0.74	1.4	<0.001
Predominant RRT modality: None	1.0	0.78	1.0	0.85	1.1	0.49	1.1	0.54	1.2	<0.001
Predominant RRT modality: PD	1.1	0.51	1.3	0.13	1.4	0.05	1.5	0.08	1.7	<0.001
Number of months on HD	1.0	<0.001	1.0	<0.001	1.0	0.06	1.0	0.03	1.0	<0.001
Number of months on PD	1.0	<0.001	1.0	0.02	1.0	0.02	1.0	0.08	1.0	<0.001

Table 7 continued

	1 year		3 years		5 years		7 years		10 years	
		p		p		p		p		p
Number of months with prior Tx	1.0	0.56	1.0	0.87	1.0	0.19	1.0	0.32	1.0	<0.001
Percent of ESRD time on HD	1.0	0.93	1.0	0.17	1.0	0.92	1.0	0.84	1.0	<0.001
Percent of ESRD time on PD	1.0	0.27	1.0	0.02	1.0	0.24	1.0	0.02	1.0	<0.001
Percent of ESRD time with prior transplants	1.0	0.30	1.0	0.60	1.0	0.73	1.0	0.59	1.0	<0.001
RRT modality: HD+Tx	1.0	0.95	0.6	<0.001	0.6	<0.001	0.7	0.03	0.5	<0.001
RRT modality: HD only	1.3	0.19	1.0	0.66	1.0	0.86	1.0	0.49	1.1	<0.001
RRT modality: None	1.0	0.87	0.7	0.01	0.9	0.21	0.8	0.07	1.0	0.04
RRT modality: PD+HD	1.5	0.10	1.2	0.08	0.9	0.38	1.4	0.05	1.0	<0.001
RRT modality: PD+HD+Tx	1.0	0.94	0.6	<0.001	0.6	<0.001	0.8	0.32	0.5	<0.001
RRT modality: PD+Tx	1.3	0.22	0.8	0.15	0.8	0.26	1.1	0.67	0.8	<0.001
RRT modality: PD only	1.5	0.06	1.1	0.50	0.9	0.58	1.2	0.11	1.2	<0.001
Number of different RRT modalities (>60 days)	1.0	0.92	1.0	0.92	1.3	0.02	1.0	1.00	1.3	<0.001
Donor Citizenship: US citizen	1.0	0.69	1.0	0.51	1.0	0.71	0.8	0.05	0.7	<0.001
Donor Citizenship: Missing	1.2	0.14	2.1	<0.001	2.3	<0.001	1.1	0.69	0.7	<0.001
Donor Citizenship: Nonresident alien	0.9	0.62	1.0	1.00	0.8	0.46	0.4	0.10	1.0	0.10
Donor Citizenship: Resident alien	1.0	0.94	0.9	0.76	0.8	0.24	0.7	0.32	0.5	<0.001
Donor Hx of DM 0-5 years	1.0	0.97	1.3	0.13	0.8	0.29	0.7	0.99	0.8	<0.001
Donor Hx of DM >10 years	1.0	0.96	1.1	0.71	1.2	0.59	0.5	0.98	0.8	<0.001
Donor Hx of DM 6-10 years	0.8	0.54	0.9	0.62	1.6	0.25	0.5	0.98	1.2	0.01
Donor Hx of DM: None	0.9	0.23	1.0	0.88	0.8	0.36	0.2	0.90	1.1	<0.001
Donor Hx of HTN:Missing	1.4	0.14	1.9	<0.001	1.3	0.29	<< 0.0 011	0.61	9.4	<0.001
Heartbeating donor: missing	0.7	0.08	0.5	<0.001	0.7	0.04	0.8	0.40	0.1	<0.001
Heartbeating donor: No	0.9	0.36	0.8	0.03	1.0	0.81	1.1	0.82	0.9	<0.001
Recipient education level: Associate/Bachelor Degree	1.2	0.54	0.9	0.52	1.0	0.92	3.1	0.30	0.4	<0.001

Table 7 continued

	1 year		3 years		5 years		7 years		10 years	
		p		p		p		p		p
Recipient education level: Grade School (0-8)	1.0	0.99	1.0	1.00	1.2	0.47	4.6	0.24	0.5	<0.001
Recipient education level: High School (9-12)	1.1	0.68	1.0	0.85	1.3	0.37	4.4	0.10	0.5	<0.001
Recipient education level: Missing	2.9	0.09	0.8	0.71	2.6	0.30	19.7	0.85	0.1	<0.001
Recipient education level: None	1.0	0.89	0.9	0.81	1.1	0.78	171.3	0.78	0.5	<0.001
Recipient education level: Postcollege Graduate Degree	1.1	0.79	0.8	0.44	0.9	0.66	2.4	0.50	0.4	<0.001
Recipient education level: Attended College/Technical School	1.1	0.65	1.0	0.94	1.2	0.49	2.3	0.35	0.5	<0.001
Recipient education level: Unknown	1.2	0.53	0.9	0.69	1.1	0.82	1.0	0.98	0.4	<0.001
Hepatitis B core Ab: negative	1.1	0.42	1.1	0.65	1.2	0.13	0.9	0.78	1.6	<0.001
Hepatitis B core Ab: not done	1.0	0.77	0.9	0.24	1.0	0.91	2.1	0.22	1.9	<0.001
Hepatitis B core Ab: positive	1.0	0.86	1.0	0.73	1.5	0.01	2.5	0.29	1.3	<0.001
Hepatitis C: cannot disclose	1.2	0.84	<< 0.0 011	0.94	0.0	0.97	37.0	0.97	5.4	<0.001
Hepatitis C: indeterminate	1.3	0.75	1.2	0.82	0.3	0.28	0.0	0.81	0.1	<0.001
Hepatitis C: negative	1.1	0.43	1.2	0.08	0.9	0.40	3.0	0.06	1.6	<0.001
Hepatitis C: not done	1.1	0.41	1.1	0.60	0.9	0.31	0.7	0.58	0.8	<0.001
Hepatitis C: positive	1.3	0.07	1.5	<0.001	1.1	0.49	6.3	0.05	1.2	<0.001
Number of Previous pregnancies: 1	1.0	0.84	0.9	0.22	1.0	0.63	0.9	0.04	1.0	<0.001
Number of Previous pregnancies: 2	1.0	0.94	1.0	0.48	1.0	1.00	0.9	0.11	0.9	<0.001
Number of Previous pregnancies: 3	1.0	0.47	1.0	0.54	1.0	0.85	0.9	0.45	1.0	<0.001
Number of Previous pregnancies: 4	1.0	0.94	1.1	0.31	1.1	0.15	1.1	0.46	1.0	0.02
Number of Previous pregnancies: 5	1.0	0.81	0.8	0.06	1.0	0.91	1.1	0.36	1.2	<0.001

Table 7 continued

	1 year		3 years		5 years		7 years		10 years	
		p		p		p		p		p
Number of Previous pregnancies: 6	0.9	0.54	0.9	0.24	1.0	0.79	0.9	0.52	1.1	<0.001
Number of Previous pregnancies: Male	1.4	<0.001	2.5	<0.001	3.2	<0.001	1.0	0.90	1.0	0.08
Number of Previous pregnancies: Missing	1.0	0.81	1.1	0.24	6.7	<0.001	1.0	1.00	1.1	<0.001
Primary Source of Payment: Free Care	0.6	0.50	0.1	<0.001	0.2	0.06	12.3	0.97	2.8	<0.001
Primary Source of Payment: US/State Govt Agency	0.5	0.14	0.3	0.01	0.5	0.33	1.0	1.00	3.3	<0.001
Primary Source of Payment: HMO/PPO	0.8	0.53	0.5	0.13	1.9	0.42	0.0	0.91	3.9	<0.001
Primary Source of Payment: Medicaid	0.5	0.09	0.3	0.02	0.7	0.65	0.0	0.89	2.9	<0.001
Primary Source of Payment: Medicare	0.5	0.12	0.3	0.01	0.6	0.43	0.0	0.89	2.0	<0.001
Primary Source of Payment: Missing	0.5	0.08	0.3	0.02	0.4	0.17	0.0	0.88	1.7	<0.001
Primary Source of Payment: Private Insurance	0.5	0.10	0.3	0.01	0.5	0.32	0.0	0.89	3.0	<0.001
Primary Source of Payment: Self	0.3	0.04	0.3	0.02	0.4	0.32	<<0.0011	0.83	3.2	<0.001
Number of pretransplant transfusions: >10	1.2	0.01	1.1	0.12	1.1	0.12	1.2	0.02	0.8	<0.001
Number of pretransplant transfusions: 1-5	1.0	0.22	1.1	0.06	1.0	0.33	1.0	1.00	1.0	<0.001
Number of pretransplant transfusions: 6-10	1.0	0.80	1.0	0.89	1.0	0.35	1.1	0.02	0.9	<0.001
Number of pretransplant transfusions: missing	1.0	0.56	1.1	<0.001	1.1	<0.001	1.1	0.04	3.6	<0.001
Recipient Citizenship: US citizen	1.2	0.04	1.2	0.01	1.3	<0.001	1.3	0.02	0.9	<0.001
Recipient Citizenship: Missing	1.3	0.01	1.6	<0.001	1.5	<0.001	1.3	0.10	0.3	<0.001
Recipient Citizenship: Nonresident alien	1.0	0.92	0.8	0.50	1.4	0.44	0.8	0.70	0.3	<0.001
Recipient age	1.0	<0.001	1.0	<0.001	1.0	<0.001	1.0	<0.001	1.0	<0.001

Table 7 continued

	1 year		3 years		5 years		7 years		10 years	
		p		p		p		p		p
Day of transplant: Friday	1.1	0.01	1.0	0.33	1.0	0.24	1.0	0.94	0.9	<0.001
Day of transplant: Monday	1.1	0.21	1.0	0.90	1.0	0.43	1.0	0.70	0.9	<0.001
Day of transplant: Saturday	1.1	0.07	1.0	0.68	1.0	0.78	1.0	0.71	1.0	<0.001
Day of transplant: Sunday	1.0	0.91	1.0	0.97	1.0	0.35	1.0	0.84	0.9	<0.001
Day of transplant: Thursday	1.0	0.72	1.0	0.90	1.1	0.18	1.0	0.65	1.0	<0.001
Day of transplant: Tuesday	1.1	0.19	1.0	0.52	1.0	0.29	1.0	0.44	1.1	<0.001

5.3.2.4. Tree-based modeling

Five different tree-based models predicting the probability of the allograft survival for 1, 3, 5, 7, and 10 years were generated. TBM were initially generated without restrictions in order not to limit the list of independent variables described above. To generate final, more parsimonious models, the optimal number of terminal nodes was determined for each model using the cross-validation procedure (S-Plus: plot(cv.tree(tree1))), where the deviance was plotted against the size of the tree to select the optimal tree size. The optimal size of the tree was identified as 93 for the model predicting 1-year survival, 40 for 3-year survival, 88 for 5-year survival, and 65 for 7-year survival. The cross-validation procedure did not indicate the optimal tree-size for the 10-year outcome model; therefore, we arbitrarily selected the model with 65 terminal nodes (the same as for 7-year outcome prediction). Following that, the second set of tree models was generated and pruned to the size identified by the cross-validation procedure. After the models were created, the set of predicted outcome values was generated in the testing datasets. The residual mean deviance of the model and misclassification error rate are presented in Table 2.

As an example, the code for the tree-based model predicted 1-year outcome is presented here:

```
finaltree1.response <- menuTree(formula = AA.GS~ DTYPE + Predom.Mod + htnnew1 + tx.sex + DSEX
+ height + UNSANGR.Cat + PKPRA + prev.tx + PRIPAY.Cat + weight + tx.race +
CVASCR + HBCORE + HCSRN + DAGE + DRACE + Dheight + Dweight + match + MRPRA +
C.COLDTIME + total.txs + RRage + time.onlist + MMF.Maint + RCITZ.Cat +
PTXTFUS.Cat + Comorb.Score + Mod.Number60 + Mod.Comb60 + dmnew1, data =
knownoutcome1.training, print.summary.p = T, print.tree.p = T, , plot.it = F, plotUniform = T, plot.addText = T,
plot.addText.what = "Response-Value", prune.p = T, prune.k = NULL, prune.best = 90, prune.method = "deviance",
predict.newdata = knownoutcome1.testing, predict.type = "response", predict.save.name = "knownoutcome1.testing")
menuCreateCategories(xname = "knownoutcome1.testing", col = "Yes", numuse =
    "Cut Points", nbin = 5, numby = "Range", cutpoints =
    "0.1,0.2,0.3,0.4,0.5,0.6,0.7,0.8,0.9")
```

Variables that were used in tree-based model construction are presented in Table 8. The table demonstrates the list of variables used for each of the five models in the order of their significance (from the root of the tree to the periphery.) While different models used similar variables in the prediction of the outcome, they vary in the priorities assigned to the particular variables.

5.3.3. Model validation

5.3.3.1. Correlation analysis

The predicted variable in this study is the probability of graft survival, which is a continuous variable. However, the actual outcome for each individual patient is binary. All records were divided into 10 groups based on predicted probability of graft survival using the following cut-points: 0-10%, >10-20%, >20-30%, >30-40%, >40-50%, >50-60%, >60-70%, >70-80%, >80-90%, and >90-100%. The observed graft survival was calculated for each group and compared to the predicted probability using cross-tabulation.

Examples for cross-tabulation procedures for the logistic regressing and tree-based model are presented here:

```
Crosstab1 <- menuCrosstabs(formula = ~ Decile.LogRegr + AA.GS, data =
knownoutcome1.testing, margin.p = T, na.action = "Fail",
drop.unused.levels = T, print.object.p = T, digits = 2, marginal.totals
= T, chi2.test = T)).
```

```
Crosstab1 <- menuCrosstabs(formula = ~ Tree.Decile.Yes + AA.GS, data =
knownoutcome1.testing, margin.p = T, na.action = "Fail",
drop.unused.levels = T, print.object.p = T, digits = 2, marginal.totals
= T, chi2.test = T)
```

If the number of patients in a particular group was low (arbitrarily selected value of <30), it was merged with next group up, except for the very last group, and that was merged with the next group down. In particular, for the 1-year prediction group, the models did not make any predictions with the probability of graft survival 0-10% and

Table 8. Variables used in the construction of tree-based model in order of their significance (from the root of the tree to the periphery)

1 year model	3 years model	5 years model	7 years model	10 years model
Donor type (living or deceased) Donor age (years) MMF-based maintenance therapy Positive hepatitis B core Ab Source of primary pay for medical services Most recent PRA level Recipient age Peak PRA level Time on waiting list Previous history of transplant Recipient race Pretransplant dialysis modalities Donor-recipient HLA match Donor weight Donor height Recipient weight Donor race Recipient history of diabetes mellitus Recipient number of pretransplant transfusions Recipient height Cold ischemia time Total number of transplants Recipient history of unstable angina Recipient's citizenship Predominant pretransplant RRT modality	Recipient race MMF-based maintenance therapy Donor age (years) Donor-recipient HLA match Previous history of transplant Donor race Donor weight Pretransplant dialysis modalities Positive hepatitis B core Ab Recipient age Donor type (living or deceased) Most recent PRA level Recipient history of diabetes mellitus Peak PRA level Total number of transplants Time on waiting list Donor height	MMF-based maintenance therapy Recipient race Donor age (years) Recipient history of unstable angina Time on waiting list Donor height Recipient comorbidity score Donor-recipient HLA match Recipient sex Peak PRA level Recipient age Pretransplant dialysis modalities Donor type (living or deceased) Total number of transplants Hepatitis C screening Recipient history of diabetes mellitus Most recent PRA level Donor race Recipient weight Cold ischemia time Positive hepatitis B core Ab Recipient's citizenship Recipient history of cerebrovascular disease Recipient number of pretransplant transfusions Donor weight Recipient height Source of primary pay for medical services	Hepatitis C screening Recipient history of cerebrovascular disease Time on waiting list MMF-based maintenance therapy Source of primary pay for medical services Donor height Recipient race Donor age (years) Recipient comorbidity score Pretransplant dialysis modalities Donor-recipient HLA match Recipient weight Peak PRA level Recipient height Predominant pretransplant RRT modality Recipient age Total number of transplants Recipient history of diabetes mellitus Donor type (living or deceased) Most recent PRA level Donor Number of pretransplant RRT modalities used	Time on waiting list Hepatitis C screening Donor type (living or deceased) Recipient race Recipient number of pretransplant transfusions MMF-based maintenance therapy Donor age (years Donor-recipient HLA match Peak PRA level Recipient comorbidity score Recipient age Total numeber of transplants Recipient history of unstable angina Donor Most recent PRA level Recipient weight Pretransplant dialysis modalities Predominant pretransplant RRT modality Donor weight Recipient sex Recipient height Number of pretransplant RRT modalities used Previous history of transplant Recipient history of diabetes mellitus Recipient's citizenship

11-20%; therefore, this group was merged with the group where the predicted probability of graft survival was 21-30%. Similarly, the 31-40% group had only 7 patients and therefore was merged with the 41-50% group. In the 3-year prediction model, none of the groups with predicted probability between 0 and 30% had any patients and therefore were merged with the 31-40% group. In the 5-year model, the last group 91-100% had 13 patients and was merged with the 81-90% group. For the 7-year prediction, the 91-100% group had only 21 patients and was merged with 81-90% group. Finally, for the 10-year prediction, none of the group greater than 60% had enough patients and were merged together in the 61-100% group.

The results of the analysis are presented in Table 9, where the percent of actual graft survival and number of patients for each of the groups of predicted probability of graft survival are presented. These results are illustrated in Figure 12.

The midpoint of each group's probability range was used as the predicted percent survival for the group and compared to observed graft survival for the group by correlation analysis. Similarly, the results of the validation in the testing dataset are presented in Figure 13 for the logistic regression model.

For the tree-based model, the prediction of the probability of graft survival from the training model achieved a good correlation with the observed survival of the testing set with r= 0.94 for 1-year survival prediction; r= 0.98 for 3-year survival prediction; r= 0.99 for 5-year survival prediction; r= 0.93 for 7-year survival prediction; and r= 0.98 for 10-year survival prediction. The results of the logistic regression model were very similar.

5.3.3.2. Receiver operator characteristics (ROC) curve analysis

The ROC analysis was performed for each model using the predictions generated on the testing dataset. The ROC curves for the tree-based models are

Table 9. Predicted probabilities and actual graft survival rates.

1 year survival	Predicted probability of survival	0-30%	31-50%	51-60%	61-70%	71-80%	81-90%	91-100%		
	Observed percent survival	51.5	52.5	76.5	69.0	78.9	85.7	91.2		
	n	33	139	162	924	4479	15598	11509		
3 year survival	Predicted probability of survival	0-40%	41-50%	51-60%	61-70%	71-80%	81-90%	91-100%		
	Observed percent survival	38.8	47.4	54.9	67.1	77.0	82.7	89.3		
	n	474	274	1914	7907	8598	3746	759		
5 year survival	Predicted probability of survival	0-10%	11-20%	21-30%	31-40%	41-50%	51-60%	61-70%	71-80%	81-100%
	Observed percent survival	8.2	17.2	25.6	41.2	45.5	57.0	64.0	73.6	81.0
	n	981	1123	520	1241	1777	4092	4262	2791	1218
7 year survival	Predicted probability of survival	0-10%	11-20%	21-30%	31-40%	41-50%	51-60%	61-70%	71-80%	81-100%
	Observed percent survival	0.9	18.1	30.7	38.9	46.0	53.1	64.9	74.3	59.2
	n	5307	548	807	792	2860	2537	2541	1323	76
10 year survival	Predicted probability of survival	0-10%	11-20%	21-30%	31-40%	41-50%	51-60%	61-100%		
	Observed percent survival	1.2	16.1	26.4	34.9	36.9	47.0	62.9		
	n	7488	1181	367	521	485	202	35		

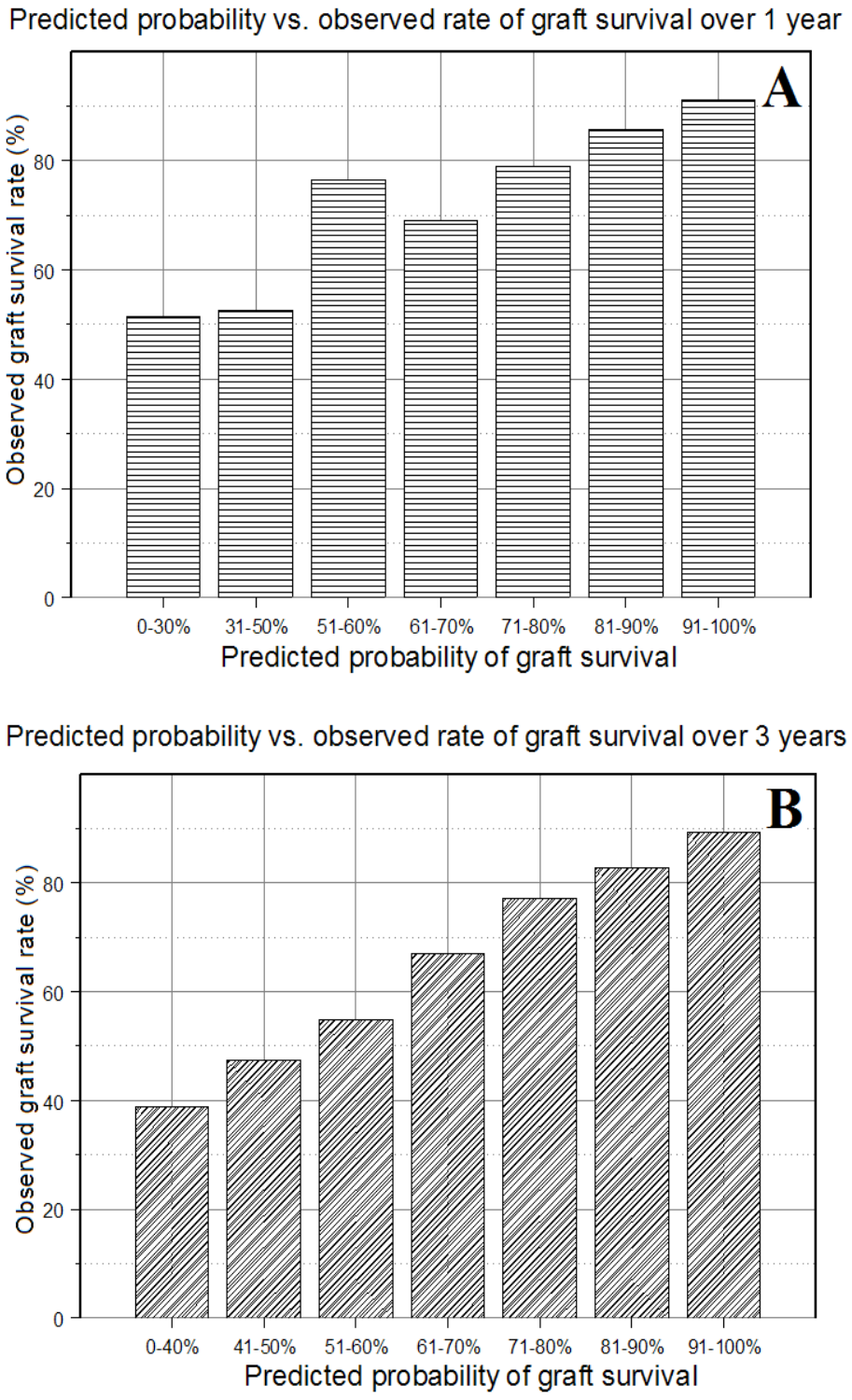


Figure 12. Bar plots of the graft survival rates vs. predicted probability of graft survival for one (Panel A), three (Panel B), five (Panel C), seven (Panel D), and ten (Panel E) years of graft survival. Predictions were generated in the independent testing dataset, separate from the training dataset upon which the models were created.

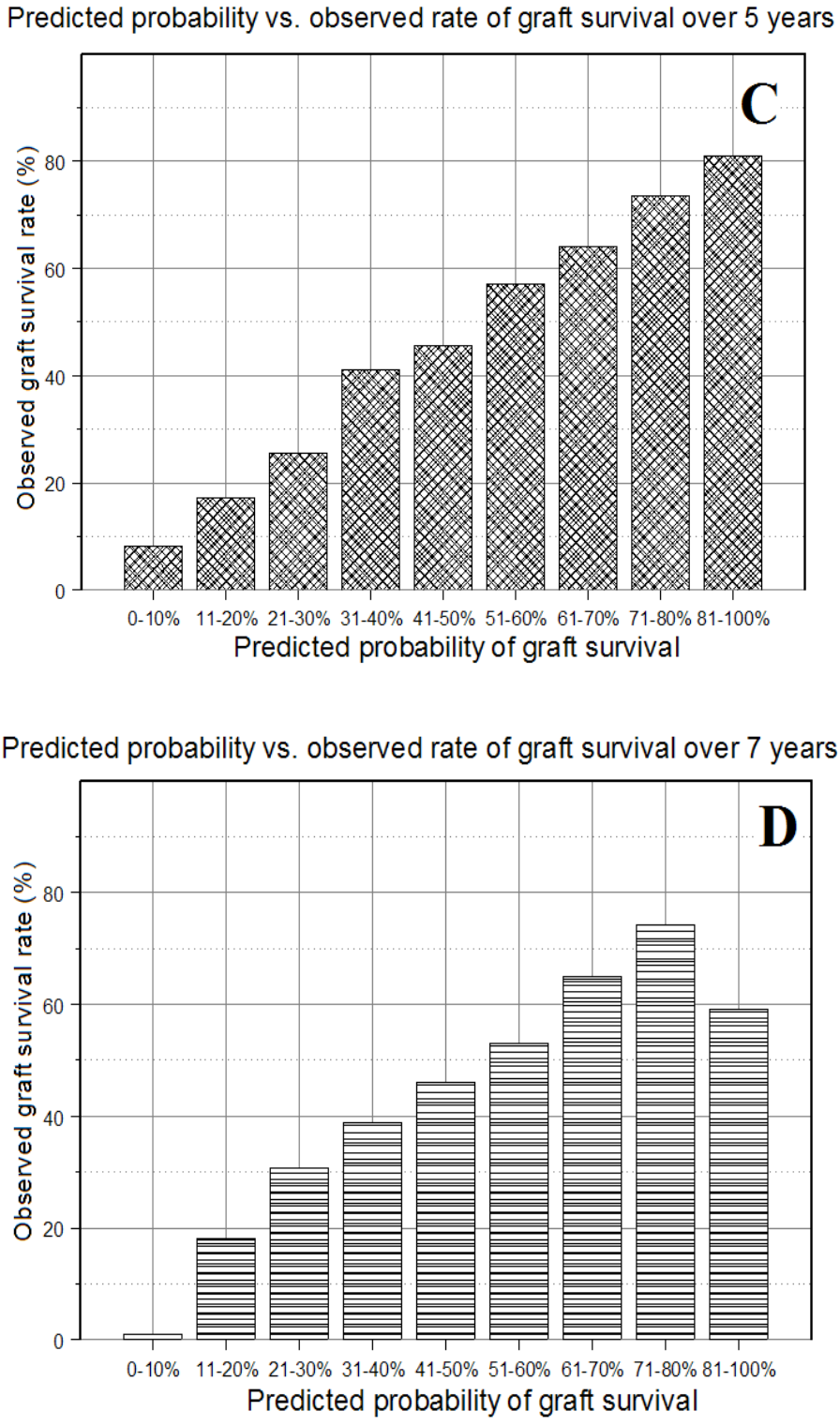
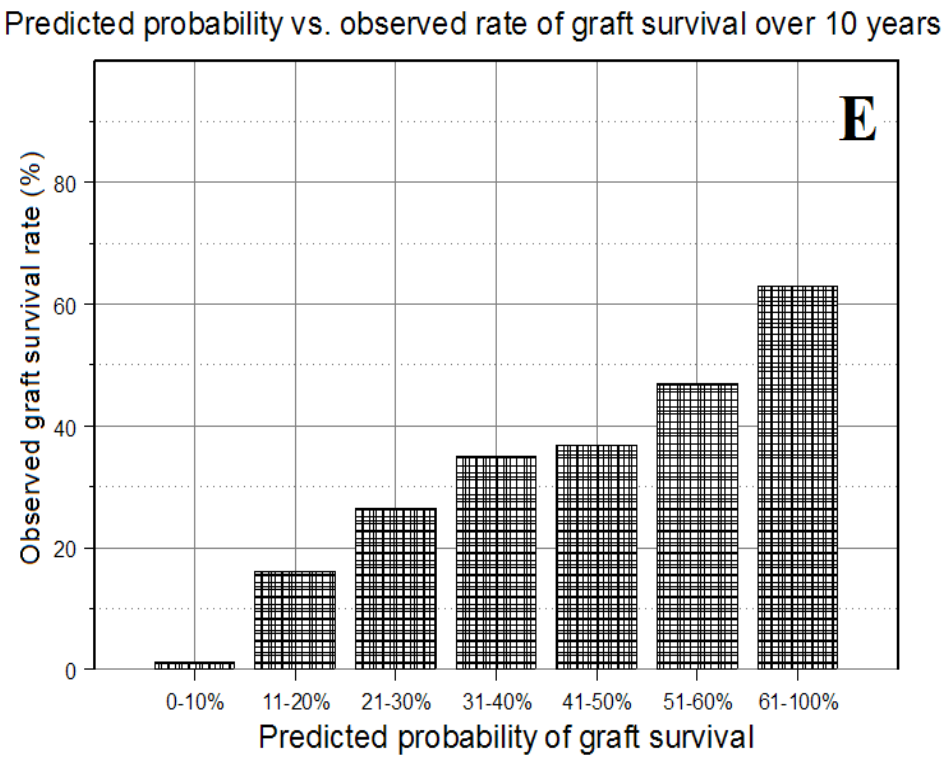


Figure 12 continued



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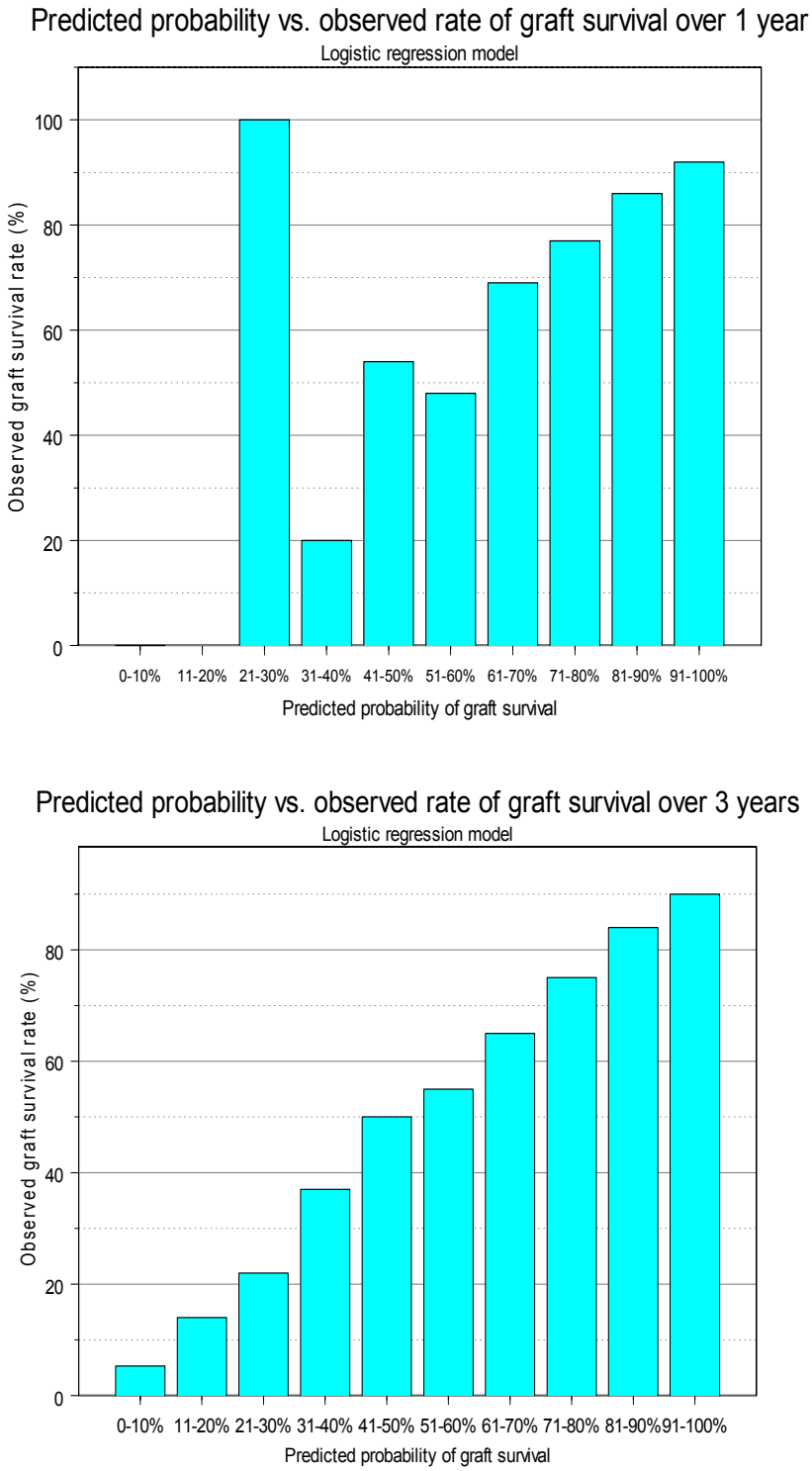
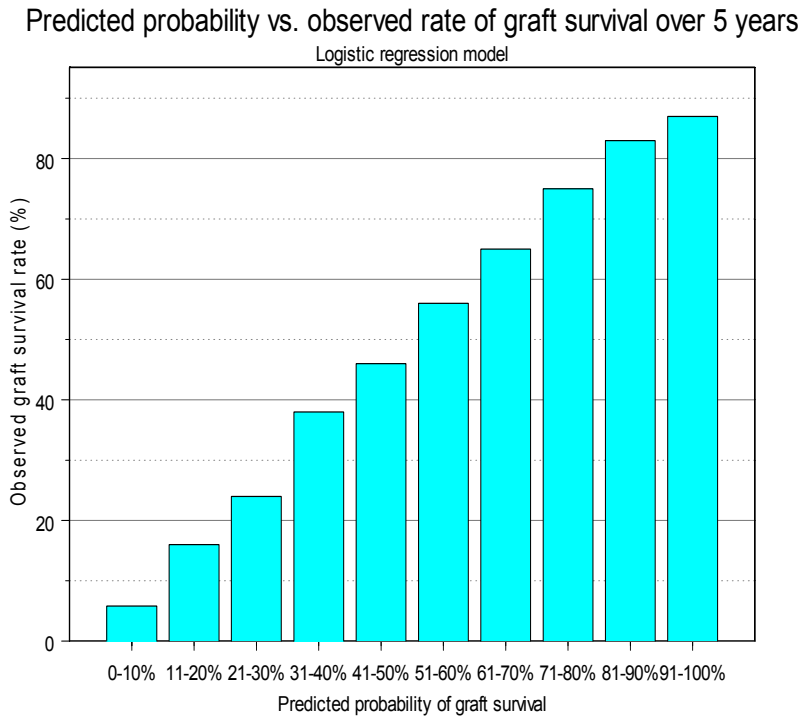


Figure 13. Bar plots of the graft survival rates vs. predicted probability of graft survival for one, three, five, seven, and ten years of graft survival for logistic regression model. Predictions were generated in the independent testing dataset, separate from the training dataset upon which the models were created.



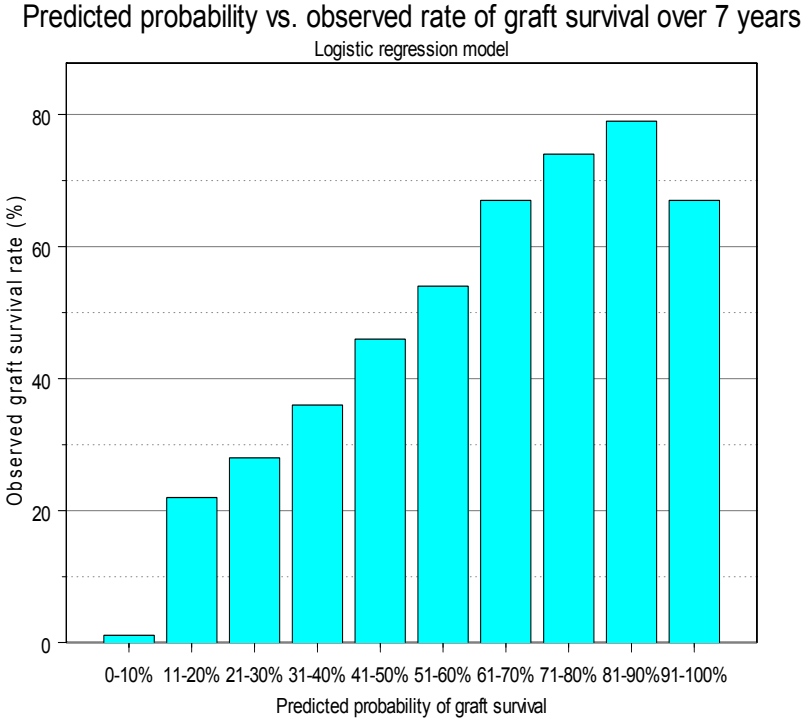


Figure 13 continued

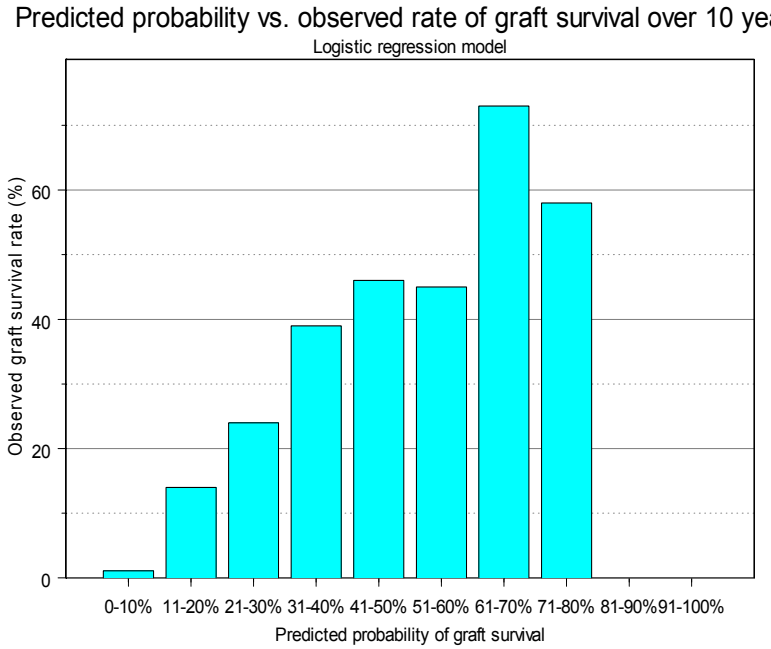


Figure 13 continued

presented in Figure 14 (the results for the regression model were very similar). The area under the ROC curve was calculated for each model using the prediction data generated on the testing dataset. All models achieved a reasonable prediction accuracy on the independent testing dataset. For 1-year prediction, the area under the ROC curve was 0.63; for 3-year prediction: 0.64; for 5-year prediction: 0.71; for 7-year prediction: 0.82; and for 10-year prediction: 0.90.

5.4. Discussion

Factors affecting kidney allograft survival were evaluated previously based on both local and national databases. Other authors attempted to generate prediction models of the transplant outcome. A neural network model was used to predict the outcome of liver transplant [57, 221] and delayed graft function after renal transplantation [51]. Multivariate modeling was employed to predict living graft recipients' creatinine based on four parameters: recipient age, BMI, creatinine clearance, and degree of relationship [222].

As far as previous studies are concerned, we found one paper in which investigators used multivariate modeling to predict the outcome of the transplantation in order to optimize deceased kidney allocation decision making in a northern Italy transplant program [112]. However, to the best of our knowledge, aside from our report in 2003 [23], no other investigators have employed working prediction models to study long-term renal allograft outcomes.

We previously presented mathematical models predicting the probability of 3-year kidney allograft survival from a deceased donor based on UNOS data [23]. That model, however, had several limitations. The model was based on the deceased donors only (as opposed to the current model based on both deceased and living donor kidney transplants), it employed a very limited set of predictors, and it was based on the

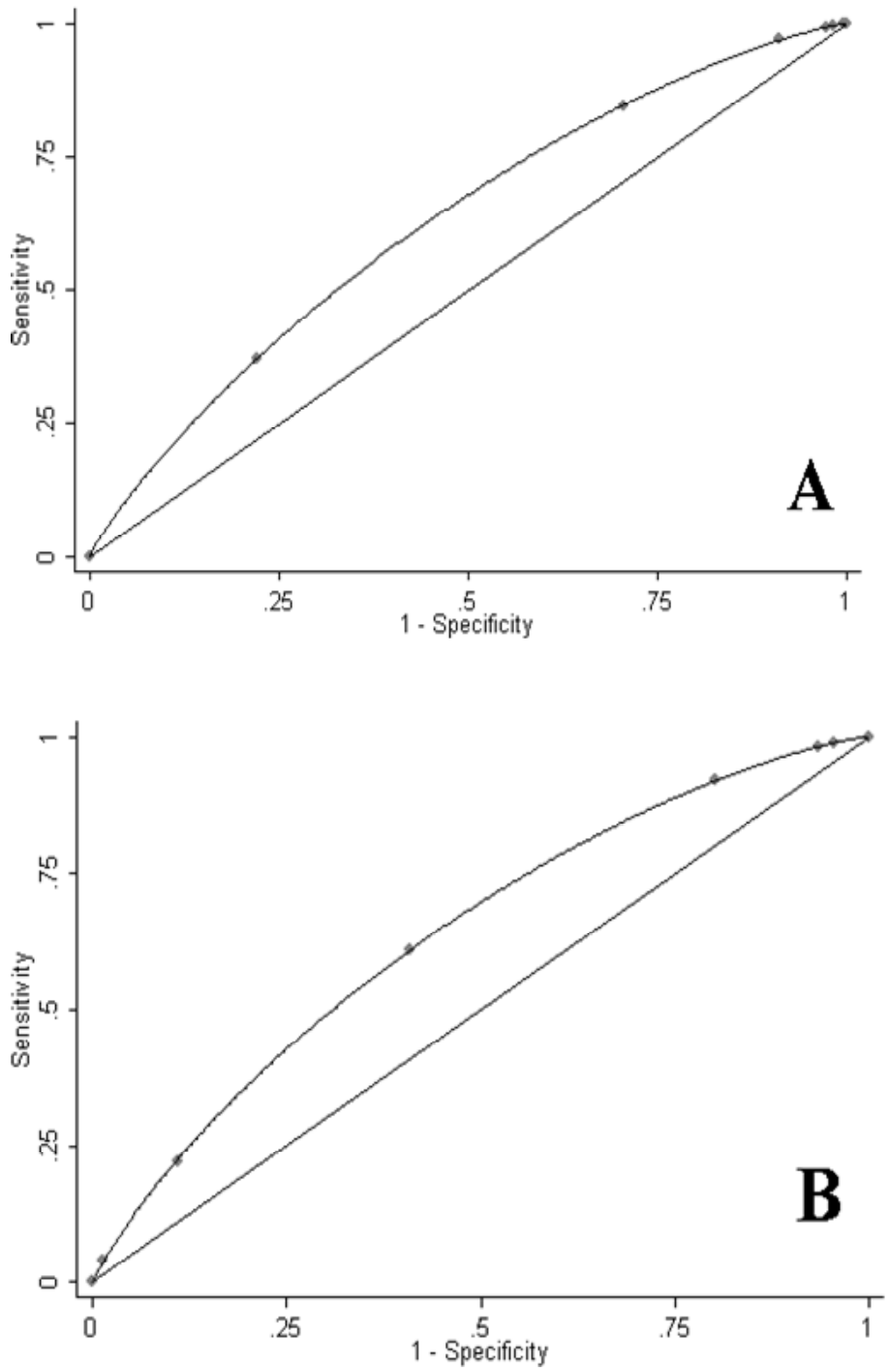


Figure 14. ROC curves for the prediction models of the one (Panel A), three (Panel B), five (Panel C), seven (Panel D), and ten (Panel E) years of graft survival. ROC curves were generated in the independent testing dataset, separate from the training dataset upon which the models were created.

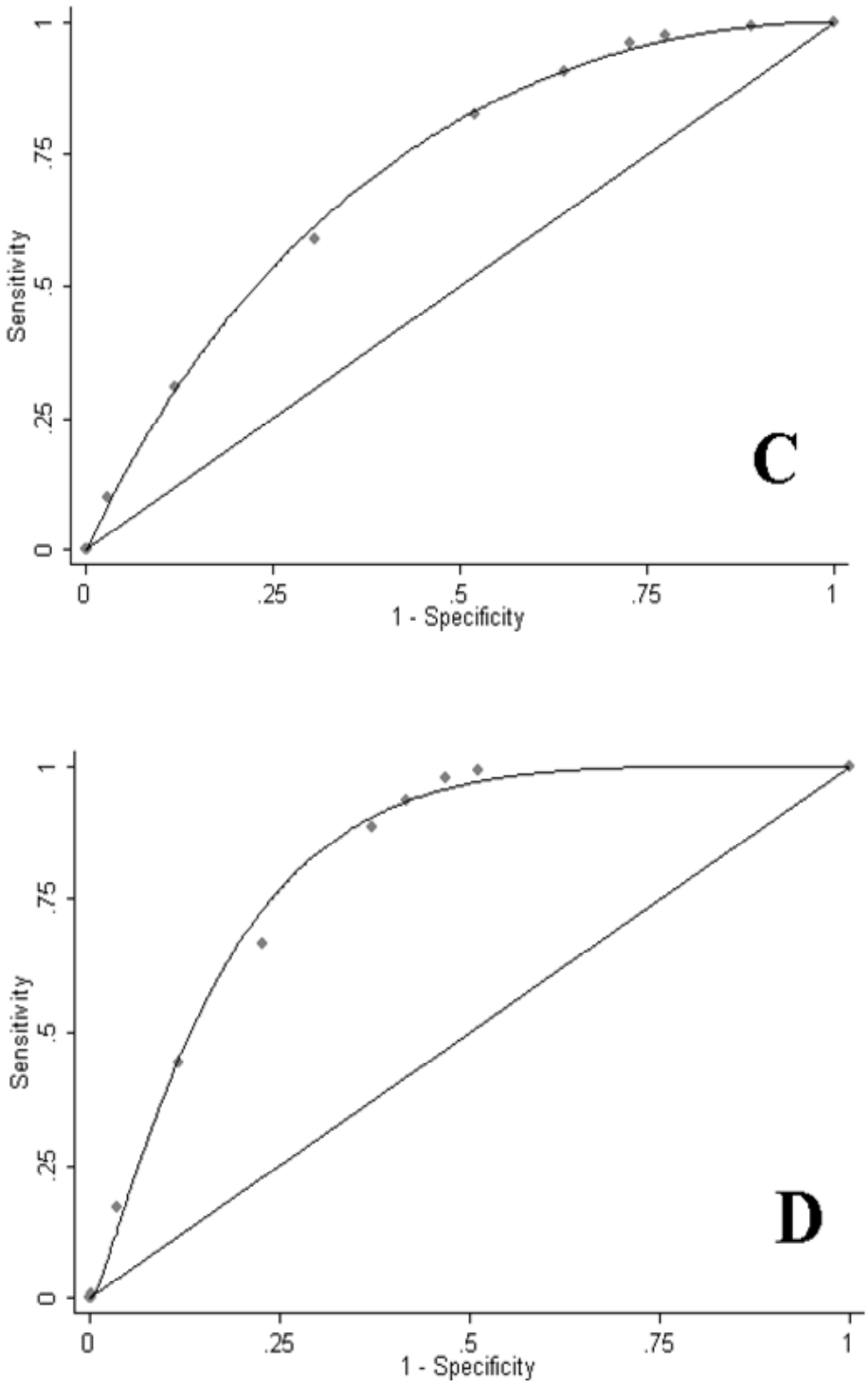


Figure 14 continued

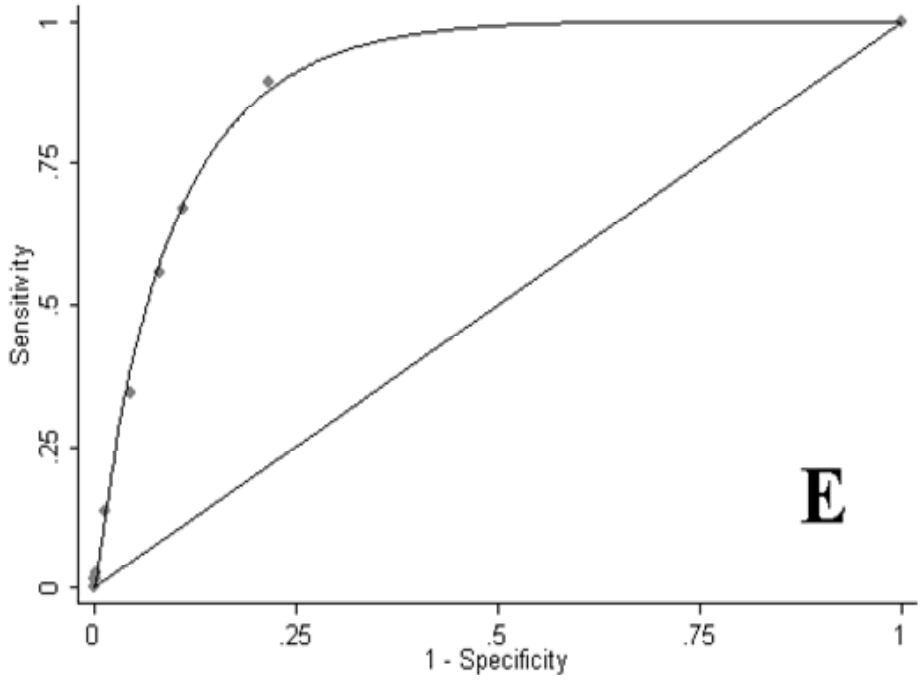


Figure 14 continued

relatively old dataset. In addition, the previously reported model predicted only 3-year allograft survival, while the currently reported model predicts the probability of 1, 3, 5, 7, and 10-year graft survival. The previous analysis was also challenging in the face of a relatively large amount of missing data. The current model is based on the more recent dataset, representing clinical practice modalities of the late 1990s. In recent years, the quality of data has improved, especially since the introduction of UNet, the online transplant data entry system, that was implemented in October 1999. In the current study, we used the data supplied by USRDS, which in addition to the UNOS data has information regarding patient dialysis course, more detailed patient comorbidity, and more comprehensive information on patients' demographics. In designing the study, our intent was to develop a prediction model to be used in the pretransplant setting; therefore, we excluded posttransplant variables that were not available until after the transplant procedure. We also did not analyze the impact of immunosuppressive therapy, immediate posttransplant graft function, and episodes of acute rejection, since this information was not available prior to the transplantation procedure.

The tree-based modeling used in this study represents a relatively new approach compared to conventional regression analysis of the data. This nonparametric modeling works when the regression variables are a mixture of categorical and continuous variables in that it identifies "splitting" variables based on an exhaustive search of all possibilities, even in problems with many hundreds of possible predictors. Simultaneously, it requires relatively little input from the analyst. This graphical algorithm, presented as a collection of simple binary rules, is much simpler to interpret by a nonstatistician than the multivariate logistic regression. Prediction algorithms evaluated in this study can potentially be used in recipient counseling and decision-making processes regarding renal transplants. Tree-based modeling is easy to implement in the computer-based decision support system to be used in the

pretransplant clinic. In addition, it can be used as a tool to identify patients at risk for premature graft failure, and to model different clinical situations, where the modifiable factors of the recipient, donor, and transplant procedures can be optimized. The identification of factors that play an important role in graft survival helps to focus efforts of transplant programs on certain individual aspects of patient care [97].

6. CONCLUSION

Predicting kidney transplant outcome based on the recipient and donor pretransplant characteristics is a first step towards personalized medicine in the management of transplant recipients. Unfortunately, these efforts are difficult to undertake due to an insufficient amount of data in any given transplant center and the unclear role of some of the potential predictors. In this project, we started with developing a pilot model of the long-term outcome prediction, and after validating the model and assessing its deficiencies, we have undertaken a series of projects to study the role of pretransplant dialysis course, socioeconomic status, immunosuppressive medications, and some other parameters in the graft and recipient survival. This knowledge and the use of new, more complete set of data allowed us to generate a more sophisticated and more comprehensive yet practical prediction model, that can be used in the future development of the decision-support system.

It should be mentioned that while different prediction models have specific advantages and disadvantages, it is difficult to predict which model would perform the best in a particular dataset. Therefore, it is reasonable to use a multimodel approach to study which model is more appropriate for a given data structure.

Certain limitations should be considered while interpreting the results of this project. The dataset used covers the time period of the last 11 years of the last century. One should realize that there will always be a time gap, the data cannot be very recent, and a certain period of follow-up is necessary. While this is the case, changes in clinical practice should be considered by the reader and potential users of the model.

Another limitation is the discrete type of the tree-based model output. While the number of terminal nodes was relatively high, the output information is still limited due to the noncontinuous nature of the predicted probability. Finally, as in every other analysis of the large registry data, the quality of the data is of concern. That concern has been alleviated, however, by the recent improvement in the UNOS data collection techniques. Also, the relatively good performance of the models indirectly indicates the reasonable quality of the input data.

This project was performed in the environment of biomedical informatics, which shaped the ultimate goal of the project to create the informatics tool potentially useful in clinical practice. Specific approaches unique to the biomedical informatics field helped to develop the tools to accomplish this goal. In particular, the initial part of the project involved manipulation of the large collection of medical data, including the combination of patient demographics, medical history, comorbidities, treatments, and outcomes. The data was reformatted, cleaned, and internally validated. Some of the variables underwent imputation of the missing values. Knowledge discovery in the databases approaches were used for initial data analysis and prediction model design. Several KDD approaches were explored in order to develop optimal prediction model and feature selection for the models. While working on this project, the final goal of improving patient care was always in sight. As results of the efforts presented here, we generated several mathematical models predicting the probability of the kidney allograft failure at different time points of the posttransplant period. Prediction models represent either regression model or recursive partitioning algorithm that can be easily coded and be used as a core for the decision support system. Other specific biomedical informatics approaches are presented in Table 10.

Table 10. Biomedical informatics aspects of this project

Project stage	**Medical informatics aspect**
Acquire data from national data registry	Medical data acquisition and manipulating large dataset, including data integration, storage, validation, formatting, imputation, and use
Data cleaning, validation, integration	
Develop preliminary prediction model	Creating the core of the decision support system Knowledge discovery in the databases
Evaluate potential predictors of the outcome	Public health and consumer use of health information
Variable selection for the prediction modeling	Machine learning techniques
Develop refined prediction model	Creating the core of the decision support system Personalized medicine Medical education using information technology Patient informatics Evaluation and technology assessment

In conclusion, we studied the role of several potential predictors in the transplant outcome and showed their association with kidney transplant outcome. Furthermore, we developed and validated a prediction model of allograft survival in patients with kidney transplants. The models predicting the probability of 1, 3, 5, 7, and 10-year allograft survival have been validated on the independent dataset and demonstrated performance that may suggest implementation in the clinical decision support system. Evaluating these models, in a prospective study, may be the subject of a future project.

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