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CLINICAL STUDY

Factors affecting eGFR 5-year post-deceased donor renal transplant: analysis and predictive model

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Abstract

Aim: Long-term survival of renal allografts has improved over the last 20 years. However, less is known about current expectations for long-term allograft function as determined by estimated glomerular filtration rate (eGFR). The aim of this study was to investigate factors which affect graft function at 5 years' post-renal transplantation. The statistically significant factors were then used to construct a predictive model for expected eGFR at five years' post-transplant. *Methods*: We retrospectively reviewed all adult patients who received a renal transplant in the Republic of Ireland between 1990 and 2004. Data collected included era of transplantation (1990–1994, 1995–1999, 2000–2004), donor and recipient age and gender, number of human leucocyte antigen mismatches, cold ischemia time (CIT), number of prior renal transplants, immunosuppressive regimen used and acute rejection episodes. Estimated GFR was calculated at 5 years after transplantation from patient data using the Modified Diet in Renal Disease (MDRD) equation. Consecutive sampling was used to divide the study population into two equal unbiased groups of 489 patients. The first group (derivation cohort) was used to construct a predictive model for eGFR five years' post-transplantation, the second (validation cohort) to test this model. *Results*: Nine hundred and seventy eight patients were analyzed. The median age at transplantation was 43 years (range 18–78) and 620 (63.4%) were male. One hundred and seventy five patients (17.9%) had received a prior renal transplant. Improved eGFR at five years' post-transplantation was associated with tacrolimus-based combination immunosuppression, younger donor age, male recipient, absence of cytomegalovirus disease and absence of acute rejection episodes as independently significant factors ($p < 0.05$). The predictive model developed using these factors showed good correlation between predicted and actual median eGFR at five years. The model explained 20% of eGFR variability. The validation model findings were consistent with the derivation model (21% variability of eGFR explained by model using same covariates on new data). *Conclusion*: The predictive model we have developed shows good correlation between predicted and actual median eGFR at five years' post-transplant. Applications of this model include comparison of current and future therapy options such as new immunosuppressive regimens.

Keywords

Allograft function, deceased donor, eGFR, kidney transplantation, predictive model

History

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Introduction

Patients with end-stage kidney disease have improved quality of life and increased overall survival after renal transplantation compared to those who remain on long-term dialysis treatment.[1] Advances in all aspects of transplantation including antimicrobial prophylaxis, surgical technique and immunosuppression regimes have significantly improved short-term renal allograft outcomes.[2,3] However, improvements in long-term outcomes have been more modest. A predictive model for long-term allograft function would be very useful in that it would provide important prognostic information.

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Several clinical factors such as recipient and donor age, the donor and recipient cytomegalovirus (CMV) disease, presence of acute rejection episode and estimated glomerular filtration rate (eGFR) at one year have been reported to be predictors of the long-term survival of renal allograft.[4,5] The purpose of this study was to examine in more detail the influence of pretransplant clinical factors on long-term (5-year) function of deceased donor kidney transplants and to develop a model to predict eGFR based on significant pretransplant factors and to validate this model.

Patients and methods

Patients

This study was a retrospective analysis of all adult deceased donor renal transplants performed in Beaumont Hospital

between January 1990 and December 2004. Beaumont Hospital is the national renal transplant centre for the Republic of Ireland. The centre has performed an average of 135 renal transplants per annum over the last 20 years. Patients who underwent primary or repeat deceased donor renal transplantation during this period were included in the study. Exclusions from the study were recipients less than 18 years and simultaneous kidney–pancreas transplants. The data was collected from the Irish Renal Transplant Registry.

The maintenance immunosuppression used in the study period was Cyclosporine (4 mg/kg twice daily) with maintenance trough level of 120–180 ng/mL 6 months post-transplant, Azathioprine (2 mg/kg once daily), Tacrolimus (0.1–0.2 mg/kg/day in two divided doses) with trough level 5–8 ng/mL 3 month post-transplant, Mycophenolate Mofetil (1.5–2.0 g daily) and Prednisolone with maintenance dose of 2.5–5 mg daily. The main induction therapy used was intravenous methylprednisolone 500 mg daily for 3 days, ATG (Anti-Thymocyte Globulin) which was only used for high risk patients (recipients with higher percentage of generated PRA) and Basiliximab which was introduced in 2004.

The study population was divided into three eras according to the time of transplantation (1990–1994, 1995–1999 and 2000–2004). We analyzed the influence of clinical and demographic factors on eGFR at 5 years' post-transplantation. Of the patients transplanted a total of 978 transplants were functioning after 5 years and the eGFR of each transplanted patient was recorded. eGFR was calculated using the Modified Diet in Renal Disease (MDRD) equation.[6] eGFR was chosen as it has been shown to be a more accurate indication for future graft function and survival than serum creatinine levels alone.[7,8]

MDRD equation was utilized for this analysis as it remains the most widely utilized equation for the estimation of GFR in clinical practice across the world. However, it has certain limitations and its reliability and accuracy decreases in extremes of GFR like in healthy adult and patients on dialysis. Also variation in muscle mass or diet may underestimate GFR using MDRD equation.

Predictors

The demographic and peri-transplant factors studied were era of transplantation, age and sex of recipient and donor, time spent on dialysis prior to transplantation, number of prior transplants, panel reactive antibody status (PRA), cold ischemia time (CIT) and human leucocyte antigen (HLA) mismatching. Post-transplant factors assessed were the immunosuppression regimen, presence or absence of delayed graft function, acute rejection (defined as biopsy proven acute cellular rejection within 3 months post transplant) and CMV disease (defined as active CMV disease for which the individual was receiving intravenous ganciclovir as treatment).

Statistical analysis

Consecutive sampling was used to select two equal groups of 489 patients. A derivation group was used to determine clinical variables that significantly affected eGFR at 5 years' post-transplant. A validation group was used to repeat this exercise to confirm significant clinical variables. A test predictive model was developed based on the significant variables and tested using the validation group patients. Consecutive sampling was based on date of transplant and recruitment into the two groups was determined by alternately grouping successive transplants. Patients transplanted on the same day were randomly chosen to be in each group. This procedure was considered the most practical and efficient means of sampling compared to a computer generated ''pseudo'' random sample.

Wilcoxon Rank sum tests and Pearson Chi squared tests were used to compare demographic variables in the derivation and validation cohorts. The Kaplan Meier method determined survival outcomes and a log rank test was used to compare survival outcomes between eras. Log of eGFR at 5 years was modeled using analysis of variance (ANOVA) on various influential variables mentioned above. Variability of the model (model sum of squared) was compared with the variability of the residuals (residual sum of squares). Corrections to the sum of squares totals were made according to the degrees of freedom (DF) to obtain the mean sum of squares. The extent to which the model explained the eGFR variability was determined with the corrected *R*-squared statistic where correction in this case was for the number of variables used in the model. A parsimonious set of predictors of eGFR at 5 years was derived using stepwise backwards regression. Adjusted *R* squared determined the variability of eGFR outcome that is attributable to the model covariates. Software used was Stata, version 10 (College Station, TX). A p value < 0.05 was deemed to be significant.

Results

Baseline characteristics

Between January 1990 and December 2004 there were 1975 renal transplants performed. Demographic detail of overall patients and the two patient cohorts were recorded and presented in Table 1. The derivation and validation cohorts were similar at baseline.

Graft survival

Overall graft survival in the study population at 1 and 5 years post-transplant was 89% and 74%, respectively. For eras 1–3 the rates were 86%, 88% and 92% for 1-year graft survival and 69%, 72% and 81% for 5-years graft survival. There was a significant difference in graft survival between different eras ($p < 0.001$; Figure 1). Causes of original end-stage kidney disease are presented in Figure 2.

Model derivation

Factors significantly affected eGFR at 5 years were donor age ($p < 0.001$), recipient sex ($p = 0.001$), episodes of acute rejection ($p = 0.006$), CMV disease ($p = 0.016$) and immunosuppression regimen used. Tacrolimus-based regimen compared to cyclosporine-based immunosuppression regimen was significantly associated with improved eGFR at follow-up ($p = 0.015$; Table 2). The difference in eGFR at 5 years post-transplant for categories of the significant

Table 1. Demographic results of predictive and test model cohorts.

Variable	Overall	Group1 (Derivation cohort)	Group 2 (Validation cohort)	*p* Value
eGFR at 5 years post-transplant	49.6 [36.9–60.9]	49.5 [37.3–61.8]	49.9 [36.6–60.2]	0.676
Recipient age	43 [32–53]	42 [32–53]	43 [33–53]	0.344
Donor age	36 [21–47]	34 [21–47]	37 [22–47]	0.379
Recipient sex M/F	63/37	64/36	63/37	0.894
Donor sex M/F	60/40	61/39	59/41	0.701
Time on dialysis (months)	16.7 [9.8–27.8]	16.7 [9.67–29.1]	16.8 [10.2–27.3]	0.796
Diabetes as primary ESRD	4.3	3.7	4.9	0.344
Transplant number >1	17.9	17.8	18	0.861
CIT (h)	20 [18–24]	20 [18–24]	20 [18–24]	0.947
PRA group[a]	75/13/12	75/15/10	76/11/13	0.169
Number HLA mismatches	3 [2–4]	3 [2–3]	3 [2–3]	0.58
Haemodialysis/peritoneal dialysis/pre-emptive	64/34/2	66/32/2	62/35/3	0.458

Notes: Patients were divided into two groups using alternating consecutive sampling.
[a]0–10%, 11–49%, 5–100%. Median [Interquartile range] used for continuous variables, percentages used for categorical variables.

Figure 1. Graft survival 5 years post-transplant by era.

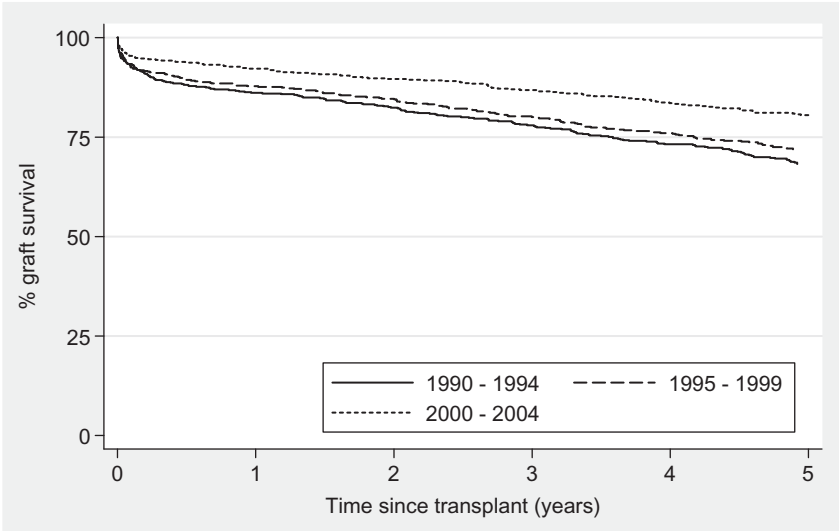
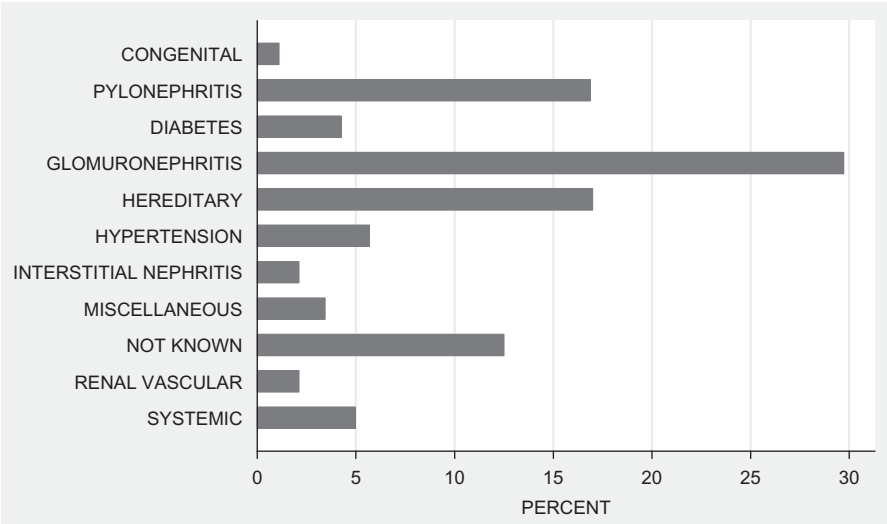


Figure 2. Causes of end stage renal disease in transplant recipients.



variables is presented in Figure 3. A prediction model comprising these significant variables explained 20% of the variability of eGFR at 5 years post-transplant (adjusted $R^2 = 0.1998$ Table 3).

Model validation

A reduced derivation model was used to predict variability of eGFR at 5 years in the validation cohort. This validation cohort produced similar results to the derivation cohort. All of

the variables were significant, apart from CMV disease ($p = 0.115$; Table 4 adjusted R^2 was 0.2052 or 21% of variability predicted by model). A comparison of predicted and actual eGFRs is presented by era of transplantation in Figure 4.

Table 2. ANOVA model for derivation cohort.

Source	*F* distribution	*p* Value
Model	4.93	<0.001
Era	1.47	0.232
Recipient age	1.29	0.266
Recipient sex	10.22	0.001
Donor age	11.95	<0.001
Donor sex	0.11	0.735
Number of HLA mismatches PRA group	0.55	0.77
Delayed graft function	1.58	0.206
Transplant number	1.76	0.185
Diabetes as primary cause of ESRD	0.76	0.517
Acute rejection	0.31	0.579
Tacrolimus use[a]	7.64	0.006
CMV disease	5.9	0.015
Residual	5.78	0.016

Note: [a]As primary immunosuppression therapy compared to cyclosporine.

Discussion

Since the first report on renal transplantation in 1955, there has been a continuing effort to improve the short- and long-term survival of renal transplants.[9] In this study we focused on clinical factors at the time of transplantation (and early post-transplant period) that could potentially affect eGFR at five years and have an impact on long-term survival of the graft. The factors chosen have been shown to be useful in the prediction of graft function over shorter periods of time.[10]

The overall graft survival seen in our transplant population compares favorably with international data. This centre is the national transplant centre which performs all renal transplants in Ireland. This gives us large numbers to analyze in a study. Furthermore, patient management is uniform according to single centre management guidelines. These qualities allow for better assessment of factors effecting eGFR at 5 years and also easy extrapolation of our results to other centers.

Advanced donor age, in our study, was found to be associated with low eGFR five years post-renal transplantation. Studies have also identified advanced donor age as a risk factor for delayed graft function (DGF), which is an independent predictor of late graft outcome and graft failure.[11] An increase in the donor's age is also found to be associated with a greater incidence of chronic allograft

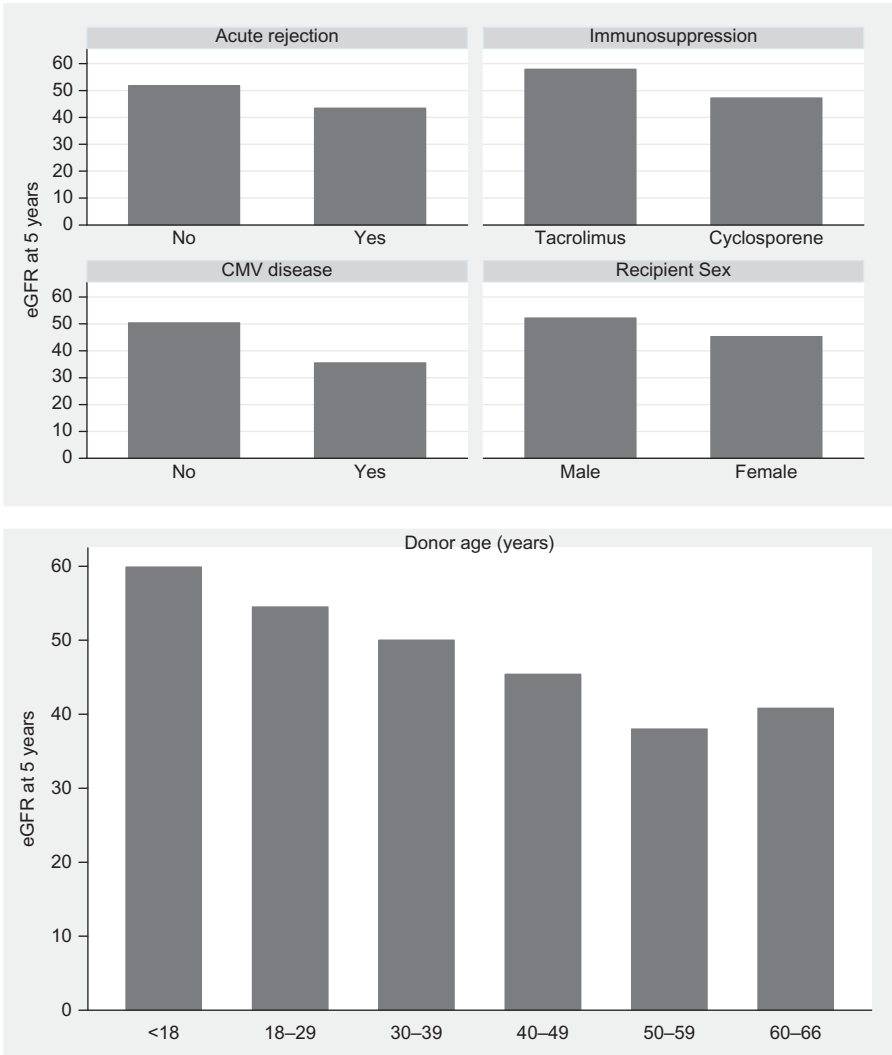


Figure 3. Factors related to eGFR at 5 years post-transplant.

nephropathy (CAN) and worst graft survival.[12] Cytomegalovirus (CMV) is the single most important infectious agent in kidney allograft recipients and is a major source of morbidity.[13] CMV infection and disease were found to be independent risk factors for clinical acute rejection during the first 100 days post-transplantation.[14,15] The impact of early CMV infection and disease on long-term outcome after transplantation remains controversial.[16–18] In this study we show that CMV disease has a significant effect on eGFR 5 years post-transplant. However, whether it has an effect on long-term graft survival remains unknown.

Tacrolimus, as an independent factor from acute rejection, was also shown to positively impact long-term graft function. Interestingly when immunosuppressive agents were compared, use of tacrolimus was associated with the higher median eGFR at 5 years post-renal transplantation (56.2 compared to 47.2 for cyclosporine-based regimen). The era effect was not independently significant when immunosuppression was added to the model as in Table 2, although median eGFR in the early 1990s, when tacrolimus was not widely used was 45.6 (transplant era 1990–1994). This median value improved to 54.8 once tacrolimus became more widely used (era 2000–2004) which is shown in Figure 4.

Table 3. Reduced ANOVA model for derivation cohort.

Source	*F* distribution	*p* Value
Model	14.04	<0.001
Recipient sex	11.84	<0.001
Donor age	12.45	<0.001
Acute rejection	11.22	<0.001
Tacrolimus	27.51	<0.001
CMV disease	8.13	0.005

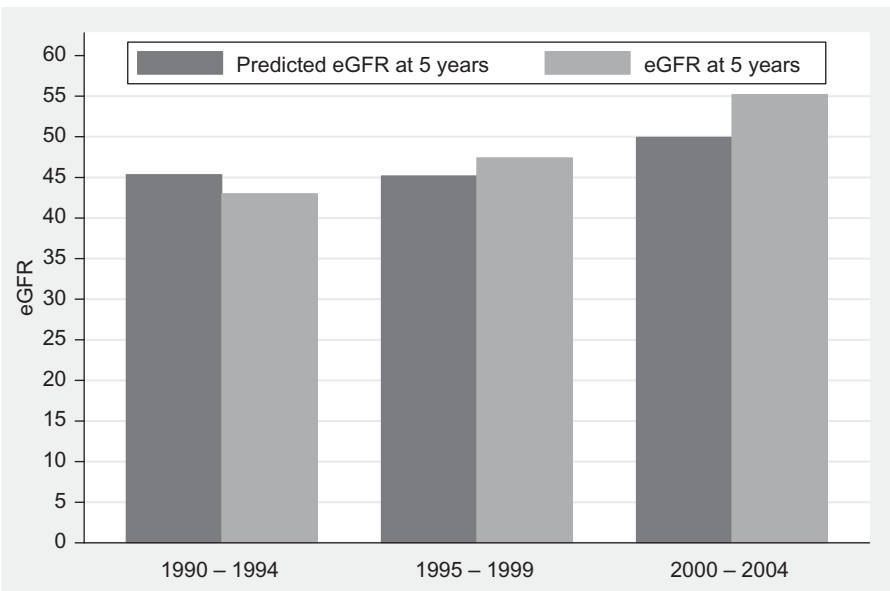
Table 4. ANOVA model for validation cohort.

Source	*F* distribution	*p* Value
Model	14.74	<0.001
Recipient sex	41.61	<0.001
Donor age	13.8	<0.001
Acute rejection	7.64	0.006
Tacrolimus	21.38	<0.001
CMV disease	2.5	0.115

Occurrence of acute rejection in this study was also identified as a factor that affects eGFR at 5 years post-transplant. In previous studies acute rejection has been shown to be one of the strongest negative prognostic factors for long-term graft survival after kidney transplantation.[19–23] These studies implied that a reduction in early acute rejection rates would lead to improvements in long-term graft survival.[17] It is worth noting that delayed graft function and CIT in this study did not show any statistically significant effect on graft function at 5 years post-transplant. This would suggest the effect of delayed graft function was reduced over the period of the study as it is known to affect function and survival over shorter periods of follow-up.[24] It has also been shown that histological damage done due to delayed graft function and CIT does not have a lasting effect on function.[25] CITs of the patients included in the study showed relatively minimal variance between groups which could account for its lack of influence.[26]

Currently there is increasing demand for kidney transplantation. This has led to an increased use of expanded criteria donors, which include all donors older than 60 years and donors older than 50 years with any two of the following criteria: hypertension, cerebrovascular cause of brain death, or terminal serum creatinine (SCr) level >1.5 mg/dL. Our predictive model can be used to guide organ allocation strategies. This model can be utilized to predict eGFR at 5 years. For example, eGFR at 5 years for a male recipient with donor age <18 years, who had no CMV disease, no acute rejection episode and had tacrolimus-based immunosuppression is predicted as 71.9 mL/min. Whereas eGFR at 5 years for a female recipient with donor age >50, who had an acute rejection episode, CMV disease and received cyclosporine-based immunosuppression is predicted to be 23.7 mL/min.

Figure 4. Pedicted and actual eGFR at 5 years per era.



The application of similar predictive models using other parameters to assess the benefit of novel therapies has been attempted over shorter time periods.[27]

Overall models predicting graft function over one year using histological criteria have also been tested and shown to have poor correlation to actual function at one year.[28] The authors believe that the inclusion of further factors not specifically linked to transplantation may increase accuracy to a suitable level. Gjertson[29] and Ortiz et al.[30] demonstrate the distinct influence of factors such as systolic and diastolic blood pressure, hyperlipidemia and glycemic control on both graft function and survival. With the inclusion of these factors a practical predictive model for five year follow-up may be possible but would require further study – Anglicheau et al.[31] came to a similar conclusion using histopathological factors in marginal donors.

Our study has several limitations. It has limitations inherent to any single centre study. Also there may be other clinical factors, such as donor cause of death, which we have not included in our predictive model, but are known to influence kidney transplant outcomes. The model does not incorporate other post-transplantation variables that have the potential to impact on long-term graft function such as blood pressure control and post-transplant diabetes.

Conclusion

The advancements in the management of deceased donor renal transplant recipients over the last 20 years have led to marked improvement in transplantation outcomes. This is due in part to reduced episodes of acute rejection and improved graft function. Combination immunosuppressive therapy including tacrolimus as opposed to cyclosporine shows a clear benefit at five years in allograft function. Finally, the development of a predictive model for graft function at five years' post-transplantation is a potentially fruitful endeavor, but improvements in the accuracy of such a model would be required through the addition of further criteria.

Declaration of interest

The authors of this manuscript have no conflicts of interest to disclose.

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