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C. Zapletal
M. W. Lorenz
G. Woeste
C. Wullstein
M. Golling
W. O. Bechstein

Predicting creatinine clearance by a simple formula following live-donor kidney transplantation

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C. Zapletal · M. W. Lorenz
G. Woeste · C. Wullstein · M. Golling
W. O. Bechstein (✉)
Department of Surgery,
Knappschaftskrankenhaus Bochum-Langendreer, Ruhr-University,
In der Schornau 23–25,
44892 Bochum, Germany
E-mail: Wolf.Bechstein@kgu.de
Tel.: +49-69-63015251
Fax: +49-6963017452

W. O. Bechstein
Department of Surgery,
Johann Wolfgang Goethe-University
Frankfurt, Frankfurt am Main, Germany

Abstract The outcome after live-donor kidney transplantation is influenced by many parameters. The aim of our study was to establish a multivariate prognostic model for calculating the recipient's creatinine clearance after transplantation. Basic immunological, donor-, recipient- and process-related variables were assessed in a series of 18 live-donor kidney transplant patients with an uncomplicated postoperative course. Multivariate analysis was carried out with automated forward and backward selection. The following four parameters were included in the predictive model: recipient age, recipient BMI, graft clearance and degree of relationship. The coefficient of determination (R^2) was 0.67. It could be shown that a significant prediction of creatinine clearance after living related kidney transplantation can be made, based on simple variables. Therefore, this formula could help to detect early complications in the post-transplantation course if the recipient's creatinine clearance drops below the predicted result.

Keywords Live-donor kidney transplantation · Kidney graft function · Donor and recipient variables · Immunological risk factors · Multivariate analysis · Outcome

Introduction

The outcome after kidney transplantation is influenced by many variables, which are thought to interact in a complex manner. These variables can be divided into immunological and non-immunological factors. They include donor and recipient characteristics and depend on procedure settings. As live-donor kidney transplantation is an elective procedure, some of those factors can be better controlled. Graft procurement and transplantation are precisely planned so that preservation and ischaemia time can be kept as short as possible. Furthermore, pre-emptive immunosuppressive treatment may be introduced to reduce the incidence of rejection episodes.

Nevertheless, immunological risk factors such as HLA-mismatch and degree of relationship may play a role in the outcome [1, 2, 3]. Furthermore, functioning nephron mass of the graft and donor/recipient weight ratios [4, 5, 6, 7, 8], as well as age, [9, 10, 11] have been described as important predictors of graft function. Therefore, outcome after live-donor kidney transplantation is not always as good as expected and can, additionally, be impaired by complications in the postoperative course. The aim of our study was to establish a multivariate prognostic model for calculating

the recipient's creatinine clearance after identification of essential donor and recipient variables.

Materials and methods

We carried out 22 live-donor kidney transplantations between October 2000 and March 2002, which were analysed retrospectively. Of them, four were excluded due to postoperative complications (three rejection episodes and one recurrence of original disease). The underlying disease in the remaining 18 patients included glomerulonephritis ($n=10$), congenital malformation of the urinary tract ($n=4$), recurrent pyelonephritis ($n=2$), progressive arteriosclerosis ($n=1$), and haemolytic uraemic syndrome (HUS; $n=1$).

Before transplantation the direct cross-lymphocytic match was checked twice and was negative. All donors and recipients were operated on by the same surgeon and received the same immunosuppressive regime. Induction therapy consisted of methylprednisolone and antithymocyte globulin. Immunosuppression was maintained by triple-drug therapy with prednisolone, tacrolimus (trough level 10–15 ng/ml) and mycophenolate mofetil (2 g/day).

In order to develop a multivariate predictive model for calculating the recipient's creatinine clearance (CrCl) we included the following variables in the analysis: age, gender and BMI of both donor and recipient, and creatinine clearance of the graft ($CrCl_{graft}$) as well as ischaemia time, HLA mismatch and the "degree of relationship".

Creatinine clearance was calculated with the Cockcroft–Gault formula. Creatinine clearance of the graft was defined as the product of the recipient's CrCl and the proportion of global renal function as given by renal scintigraphy. The variable "degree of relationship" differentiated between living unrelated, parent–offspring and sibling transplants.

The objective of the resulting formula was to predict what we called the "plateau CrCl". CrCl of the recipient was recorded at 1- to 2-week intervals, starting at the time of discharge [postoperative day (POD) 21 ± 4]. The median CrCl over the first 3 months after transplantation (79.3 ± 22.2; 47.41–126.14 ml/min) was named "plateau CrCl". By then, we should have eliminated the early fluctuations of the post-transplantation creatinine levels that result from ischaemia/reperfusion, changes of body hydration and variations in the tacrolimus trough level.

Statistics

Calculations were made with SAS statistical software package version 8.2. In a multiple linear regression model the most important variables were sought by means of automated parameter selection with two different methods: forward selection, with an entry criterion of a P value less than 00.5, and backward selection, with an exclusion criterion of a P value greater than 00.1.

Forward selection is based on an algorithm that starts with an empty ("zero") model and adds the best additional covariate factors in a stepwise fashion, as long as it fulfils the entry criterion. The backward-selection algorithm, in contrast, starts with a complete model (with all covariates included) and involves the stepwise removal of the worst factor, as long as the exclusion criterion is met. To avoid "over-fitting" of the model, we restricted the number of parameters to four. Model prerequisites of the final model (normality of parameters and residuals, linearity) were tested by means of qq-plots and residual plots. The model's quality was reported as coefficient of determination (R^2) and graphically demonstrated by the plotting of observed against predicted "plateau CrCl".

Results

To characterise our study cohort, we gave all included parameters as means ± standard deviation and as range (Table 1). Univariate analyses between the target variable and the chosen parameters are shown in Table 2. Figure 1 shows the degree of relationship among our patients.

The univariate analysis showed significant correlation between the "plateau CrCl" and graft clearance, as well

Table 1 Variables included in the analysis

Parameter	Mean ± SD	Range
Donor age (years)	46.9 ± 11.2	27–64
Recipient age (years)	38.6 ± 15.7	16–64
Donor BMI (kg/m^2)	25.7 ± 3.5	19.9–33.9
Recipient BMI (kg/m^2)	24.4 ± 3.5	19.2–30.5
Cold ischaemia time (min)	207.17 ± 36.25	133–249
Plateau $CrCl_{Recipient}$ (ml/min)	79.3 ± 22.2	47.41–126.14
CrCl of donor before donation (ml/min)	104.43 ± 29.25	63.19–173.5
Scintigraphic proportion of renal function of the graft (%)	49 ± 3.8	39–55
CrCl of the graft (ml/min)	51.2 ± 15.4	29.1–90.2

Table 2 Univariate analysis: Pearson correlation between "plateau" CrCl and all variables included in the analysis. Significant correlation between "plateau" CrCl/donor BMI and "plateau" CrCl /CrCl of the graft

Parameter	Correlation coefficient (R)	*P*
Donor age (years)	−0.38	0.12
Recipient age (years)	−0.382	0.118
Donor BMI (kg/m^2)	**0.582**	**0.024**
Recipient BMI (kg/m^2)	0.238	0.342
Cold ischaemia time (min)	0.012	0.963
CrCl of the graft (ml/min)	**0.536**	**0.022**
Parent–offspring transplants	−0.142	0.574
Sibling transplants	0.078	0.757
Unrelated transplants	–	–
HLA mismatch	−0.112	0.658

as between "plateau CrCl" and donor BMI. The latter was not included in the multivariate model, but donor weight contributes to the calculation of creatinine clearance according to the Cockcroft–Gault formula.

In the multivariate analysis the automated forward and backward selection confirmed that recipient age and BMI, graft clearance and parent–offspring transplants were among the four most important parameters. From this model the following formula for recipients' plateau CrCl was constructed (Table 3):

$\mathbf{CrCl_{recipient} = 52 - 0.26 \times graft\ clearance - 1.4 \times age_{recipient} + 3.1 \times BMI_{recipient} - 28 \times degree\ of\ relationship}$ with the following parameter definition and units:

graft clearance = $clearance_{donor}$ × scintigraphic proportion of global function of the graft (ml/min), age (years), BMI kg/m^2. The degree of relationship is equal to 1 in the case of a parent–offspring transplant and zero in the case of a sibling or unrelated-donor transplant.

The quality of this prognostic model is satisfactory ($R^2 = 0.67$). Residuals are normally distributed. Residual plots showed good linearity between the extracted parameters and the target variable. In Fig. 2 the observed "plateau CrCl" is plotted against the predicted values. The model we chose is not intended to clarify pathophysiological aspects ("explaining model") but to predict the outcome ("predictive model").

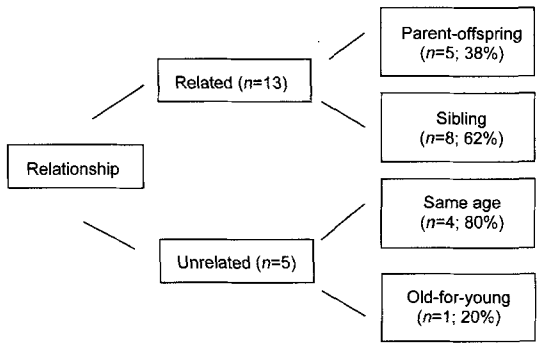

Fig. 1 Relationship and age of donor–recipient pairs

Table 3 Best prognostic model resulting from multivariate analysis. Graft clearance = $CrCl_{donor}$ × scintigraphic proportion of global function of the graft (ml/min). CrCl was calculated with the Cockcroft–Gault formula

Parameter	Regression coefficient	Standard error	*P*	R^2 contribution
Constant	52	30	0.1064	–
Graft clearance	0.26	0.27	0.3569	0.2868
Recipient age	−1.4	0.37	0.0020	0.1335
Recipient BMI	3.1	1.3	0.0276	0.0977
Parent	−28	11	0.0262	0.1549
Global	–	–	0.0038	0.6729

Discussion

In contrast to the complexity of contributing factors mentioned above, this new formula allows for the direct calculation of early graft function after live-donor kidney transplantation. All the included variables are well known as risk factors in kidney transplantation. However, as the model was chosen with predictive intention, the contribution to pathophysiological aspects might be limited.

First of all, the quality of the graft is of major importance with regard to outcome after transplantation. Creatinine clearance, in a multivariate analysis, has

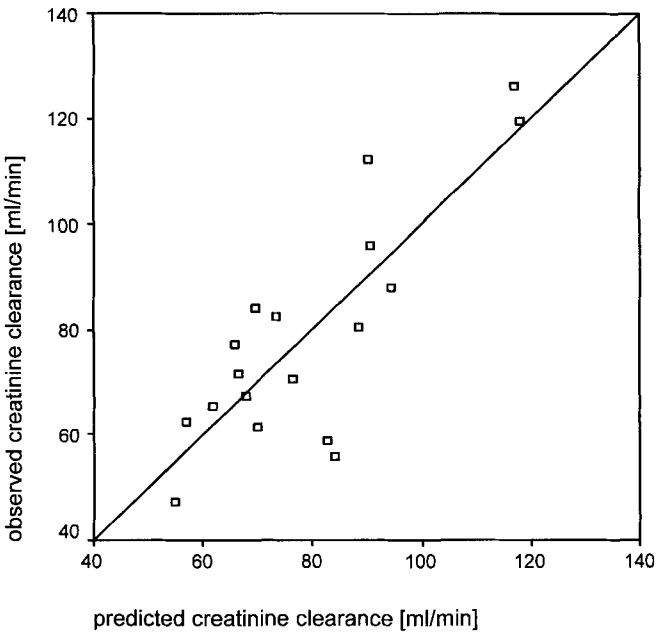

Fig. 2 Observed CrCl of the recipient ("plateau") vs predicted values

been shown to have a great impact on renal graft function after cadaveric kidney transplantation [5]. With ageing, the number of functioning nephrons decreases, and progressive arteriosclerosis limits the functional capacity of a kidney [4, 12]. Therefore, the calculated creatinine clearance (Cockcroft–Gault formula) is a more precise parameter for determination of kidney function than is serum creatinine, as recipient age and gender are additionally entered into the formula. In our series the proportion of global donor kidney function, as assessed by renal scintigraphy, was taken into account, additionally, in order to describe precisely the functional capacity of each single graft. This graft clearance showed the best results in respect of the predictive value in several models when compared with serum creatinine or creatinine clearance of the donor (data not shown).

Differences in metabolic requirements between donor and recipient, expressed as a mismatch in weight or body surface area, influence the serum creatinine after transplantation [7, 8]. In our formula this is taken into consideration, as the BMI of the recipient is included as one important factor predicting creatinine clearance after transplantation. Including donor and recipient BMI as separate parameters showed better results in different models than choosing the weight or calculating for any BMI or weight ratios.

With regard to age, the recipient's age was selected among the four essential parameters that build the predictive model. Donor age is indirectly included, as this variable is part of the Cockcroft–Gault formula for calculation of "graft clearance".

Recipient age has been shown to influence long-term graft survival [10] and the development of chronic allograft nephropathy [11]. Older recipients are more likely to suffer from an accompanying disease such as high blood pressure, ischaemic heart disease, or arteriosclerosis and may have different pharmacokinetics from immunosuppressive drugs. Those factors might even influence the creatinine clearance in the early postoperative course after live-donor kidney transplantation.

Among immunological factors, HLA mismatch and degree of relationship were included in the analysis. In our cohort HLA mismatch was not selected in the predictive model. The significance of HLA mismatch in living-donor kidney transplantation is controversial. While Terasaki et al. [13] emphasised that short ischaemia times could eliminate the effects of HLA mismatching, Opelz [1] stressed the impact of HLA compatibility on long-term survival. In our multivariate analysis other variables seem to be of higher importance.

To analyse the importance of relationship we firstly only differentiated between related and unrelated transplants and found a negative effect for related transplantations. Further analysis revealed that this was due to the number of parent–offspring transplants when the grafts were generally older [2]. Sibling and unrelated transplant patients, when the donors belonged to the same generation as the recipients, did better in the postoperative course (Table 3).

As expected, ischaemia time has not been extracted as one of the important variables in live-donor kidney transplantation. Whereas the influence of cold ischaemia time in cadaveric kidney transplantation is widely accepted, ischaemia time is kept as short as possible in living-related transplantation. This might be of special benefit with regard to the use of grafts from older donors [9].

Despite the fact that this multivariate analysis was done retrospectively and is based upon a small population, the coefficient of determination is sufficiently high. This study confirms that a variety of interacting parameters is responsible for the outcome after live-donor kidney transplantation. Nevertheless, a small number of simple donor and recipient parameters seems sufficient for predicting the outcome to a reasonable degree.

We suggest that the use of this formula, for a kidney transplant recipient, could probably help us to detect early complications after living-related kidney transplantation if the recipient's creatinine clearance drops beneath the predicted result.

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