Nomogram That Predicts Graft Survival Probability Following Living-Donor Kidney Transplant

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Abstract

Objectives: **The goal of this project was to develop a nomogram that predicts the probability of graft survival at 5 years.**

Materials and Methods: **From our dataset, 1581 patients were used to construct a nomogram (modeling group), the remaining 319 patients (testing group) were used for its validation. Initially, the modeling group variables were correlated with graft survival by univariate analysis. Significant factors were subjected to a multivariate analysis using a Cox regression model. The results formed the basis of our nomogram construction. Internal validation was done first by discrimination using the concordance index. Second, the calibration was assessed graphically. And finally, for external validation, the nomogram was used to predict graft survival using the testing group. The predicted probability(s) was compared with the actual survival estimates.**

Results: **Validation of the nomogram yielded a concordance index of 0.77, and the observed correspondence between predicted and actual outcomes suggested a high level of calibration. Nomogram predictions of the testing group revealed no differences in the means of predicted and observed graft survival at 5 years, with a high correlation coefficient and accepted predictive accuracy (concordance index, 0.72).**

Conclusions: **We developed a well-validated and reasonably precise nomogram for predicting 5-year graft survival.**

Key words: *Renal transplantation, Prognostic model, Prediction, Regression modeling, Prognostic tools*

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Various methods have been developed to predict outcomes after the treatment of several diseases. These included nomograms, artificial neural networks, classification and regression tree analyses, and risk group stratification models (1-3).

The ability to evaluate each variable as a continuous variable provides a great advantage over categorical models, because many prognostic factors do not necessarily demonstrate a threshold effect. Simultaneous evaluation of these variables, all of which have an association with the desired outcome, is a major advantage of nomograms. Nomograms are a graphic representation of a statistical model that incorporate multiple continuous variables to predict a patient's risk of developing a specific endpoint (recurrence, survival, complications) (4). Each variable is assigned a scale of points according to its prognostic significance. The total score for all the variables is converted to an estimated probability of reaching the endpoint (5).

We developed a nomogram to predict the probability of 5-year graft survival after transplant in the living-donor setting.

Material and Methods

Patient population

Between March 1976 and June 2007, 1900 consecutive living-donor kidneys were transplanted at the Urology & Nephrology Center in Mansoura, Egypt. For recipients, our exclusion criteria included sensitization with a positive lymphocytotoxic crossmatch, recent malignancy, addiction, psychiatric disorders, type 1

diabetes mellitus, and significant extrarenal organ failure (pulmonary, hepatic, and cardiac). Absolute contraindications to donation included active infections, diabetes, any renal function impairment, arterial hypertension, and positive serology for hepatitis B or C viruses. There were 1564 related donors and 336 unrelated donors, including 118 spouses.

Of this group, 1581 patients were used for knowledge acquisition and model construction (modeling group). Patients who had received transplants between January 1992 and December 1995 (319 patients) were not included but were used later as a testing group for external validation of the constructed model. Graft loss was defined either as graft failure or a patient's death.

All protocols, experimental studies, and clinical trials in the study were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all patients.

Statistical methods

The probability of graft survival was calculated using the Kaplan-Meier method. Univariate analyses were done to correlate graft survival with various preoperative, operative, and postoperative variables. Differences were determined by the log-rank test. A *P* value of less than .05 was considered statistically significant. Significant factors were further analyzed using the Cox proportional hazards regression model to determine those that act independently. For this purpose, we used SPSS software (Statistical Product and Services Solutions, version 11.0, SPSS Inc, Chicago, IL, USA). The prediction error was calculated with the following equation:

$$\text{Prediction error} = \sqrt{\left(\frac{\text{Predicted data} - \text{Observed data}}{\text{Observed data}}\right)^2}$$

Construction of the model

The results of the multivariate analysis were used to build up the nomogram. To this end, the R software package version 2.5.1 was used (The R Foundation for Statistical Computing, Bell Laboratories, Lucent Technologies, USA, including Frank Harrel's Design and Hmisc libraries). Each variable was assigned a scale of points according to its prognostic significance, which ranged from 0 to 100. The point's values for individual cases were summed to give a total points value. The total sum thus calculated was correlated to the 5-year graft survival probability of the same case.

Validation of the nomogram

Validating the nomogram involved internal as well as external validation. Internal validation initially was done by discrimination. The degree of discrimination was quantified with the concordance index (C-index) on a scale of 0.5 to 1. This is identical to that of the area under a receiver operating characteristic curve. The C-index provides the probability that in a randomly selected pair of cases, one graft would survive and the other would not. The case with a graft loss should have the worse predictive outcome of the nomogram.

The second method for internal validation is by calibrating the nomogram. Calibration was assessed by grouping patients with respect to their nomogram-predicted graft survival probabilities and then comparing the group means with observed Kaplan-Meier estimates. For both the discrimination and calibration steps, a total of 200 bootstrap re-samples were used to obtain less-biased estimates (6). Bootstrapping is a computer-intensive resampling method involving repeated simple random samples, with replacement, of the same size as the original sample from the data (sample within a sample).

The testing group was utilized for external validation. Degree of discrimination was achieved by the C-index. In addition, the predicted probabilities of 5-year graft survival were compared with the observed data using Hosmer-Lemeshow goodness-of-fit test. A *P* value of less than .05 was considered statistically significant. Furthermore, computation of correlation coefficient between predicted and observed data was done with a linear regression test (Pearson product moment correlation analysis).

Results

Basic data

The overall 5-year graft survival was 79.18% ± 1.13%. Figure 1 illustrates the survival probability of the modeling group and the test group. The survival probability relative to pretransplant predictors is given in Tables 1 A through D. The impact of technical and posttransplant variables is given in Tables 2 and 3. Based on this univariate analysis, 5 pretransplant factors were significant: the recipient age; the donor age; HLA-A, B, and DR matching; genetic consideration; and number of blood

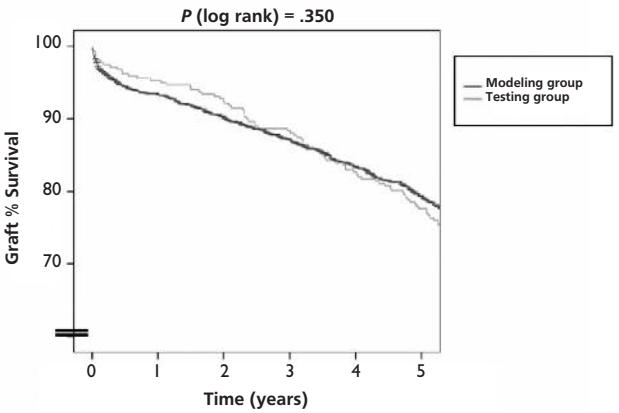

Figure 1. Survival difference between the modeling group and the test group was not significant.

Table 1A. Graft survival predictors: pretransplant factors.

	n	5-year survival (%)	95% CI	*P* value (log rank)
Recipient's age (years)				
≤ 20	305	78.5	73.3 - 83.7	
21-30	584	82.4	79.0 - 85.8	
31-40	447	77.9	73.8 - 82.1	
41-50	201	75.9	69.6 - 82.3	
> 50	44	66.1	47.6 - 84.6	.019
Donor's age (years)				
≤ 30	509	81.3	77.6 - 85.0	
31-40	624	80.2	76.7 - 83.6	
41-50	303	75.4	70.1 - 80.7	
> 50	145	74.2	66.0 - 82.4	.005
Recipient's sex				
Male	1187	79.9	77.4 - 82.4	
Female	394	77.1	72.5 - 81.6	.678
Donor's sex				
Male	756	79.5	76.4 - 82.7	
Female	825	78.8	75.7 - 81.9	.906
The sex of donor /recipient pairs				
Male-male	562	78.5	74.8 - 82.2	
Male-female	609	81.4	77.9 - 84.8	
Female-male	207	76.9	70.4 - 83.4	
Female-female	203	76.4	69.9 - 82.8	.620
Donor relationship				
Related	1331	79.5	77.1 - 81.9	
Unrelated	250	77.6	71.8 - 83.4	.297

Table 1B. Graft survival predictors: pretransplant factors (hematologic factors).

	n	5-year survival (%)	95% CI	*P* value (log rank)
ABO compatibility				
Identical	1271	79.2	76.7 - 81.6	
Compatible	310	79.3	74.2 - 84.3	.654
Type of blood transfusion				
No transfusion	815	82.1	78.9 - 85.3	
Third party	757	76.7	73.6 - 79.8	
Donor specific	9	---	---	.097
Number of blood transfusions				
0	815	82.1	78.9 - 85.3	
1-2	240	83.7	78.9 - 88.4	
3-4	232	75.4	69.7 - 81.0	
≥ 5	294	72.6	67.5 - 77.8	.013

Table 1C. Graft survival predictors: pretransplant factors (immunologic factors).

	n	5-year survival (%)	95% CI	*P* value (log rank)
HLA-A, B, DR (class 1) MM				
0	132	86.5	80.0 - 93.0	
1	198	84.8	79.4 - 90.1	
2	897	78.6	75.6 - 81.6	
3	242	76.1	70.2 - 81.9	
4	81	79.3	69.9 - 88.7	.002
HLA-A, B, DR (class 2) MM				
0	184	87.0	81.5 - 92.4	
1	1369	79.0	76.6 - 81.4	
2	---	---	---	.013
Genetic consideration				
HLA-ID siblings	139	84.8	78.2 - 91.4	
One haplotype MM (R)	981	80.1	77.3 - 82.9	
Two haplotype MM (R+UR)	442	77.1	72.9 - 81.4	.003

Abbreviations: HLA-ID, HLA-identical; MM, mismatch; R, related; UR, unrelated

Table 1D. Graft survival predictors: pretransplant factors (current and past medical).

	n	5-year survival (%)	95% CI	*P* value (log rank)
Bilharziasis				
Negative	1130	79.8	77.1 - 82.5	
Positive	451	77.6	73.8 - 81.5	.486
Original kidney disease				
Glomerulonephritis	179	76.6	70.1 - 83.2	
Chronic pyelonephritis	222	83.7	78.5 - 88.8	
Nephrosclerosis	42	69.6	55.2 - 84.0	
Obstructive uropathy	42	82.5	69.4 - 95.6	
Amyloidosis	27	83.8	69.1 - 98.4	
Polycystic kidney	36	70.4	52.4 - 88.3	
Hypoplasia	10	78.8	52.5 - 105.0	
Others specify	106	69.1	56.7 - 81.5	.099
Types of glomerulonephritis				
Mesangial	35	71.9	55.8 - 87.9	
Membranous	20	42.9	20.6 - 65.1	
Focal segmental glomerulosclerosis	58	86.7	77.4 - 96.0	
Mesangioproliferative	20	61.3	36.2 - 86.4	
Crescentic	11	88.9	68.4 - 109.4	
Hereditary	35	85.1	72.9 - 97.2	.099
Pretransplant hypertension				
Normotensive	665	80.6	77.3 - 84.0	
Hypertensive	916	78.2	75.2 - 81.1	.223
No. of transplants received				
First	1517	78.9	76.6 - 81.2	
Second	63	84.6	75.3 - 93.9	
Third	1	---	---	.701

transfusions. The time to the onset of diuresis was the only significant factor among the technical predictors. Four variables had a significant impact among the posttransplant factors, namely: primary immunosuppression protocol, total steroid dose during first 3 months after transplant, acute tubular necrosis, and number of acute rejection episodes during the first 3 months after transplant. Of these variables, only 8 maintained statistical significance with multivariate analysis (Table 4). Figure 2 indicates the points assigned to these factors, the sum of the total points, and the corresponding graft survival.

Table 2. Graft survival predictors: technical predictors.

	n	5-year survival (%)	95% CI	*P* value (log rank)
No. of renal arteries				
Single	1406	79.1	76.7 - 81.4	
Multiple	175	79.3	72.4 - 86.2	.784
Total ischemia time (min)				
≤ 30	108	79.8	71.9 - 87.7	
(30-60)	1265	79.0	76.6 - 81.5	
> 60	208	79.7	72.8 - 86.7	.510
Time to diuresis				
Immediate (< 10 min)	1444	80.6	78.3 - 82.8	
Delayed (> 10 min)	137	63.5	54.8 - 72.2	< .001
Primary urinary recontinuity				
Uretero-vesical (Leadbetter)	175	65.5	58.4 - 72.6	
Uretero-vesical (Lich-Gregoire)	1376	81.0	78.7 - 83.4	
Uretero-ureteral	25	75.6	58.6 - 92.6	
Pyelo-ureteral	3	—	—	
Ileal conduit	2	—	—	.130

Table 3. Graft survival predictors: posttransplantation predictors.

	n	5-year survival (%)	95% CI	*P* value (log rank)
Induction therapy				
No	832	77.4	74.5 - 80.3	
Yes	749	81.9	78.4 - 85.3	.440
Primary immunosuppression				
Azathioprine-based	239	71.4	65.4 - 77.5	
Cyclosporine-based	274	76.3	70.5 - 82.1	
Triple	717	78.8	75.7 - 82.0	
Rapa-based	201	88.2	77.1 - 99.1	
FK	150	86.5	80.8 - 92.1	< .001
Total steroid dose (during first 3 months)				
< 5 g	935	83.7	80.9 - 86.5	
(5-10 g)	476	77.5	73.6 - 81.3	
> 10 g	170	64.5	57.2 - 71.7	< .001
ATN				
No	1484	80.0	77.8 - 82.3	
Yes	97	64.9	54.5 - 75.4	< .001
No. of acute rejection episodes during first 3 months				
No rejection	1171	81.9	79.5 - 84.3	
1 rejection	303	75.4	70.0 - 80.9	
More than 1 rejection	107	58.8	48.2 - 69.3	< .001
Urologic complications				
No	1468	79.5	77.2 - 81.8	
Yes	113	75.3	67.2 - 83.4	.379
Posttransplant hypertension				
Normotensive	656	77.5	73.8 - 81.3	
Sustained	623	80.9	77.7 - 84.2	
Newly developed	302	81.5	76.9 - 86.0	.090
Posttransplant diabetes				
No	1663	78.1	80.5 - 76.9	
Yes	237	79.8	85.7 - 73.9	.698

Abbreviations: ATN, acute tubular necrosis; FK, tacrolimus; Rapa, sirolimus.

Nomogram performance and validation

The value of the concordance index as a function of the internal validation was 0.77. Figure 3 illustrates calibration of the nomogram whereby its prediction of 5-year graft survival was compared with the actual outcome. When external validation was done, the computed C-index of the nomogram prediction was 0.72. Comparisons between the predicted and observed graft survival probabilities are shown in

Table 4. Cox proportional hazard analysis.

	Regression estimate (B)	Relative risk Exp (B)	95.0% CI	*P* value
Recipient's age (years)				
< 20	----	1		
20 –	–0.111	0.895	0.7 - 1.14	.305
30 –	–0.094	0.911	0.7 - 1.2	.513
40 –	0.323	1.381	1.0 - 1.9	.040
50+	0.069	1.072	0.6 - 2.0	.877
Donor's age (years)				
< 30	----	1		
30 –	–0.002	0.998	0.8 - 1.2	.688
40 –	0.201	1.223	1.0 - 1.6	.038
50 +	0.414	1.513	1.1 - 2.1	.002
Number of blood transfusions				
0	----	1		
1-2	–0.058	0.943	0.7 - 1.2	.653
3-4	0.162	1.175	0.9 - 1.5	.150
≥ 5	0.254	1.289	1.0 - 1.6	.031
HLA-A, B, DR (class 1) MM				
0	----	1		
1	–0.533	0.587	0.3 - 1.1	.116
2	–0.432	0.649	0.3 - 1.4	.269
3	-0.581	0.559	0.2 - 1.4	.208
4	-1.025	0.359	0.0 - 3.2	.361
HLA-A, B, DR (class 2) MM				
0	----	1		
1	0.172	1.187	0.8 - 1.8	.431
2	—	—	—	—
Genetic consideration				
HLA-identical siblings	----	1		
1 haplotype MM (R)	0.363	1.437	0.6 - 3.4	.178
2 haplotype MM (R+UR)	0.581	1.788	0.7 - 4.3	.007
Time to diuresis				
Immediate (< 10 min)	----	1		
Delayed (> 10 min)	0.247	1.28	1.0 - 1.7	.045
Primary immunosuppression				
Azathioprine-based	----	1		
Cyclosporine-based	0.094	1.089	0.8 - 1.5	.521
Triple-based	0.105	1.124	0.8 - 1.5	.502
FK-based	–0.805	0.415	0.2 - 0.9	.010
Rapa-based	–0.314	0.707	0.4 - 1.2	.160
Total steroid dose (during first 3 months)				
< 5 g	----	1		
(5-10)	0.107	1.113	0.9 - 1.4	.228
> 10	0.484	1.622	1.3 - 2.1	< .001
ATN				
No	----	1		
Yes	0.278	1.321	1.0 - 1.8	.046
No. of acute rejection episodes (during first 3 months)				
No rejection	----	1		
1 rejection	0.112	1.118	0.9 - 1.4	.569
More than 1 rejection	0.648	1.912	1.3 - 2.7	.001

Abbreviations: FK, tacrolimus; MM, mismatch; R, related; Rapa, sirolimus; UR, unrelated.

Table 5. Comparison between nomogram predicted and observed graft survival of test group.

Years	Mean predicted	Mean observed	*P* value	Prediction error (%)
1	93.59 ± 1.17	91.67 ± 1.12	.751	2
2	88.74 ± 1.14	88.58 ± 1.48	.380	0.1
3	86.65 ± 1.68	85.97 ± 1.65	.802	0.7
4	83.39 ± 3.34	82.21 ± 2.14	.766	1
5	79.24 ± 4.07	71.80 ± 2.34	.620	10

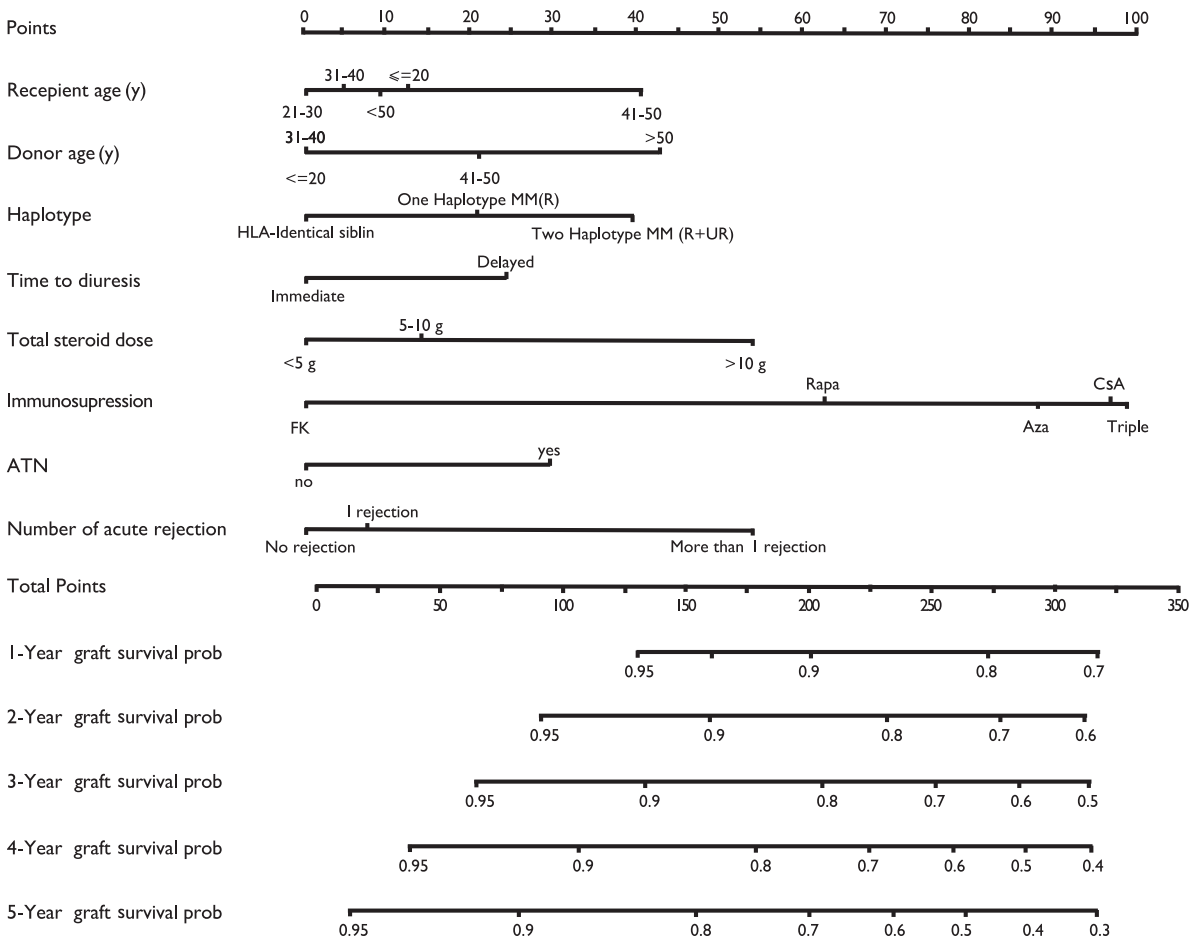

Figure 2. Five-year nomogram inputs are assigned points according to the degree of their impact on graft survival and included recipient age, donor age, haplotype [HLA identical sibling, 1 haplotype mismatch between recipients and living-related donors (1 haplotype MM{R}), 2 haplotype mismatch between recipients and living-related and living-unrelated donors (2 haplotype MM {R+UR})], time to onset of diuresis, total steroid dose, immunosuppression [tacrolimus (FK), sirolimus (Rapa), azathioprine (Aza), cyclosporine (CsA), triple immunosuppression in the form of steroids plus cyclosporine plus azathioprine (Triple)], acute tubular necrosis (ATN), and number of acute rejections. The 5-year graft survival probabilities (Prob) are estimated according to the total risk points earned for each patient.

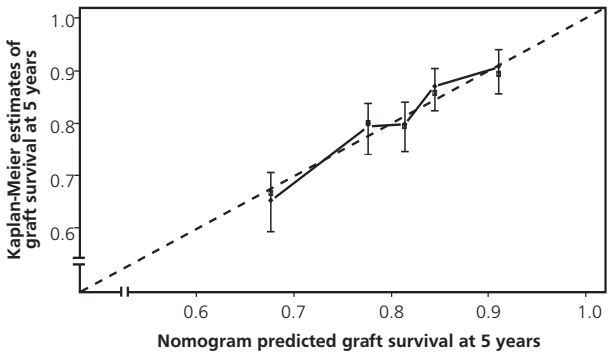

Figure 3. Calibration plot for predicting 5-year graft survival. The dashed line represents the performance of an ideal nomogram in which the predicted outcome corresponds perfectly with actual ones. The solid line represents the performance of the constructed nomogram. The boxes indicate the bootstrap corrected estimates of the predicted graft survival. The vertical bars indicate the 0.95% confidence intervals based on bootstrapping analysis.

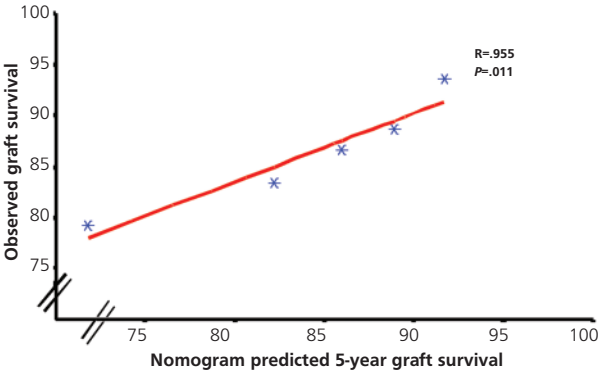

Figure 4. Relation between predicted and observed graft survival. The asterisks represent the summed survival data from nomogram predicted 5-year graft survival and observed graft survival.

Table 5 and show no differences with acceptable prediction error. The relation between the predicted and observed data, as studied by linear regression, is represented in Figure 4. The r-value of 0.955 indicates a strong positive correlation.

Discussion

The importance of possibly predicting the outcome following a renal transplant does not need emphasis. This would allow the choice of the best possible kidney donor and the optimum immunosuppressive therapy for a given patient. Several methods have been used to construct such models. A multivariate analysis was used to predict the outcome of renal transplant from a deceased donor to optimize allocation of the recovery of organs (7). In another study, multivariate analyses were used to predict creatinine levels in recipients of kidneys from living donors (8). The probability of deceased-donor graft survival was studied using a tree regression model (9, 10). Neural networking has been used to predict the possibility of delayed graft function following deceased-donor renal transplant (11).

To generate an accurate prediction model, several conditions should be met: use of a robust dataset that represents a large patient population, a significant number of events of interest within the study dataset, and incorporation of prognostically significant variables into the model (4). In addition, the generated model should be validated using independent testing groups (12-15).

In this study, we opted to construct a nomogram to predict the outcome following a living-donor renal transplant. Eleven variables had a significant impact with univariate analysis. Out of these, 8 maintain their significance when a multivariate analysis was used. Because 8 factors were used in the Cox proportional hazards regression model, this would require that at least 80 events be observed. In our study, the number of incorporated events in the modeling group was 966 events and in the test group, it was 130 events. This indicates that the statistical requirements for the regression analysis used in this study were satisfactory.

The data generated from our multivariate analysis were used to construct this nomogram. This model provides several advantages. It is simple to interpret by clinicians. Accordingly, it can be used in decision making without a need to do any sophisticated calculations. In addition, it provides a more-tailored probability than classification by risk group. Again, it can be used to stratify patients by establishing a risk cutoff point for treatment decision making (16). It is flexible enough to incorporate new predictors when indicated.

The accuracy of our nomogram has been thoroughly tested using internal as well as external validation methodologies. The value of the C-index as calculated by internal and external validation (0.77 and 0.72, respectively) compares favorably with other publications (17). Furthermore, there were no statistically significant differences between the means of the predicted and observed survival data with acceptable prediction error. When the results of the predicted and observed data were studied by linear regression, the resulting r-value indicates a strong positive correlation. The coefficient of determination ($R^2 = 0.912$) means that 0.912% of variation in the predictive values could be explained by changes in the observed ones.

In conclusion, we have developed a well-validated and a reasonably precise nomogram for predicting 5-year graft survival among patients who receive a kidney from a living donor. In a future study, we will compare the accuracy of this system with that in which artificial neural networks are used.

References

1. Grossberg JA, Reinert SE, Monaco AP, Gohh R, Morrissey PE. Utility of a mathematical nomogram to predict delayed graft function: a single-center experience. Transplantation. 2006;81(2):155-159.
2. Djavan B, Remzi M, Zlotta A, Seitz C, Snow P, Marberger M. Novel artificial neural network for early detection of prostate cancer. J Clin Oncol. 2002;20(4):921-929.
3. Kattan MW. Comparison of Cox regression with other methods for determining prediction models and nomograms. J Urol. 2003 Dec;170(6 Pt 2):S6-9; discussion S10.
4. Kattan MW. When and how to use informatics tools in caring for urologic patients. Nat Clin Pract Urol. 2005;2(4):183-190.
5. Kattan MW. Nomograms are superior to staging and risk grouping systems for identifying high-risk patients: preoperative application in prostate cancer. Curr Opin Urol. 2003;13(2):111-116.
6. Heymans MW, van Buuren S, Knol DL, van Mechelen W, de Vet HC. Variable selection under multiple imputation using the bootstrap in a prognostic study. BMC Med Res Methodol. 2007;7:33.
7. Poli F, Scalamogna M, Cardillo M, Porta E, Sirchia G. An algorithm for cadaver kidney allocation based on a multivariate analysis of factors impacting on cadaver kidney graft survival and function. Transpl Int. 2000;13(suppl 1):S259-S262.
8. Zapletal C, Lorenz MW, Woeste G, Wullstein C, Golling M, Bechstein WO. Predicting creatinine clearance by a simple formula following live-donor kidney transplantation. Transpl Int. 2004;17(9):490-494.
9. Goldfarb-Rumyantzev AS, Scandling JD, Pappas L, Smout RJ, Horn S. Prediction of 3-yr cadaveric graft survival based on pre-transplant variables in a large national dataset. Clin Transplant. 2003;17(6):485-497.

10. Krikov S, Khan A, Baird BC, et al. Predicting kidney transplant survival using tree-based modeling. ASAIO J. 2007;53(5):592-600.
11. Brier ME, Ray PC, Klein JB. Prediction of delayed renal allograft function using an artificial neural network. Nephrol Dial Transplant. 2003;18(12):2655-2659.
12. Kattan MW, Stapleton AM, Wheeler TM, Scardino PT. Evaluation of a nomogram used to predict the pathologic stage of clinically localized prostate carcinoma. Cancer. 1997;79(3):528-537.
13. Graefen M, Karakiewicz PI, Cagiannos I, et al. Validation study of the accuracy of a postoperative nomogram for recurrence after radical prostatectomy for localized prostate cancer. J Clin Oncol. 2002;20(4):951-956.
14. Eilber FC, Brennan MF, Eilber FR, Dry SM, Singer S, Kattan MW. Validation of the postoperative nomogram for 12-year sarcoma-specific mortality. Cancer. 2004;101(10):2270-2275.
15. Peeters KC, Kattan MW, Hartgrink HH, et al. Validation of a nomogram for predicting disease-specific survival after an R0 resection for gastric carcinoma. Cancer. 2005;103(4):702-707.
16. Shabsigh A, Bochner BH. Use of nomograms as predictive tools in bladder cancer. World J Urol. 2006;24(5):489-498.
17. Karakiewicz PI, Benayoun S, Kattan MW, et al. Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. J Urol. 2005;173(6):1930-1934.