Prediction of delayed renal allograft function using an artificial neural network

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Prediction of delayed renal allograft function using an artificial neural network

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Abstract

Background. Delayed graft function (DGF) is one of the most important complications in the post-transplant period, having an adverse effect on both the immediate and long-term graft survival. In this study, an artificial neural network was used to predict the occurrence of DGF and compared with traditional logistical regression models for prediction of DGF.

Methods. A total of 304 cadaveric renal transplants performed at the Jewish Hospital, Louisville were included in the study. Covariate analysis by artificial neural networks and traditional logistical regression were done to predict the occurrence of DGF.

Results. The incidence of DGF in this study was 38%. Logistic regression analysis was more sensitive to prediction of no DGF (91 *vs* 70%), while the neural network was more sensitive to prediction of yes for DGF (56 *vs* 37%). Overall prediction accuracy for both logistic regression and the neural network was 64 and 63%, respectively. Logistic regression was 36.5% sensitive and 90.7% specific. The neural network was 63.5% sensitive and 64.8% specific. The only covariate with a $P < 0.001$ was the transplant of a white donor kidney to a black recipient. Cox proportional hazard regression was used to test for the negative effect of DGF on long-term graft survival. One year graft survival in patients without DGF was $92 \pm 2\%$ *vs* $81 \pm 3\%$ in patients with DGF. The 5-year graft survival was not affected by DGF in this study.

Conclusion. Artificial neural networks may be used for prediction of DGF in cadaveric renal transplants. This method is more sensitive but less specific than logistic regression methods.

Keywords: artificial neural network; delayed graft function; kidney transplantation; logistic regression; prediction

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Introduction

Delayed graft function (DGF) is the most common complication affecting kidney allografts in the immediate post-transplantation period. It has been defined as the need for dialysis in the first week after surgery [1,2]. Other authors have defined DGF as the time taken by the kidney to attain a threshold Cockroft calculated creatinine clearance of ≥ 10 ml/min [3,4] or a serum creatinine > 2.5 mg/dl at 2 weeks post-transplant [5]. The incidence of DGF has been variously reported as 8–50% of primary cadaveric renal transplantation in the USA [6] and as ∼34% of cadaveric transplants in a European Multicentre Study Group report [7]. The clinical manifestations of DGF vary along a spectrum of severity from a subtle slowing of the expected decline in serum creatinine to a prolonged oliguria requiring dialytic support for a number of days after transplantation. Even the most benign consequences of DGF are still quite significant, and include prolonged hospitalization, higher cost of transplantation, increased complexity of management of immunosuppression and the adverse effects on the rehabilitation of transplant recipients [8,9]. However the most ominous consequences of DGF are on the long-term graft survival. Many studies have now shown that DGF adversely affects both 1- and 5-year graft survival [2,7]. However, Topperman *et al.* [1] and Boom *et al.* [4] failed to show an independent effect of DGF on graft survival.

In addition to the above, DGF may also be associated with acute rejection in ∼9.7% of cases as per the USRDS data [6]. The mechanisms involved in the aetiology of DGF may be ischaemic or immunological, and may act synergistically [10].

To prevent acute renal failure (ARF) with DGF, many centres use anti-lymphocyte therapy for immunosuppression and avoid nephrotoxic immunosuppressants such as cylosporin A. However, use of anti-lymphocyte globulin is associated with an increased risk of infection, long-term risk of malignancy and lymphoproliferative disorders, and added costs. The selective use of anti-lymphocyte therapy in only those

at the highest risk of developing DGF/ARF would limit the risk of infection and reduce costs.

Selective therapy with anti-lymphocyte therapy would require the ability to predict which patients are most likely to develop DGF. One method to predict such events would be to use computer-assisted models for prediction known as artificial neural networks. Neural networks have been applied successfully to non-medical tasks such as economic forecasting, predicting currency exchange rates [11], stock market trends [12], commodity price movements and forecasting electric load distribution [13]. Neural networks have also been used to predict clinical outcomes. Baxt *et al.* [14], using an artificial neural network to predict acute myocardial infarction, found artificial neural networks to have a greater degree of sensitivity and specificity than emergency room physicians.

We tested the hypothesis that artificial neural networks can predict the development of DGF following kidney transplantation. Neural networks are useful in predicting overall clinical outcomes; they cannot identify individual risk factors for a given clinical event.

Therefore, we also employed traditional logistical regression analysis to construct a model to predict ARF that also identified individual clinical factors that correlated with ARF. We report that neural networks predicted the absence of ARF 70% of the time and the presence of DGF 37% of the time. The logistic regression model accurately predicted the absence of DGF 91% of the time and the presence of DGF with 37% accuracy. Logistic regression analysis revealed that transplantation of kidneys from white donors to a black recipient significantly correlated ($P < 0.0001$) with the development of post-transplant ARF. These data indicate that computer models may be useful in guiding the selective use of immunosuppressants in patients with post-transplant ARF and in identifying factors that predispose to ARF/DGF.

Methods

The data consist of 304 cadaveric renal transplant patients that received their transplants after 1984 and received initial immunosuppression of cyclosporin, azathioprine and prednisone. All transplants took place at the Jewish Hospital, Louisville, KY. ARF after transplantation was defined using the UNOS criteria of those patients that required some form of renal replacement therapy within 7 days of receiving their transplant. The covariates that were included in the analysis were (i) recipient age, height, weight, body surface area, gender and race; (ii) donor gender and race; (iii) HLA match; and (iv) cold ischaemic time. Patients who had missing data other than height and weight were excluded from the analysis. For those patients who were missing height or weight data, the gender average was substituted for that missing value. The data were divided into two groups for analysis. Group 1 had 198 patients and was used to determine the parameter estimates of the logistic regression and neural network analysis. Group 2 had 106 patients and was used as an independent validation set. Approval for this chart review was obtained from the University Human Studies Committee.

An artificial neural network was used for prediction purposes. The type of neural network used was a multilayer feedforward perceptron. This type of neural network is similar to logistic regression and has been described elsewhere [15]. Briefly, the dependent variable DGF is predicted as a non-linear function of a linear combination of the product of the independent variables and the neural network parameters. The mathematical representation of a neural network follows. Let

$$z_1 = f\left(\alpha_1 + \beta_{11}x_1 + \beta_{12}x_2 + \ldots + \beta_{1n}x_n\right) \quad (1)$$

$$z_m = f\left(\alpha_m + \alpha_{m1}x_1 + \beta_{m2}x_2 + \ldots + \beta_{mn}x_n\right) \quad (2)$$

Where z_m is the output from hidden node m, m is the number of nodes in the hidden layer, n is the number of covariate, α is the parameter associated with the intercept, x_n is the nth covariate, β_{mn} is the parameter associated with the mth hidden node and nth covariate, and $f(\cdot)$ is termed the activation function. Then let

$$y = g\left(a + b_1z_1 + \ldots + b_mz_m\right) \quad (3)$$

Where y is the output of the neural network, a is the parameter associated with the bias, b is the parameter associated with the output from the mth hidden node, z_m is the output from the mth hidden node, and $g(\cdot)$ is termed the output function. The arbitrary functions $f(\cdot)$ and $g(\cdot)$ may be any function but most often are the logistic function

$$e^x/(1 + e^x) \quad (4)$$

the hyperbolic tangent function

$$(e^{-x} + e^x)/(e^x - e^{-x}) \quad (5)$$

or the linear function. If f and g are both linear, then neural networks are nothing more than linear regression. In the neural network that we used, the functions f and g were both the hyperbolic tangent function shown in Equation 5.

Demographic data were tested for differences between the black and white group using χ^2 for categorical data and Student's *t*-test for continuous data.

Logistic regression analysis was performed to predict initial DGF in the patients in group 1. The regression model was built using forward selection with the change in the likelihood ratio as the inclusion criterion. A second logistic regression analysis of the complete data set was performed to identify important covariates for DGF. A Cox proportional hazard analysis of the complete data set was performed to test the effect of DGF on 1- and 5-year graft survival.

Results

The study population was abstracted from the transplant database at the Jewish Hospital, Louisville, KY. This population consisted of 1109 kidney transplants that took place from September 1964 to March 1995. The data were filtered to provide only those recipients that had received cyclosporin, azathioprine and prednisone for induction of immunosuppression. This was accomplished by taking only patients from 1984–1995 and excluding living related transplants. Of these kidneys, 85 represented a second, eight represented a third, and one represented a forth kidney transplant in

Table 1. Demographic data on the transplant population divided by recipient race

	White (n = 229)		SEM	Black (n = 75)		SEM
	Mean	SD		Mean	SD	
Body surface area	1.4713	0.2712	1.8E-02	1.5220	0.2428	2.8E-02
Cold ischaemic time	1350.15	452.70	29.92	1385.39	456.70	52.74
Age	40.1139	12.5196	0.8273	39.6701	11.2803	1.3025
Recipient height	64.90	4.53	0.30	66.50	4.93	0.57
Recipient weight	149.55	28.12	1.86	161.06	33.13	3.83
AB loci match	1.8472	0.8368	5.5E-02	1.6000	0.7352	8.5E-02
DR loci match	1.0873	0.5141	3.4E-02	1.0267	0.4925	5.7E-02

the same patient. Presence or absence of DGF was reported in a total of 724 transplants, and the DGF rate was 38%. This resulted in a study population of 304 kidney transplant patients who had complete demographic information. The percentage of these remaining patients who had DGF was 45%.

The demographic information by race is shown in Table 1. Black recipients were not different from whites in body surface area, age, cold ischaemic time, and number of A, B, DR matches. Black recipients' height and weight were slightly greater than those of white recipients ($P < 0.05$).

The results of the logistic regression and neural network analysis for prediction of the test data set of group 2 are shown in Tables 2 and 3 using a cut-off point of 0.5 for the logistic regression and 0 for the neural network. These cut-off points were chosen as the middle of the prediction range. Logistic regression analysis was more sensitive to predictions of no DGF (91 *vs* 70%) while the neural network was more sensitive to prediction of yes for DGF (56 *vs* 37%). The overall prediction accuracy was similar for both logistic regression (64%) and the neural network (63%). The receiver operating characteristic (ROC) curves for both prediction methods are shown in Figure 1. The closer the ROC area under the curve is to 1.0, the more sensitive and specific the prediction method is. The area under the curve for logistic regression was 0.636 ± 0.054 and for the neural network was 0.668 ± 0.053. The area under the curve for these two methods was not different ($P = 0.485$). At optimum points along the curves, the logistic regression was 36.5% sensitive and 90.7% specific. The neural network was 63.5% sensitive and 64.8% specific. Therefore, while there was no overall difference between the methods' predictive accuracy, the neural network provided superior prediction of the presence of DGF and logistic regression provided superior prediction of the absence of DGF.

Logistic regression of the combined data (groups 1 and 2) was performed to determine the risk factors for DGF for this patient population. The results of this analysis when all covariates are entered into the model simultaneously are shown in Table 4. The results of the analysis when a forward selection technique is used are shown in Table 5. The only covariate in the model that resulted in a *P*-value < 0.05 was the interaction term indicating that a kidney from a white donor was

Table 2. Neural network prediction of delayed graft function in the test data set

	Predicted DGF		Total
	No	Yes	
Observed DGF			
No	38	16	54
Yes	23	29	52
Total	61	45	106

Table 3. Logistic regression prediction of delayed graft function in the test data set

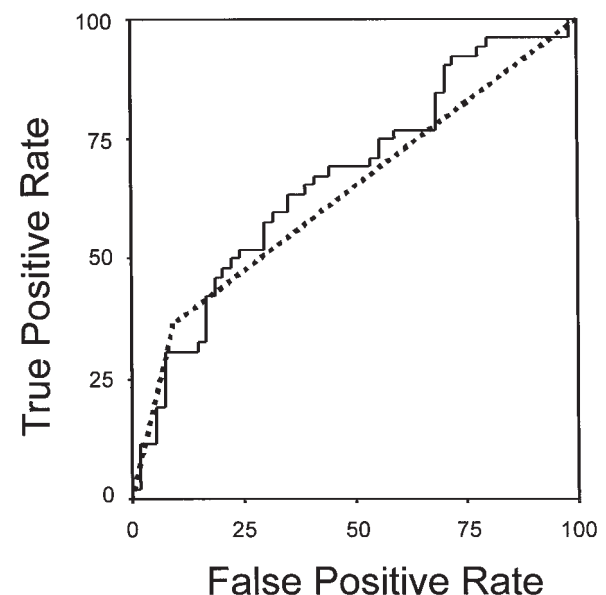|	Predicted DGF		Total
	No	Yes	
Observed DGF			
No	49	5	54
Yes	33	19	52
Total	82	24	106

Fig. 1. ROC curves for logistic regression (dashed line) and neural network (solid line) predictions of delayed graft function.

Table 4. Results of the logistic regression analysis of the complete data set for delayed graft function

Covariate	Reference group	OR	95% CI	*P*-value
Recipient black	Recipient white	0.33	0.069–1.60	0.1706
Recipient female	Recipient male	0.68	0.41–1.13	0.1425
CIT > mean	CIT ≤ mean	1.00	0.56–1.83	0.9790
Body surface area > mean	Body surface area ≤ mean	0.68	0.27–1.71	0.4129
0 DR match	1 or 2 DR match	1.14	0.50–2.60	0.7489
Donor white × recipient black	All others	12.34	2.36–64.55	0.0029
Recipient black × CIT > mean	All others	2.44	0.74–8.06	0.1431

OR, odds ratio; CI, confidence interval; CIT, cold ischaemic time.

Table 5. Results of the logistic regression analysis of the complete data set for delayed graft function using a forward selection technique

Covariate	Reference group	OR	95% CI	*P*-value
Donor white × recipient black	All others	4.46	2.41–8.26	0.0000
Recipient black × CIT > mean	All others	2.32	0.89–6.00	0.0824

OR, odds ratio; CI, confidence interval; CIT, cold ischaemia time.

transplanted into a black recipient. There were a total of 64 black recipients who received a white donor kidney, and 47 (73%) of these kidneys had DGF. The white × black interaction term resulted in an odds ratio of 12.34 for the full model as shown in Table 4, and 4.46 in the reduced model as shown in Table 5. The opposite transplantation of a black kidney into a white recipient occurred in only eight cases and the transplantation of a black kidney into a black recipient occurred in only 11 cases, thus precluding further meaningful analysis. ANOVA was performed to determine the presence of any two-way interaction between black race and other covariates. As shown in Table 5, ANOVA revealed a two-way interaction between black race and cold ischaemic time. Thus, black race is associated with increased risk of ARF for those recipients who received kidneys from white donors and with a cold ischaemic time greater than ∼21 h.

A Cox proportional hazard regression model was used to test for a negative effect of DGF on graft survival. DGF was tested along with several other covariates. One-year graft survival was significantly affected by both DGF ($P = 0.0217$) and recipient body surface area ($P = 0.0021$). The 1-year Kaplan–Meier mean ± SE survival for patients who had no renal failure was 9.22% and was 8.13% in patients with ARF. Five-year graft survival was not affected by the presence of DGF, and only body surface area was significantly significant ($P = 0.0328$). Thus, these data confirm that DGF has a negative impact on short-term graft survival.

Discussion

The goal of this work was to test methods that would allow the choice of initial immunosuppression to be guided by a prediction of the risk of DGF in an individual transplant recipient. We evaluated artificial neural networks as a tool to predict DGF. Artificial neural networks are an extension of traditional statistical techniques. They are most closely related to logistic regression for prediction and discriminant analysis for classification. Neural network predictors have been shown to offer a more flexible modelling environment than any of the traditional approaches, including other statistical methods [16]. Predictions from the neural network were compared with a standard technique of logistic regression, which also allows us to evaluate the data for specific risk factors in this population for DGF. In general, both methods provided similar overall predictive accuracy. Both the neural network and logistic regression methods provided accurate predictions in ∼64% of cases evaluated. A more sensitive analysis of the data using ROC curves also reaches the same conclusion, that there is no difference between predictions.

Analysis of the complete data set allowed us to determine individual risk factors for DGF in our patient population. In the present analysis, only one factor was associated with a statistically significant risk and that is transplantation of kidneys from a white donor to black recipients. The relative risk of DGF for a black recipient receiving a kidney from a white donor was 12.64. The higher incidence of poor outcome in black recipients has been reported by other authors; Ojo *et al.* [6] and Feldman *et al.* [5] with an odds ratio of 1.63–2.17.

Other risk factors associated with DGF as reported by Boom *et al.* [4] include recipient pre-transplant mean arterial pressure < 100, female donor to a male recipient, cold ischaemia time > 28 h, peak panel-reactive antibody (PRA) > 50% and donor age > 50 years.

In this analysis, we did not find a relationship of cold ischaemia time and HLA mismatch with DGF. The absence of any influence of cold ischaemia and HLA mismatch may be a centre effect. The overall HLA match among our patients was good (AB match

1.8 ± 0.8; DR match 1.1 ± 0.5) and cold ischaemia times are limited (1353 ± 453 min) because the majority of the kidneys were procured locally.

Poor outcome among black recipients has been reported by various authors. Feldman *et al.* [5] in a series of 325 cadaveric allografts reported that 62.6% of 91 black recipients had DGF compared with 48.3% of 234 white recipients. Sanfillipo and colleagues [15] in a series of 3800 cadaveric renal transplants in the pre-cyclosporin era found black race to be a significant predictor of DGF. Cacciarelli *et al.* [16] in a study of 495 cadaveric allograft recipients between 1983 and 1987 found that 58% of 176 black recipients required dialysis post-transplant compared with 46% of 221 white recipients, a difference that was statistically significant.

Postulated explanations for the poorer outcome in black recipients of a cadaveric renal transplant have been a greater number of HLA mismatches, greater immune responsiveness, less bioavailability of cyclosporin, prolonged cold ischaemia time, lengthy duration of prior dialysis therapy, prior blood transfusion and a higher peak PRA [4].

Graft survival at 1 and 5 years has also been found to have a poorer outcome. A recent UNOS scientific renal transplant registry reports that blacks have the worst 1- and 5-year graft survival compared with all other ethnic groups, 79 and 48%, respectively [17]. Ojo *et al.* [6] in an analysis of the USRDS data reported that African Americans had a relative risk of 1.34 for a poorer 5-year graft survival obtained by a Cox non-proportional hazard regression analysis.

The increased risk of DGF in black patients that we observed cannot be readily explained. Immunological differences and cold ischaemia may be aetiological factors for DGF in black patients, but in our data set cold ischaemia and HLA match were equivalent between white and black recipients. Thus, the aetiology of increased DGF in black patients in our centre is not clear. However, our data do support the hypothesis that DGF may significantly contribute to poorer overall graft survival in black patients.

We conclude that the application of computer modelling to predict outcomes in renal transplantation is promising. In this first application of an artificial neural network to predictions in renal transplantation, a neural network provided predictions that are at least equivalent to those of logistic models which are a more traditional technique. The combination of neural networks and logistic regression offers the promise of highly sensitive and specific prediction of ARF following kidney transplantation. Also, logistic regression analysis revealed an individual factor highly correlative with DGF; the markedly increased risk of black

transplant recipients for DGF. These findings indicate that the use of computers to predict DGF may be useful in guiding the selective use of anti-lymphocyte therapy, particularly in black patients who are at a markedly increased risk of DGF.

Conflict of interest statement. None declared.

References

1. Troppman C, Benedetti E, Almond S, Gruessner RWD, Najarian JS, Matas AJ. Delayed graft function, acute rejection and outcome after cadaveric renal transplantation. *Transplantation* 1995; 59: 962–968
2. Feldman HI, Berlin A, Roth DA *et al.* Delayed function reduces renal allograft survival independent of acute rejection. *Nephrol Dial Transplant* 1996; 11: 1306–1313
3. Giral-classe M, Hourmant M, Cantorvich D *et al.* Delayed graft function for more than six days strongly decreases long term survival of transplanted kidneys. *Kidney Int* 1998; 54: 972–978
4. Boom H, Mallat MJK, DeFijter JW, Zwinderman AH, Paul LC. Delayed graft function influences renal function but not survival. *Kidney Int* 2000; 58: 859–866
5. Feldman HI, Burns E, Roth DA *et al.* Race and delayed allograft function. *Nephrol Dial Transplant* 1998; 13: 704–710
6. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* 1997; 63: 968–974
7. Koning OHJ, Ploeg RJ, Hajo Van Bockel J *et al.* Risk factors for delayed graft functions in cadaveric kidney transplantation *Transplantation* 1997; 63: 1620–1628
8. Almond PS, Troppman C, Escobar F, Frey DJ, Matas AJ. Economic impact of delayed graft function. *Transplant Proc* 1991; 23: 1304
9. Rosenthal JT, Danovitch GM, Wilkinson A, Ettenger RB. The high cost of delayed graft function in cadaveric renal transplantation. *Transplantation* 1991; 51: 1115
10. Shoskes DA, Halloran PF. Delayed graft function in renal transplantation. Etiology management and long term significance. *J Urol* 1996; 155: 1830–1840
11. Refenes AN, Azema-Barac M, Chen L, Karouss AS. Currency exchange rate prediction and neural networks design strategies. *J Neural Comput Appl* 1993; 1: 46–58
12. Kimoko T *et al.* Stock market prediction with modular neural networks. *Proceedings of the International Joint Conference on Neural Networks.* Washington, DC; 1990
13. Park DC, Eisharkawi MA, Marks RJ, Atlas LE, Dambarg MJ. Electric load forecasting using artificial neural networks. *IEEE Trans Power Systems* 1991; 6: 442–449
14. Baxt WG. Use of a artificial neural network for the diagnosis of myocardial infarction. *Ann Intern Med* 1991; 115: 843–848
15. Sanfillipo F, Vaugn WK, Specs EK, Lucas BA. Detrimental effects of delayed graft function in cadaveric renal transplantation. *Transplantation* 1984; 38: 643–648
16. Cacciarelli T, Sumrani N, Delaney V *et al.* The influence on long-term outcome in the cyclosporine era. *Clin Nephrol* 1993; 39: 335–339
17. UNOS Data