We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Comparison Between an Artificial Neural Network and Logistic Regression in Predicting Long Term Kidney Transplantation Outcome

Giovanni Caocci, Roberto Baccoli, Roberto Littera,
Sandro Orrù, Carlo Carcassi and Giorgio La Nasa

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53104

1. Introduction

Predicting clinical outcome following a specific treatment is a challenge that sees physicians and researchers alike sharing the dream of a crystal ball to read into the future. In Medicine, several tools have been developed for the prediction of outcomes following drug treatment and other medical interventions. The standard approach for a binary outcome is to use logistic regression (LR) [1,2] but over the past few years artificial neural networks (ANNs) have become an increasingly popular alternative to LR analysis for prognostic and diagnostic classification in clinical medicine [3]. The growing interest in ANNs has mainly been triggered by their ability to mimic the learning processes of the human brain. The network operates in a feed-forward mode from the input layer through the hidden layers to the output layer. Exactly what interactions are modeled in the hidden layers is still under study. Each layer within the network is made up of computing nodes with remarkable data processing abilities. Each node is connected to other nodes of a previous layer through adaptable inter-neuron connection strengths known as synaptic weights. ANNs are trained for specific applications through a learning process and knowledge is usually retained as a set of connection weights [4]. The backpropagation algorithm and its variants are learning algorithms that are widely used in neural networks. With backpropagation, the input data is repeatedly presented to the network. Each time, the output is compared to the desired output and an error is computed. The error is then fed back through the network and used to adjust the weights in such a way that with each iteration it gradually declines until the neural model produces the desired output.

ANNs have been successfully applied in the fields of mathematics, engineering, medicine, economics, meteorology, psychology, neurology, and many others. Indeed, in medicine, they offer a tantalizing alternative to multivariate analysis, although their role remains advisory since no convincing evidence of any real progress in clinical prognosis has yet been produced [5].

In the field of nephrology, there are very few reports on the use of ANNs [6-10], most of which describe their ability to individuate predictive factors of technique survival in peritoneal dialysis patients as well as their application to prescription and monitoring of hemodialysis therapy, analyis of factors influencing therapeutic efficacy in idiopathic membranous nephropathy, prediction of survival after radical cystectomy for invasive bladder carcinoma and individual risk for progression to end-stage renal failure in chronic nephropathies.

This all led up to the intriguing challenge of discovering whether ANNs were capable of predicting the outcome of kidney transplantation after analyzing a series of clinical and immunogenetic variables.

Figure 1. The prediction of kidney allograft outcome…. a dream about to come true?

2. The complex setting of kidney transplantation

Predicting the outcome of kidney transplantation is important in optimizing transplantation parameters and modifying factors related to the recipient, donor and transplant procedure [8]. The biggest obstacles to be overcome in organ transplantation are the risks of acute and chronic immunologic rejection, especially when they entail loss of graft function despite adjustment of immunosuppressive therapy. Acute renal allograft rejection requires a rapid increase in immunosuppression, but unfortunately, diagnosis in the early stages is often difficult [11]. Blood tests may reveal an increase in serum creatinine but which cannot be considered a specific sign of acute rejection since there are several causes of impaired renal function that can lead to creatinine increase, including excessive levels of some immunosuppressive drugs. Also during ischemic damage, serum creatinine levels are elevated and so provide no indication of rejection. Alternative approaches to the diagnosis of rejection are fine needle aspiration and urine cytology, but the main approach remains histological assessment of needle biopsy.[10] However, because the histological changes of acute rejection develop gradually, the diagnosis can be extremely difficult or late [12]. Although allograft biopsy is considered the gold standard, pathologists working in centres where this approach is used early in the investigation of graft dysfunction, are often faced with a certain degree of uncertainty about the diagnosis. In the past, the Banff classification of renal transplant pathology provided a rational basis for grading of the severity of a variety of histological features, including acute rejection. Unfortunately, the reproducibility of this system has been questioned [13]. What we need is a simple prognostic tool capable of analyzing the most relevant predictive variables of rejection in the setting of kidney transplantation.

3. The role of HLA-G in kidney transplantation outcome

Human Leukocyte Antigen G (HLA-G) represents a "non classic" HLA class I molecule, highly expressed in trophoblast cells. [14] HLA-G plays a key role in embryo implantation and pregnancy by contributing to maternal immune tolerance of the fetus and, more specifically, by protecting trophoblast cells from maternal natural killer (NK) cells through interaction with their inhibitory KIR receptors. It has also been shown that HLA-G expression by tumoral cells can contribute to an "escape" mechanism, inducing NK tolerance toward cancer cells in ovarian and breast carcinomas, melanoma, acute myeloid leukemia, acute lymphoblastic leukemia and B-cell chronic lymphocytic leukemia. [15] Additionally it would seem that HLA-G molecules have a role in graft tolerance following hematopoietic stem cell transplantation. These molecules exert their immunotolerogenic function towards the main effector cells involved in graft rejection through inhibition of NK and cytotoxic T lymphocyte (CTL)-mediated cytolysis and CD4+T-cell alloproliferation. [16]

HLA-G transcript generates 7 alternative messenger ribonucleic acids (mRNAs) that encode 4 membrane-bound (HLA-G1, G2, G3, G4) and 3 soluble protein isoforms (HLA-G5, G6, G7). Moreover, HLA-G allelic variants are characterized by a 14-basepair (bp) deletion-inser-

tion polymorphism located in the 3'-untranslated region (3'UTR) of HLA-G. The presence of the 14-bp insertion is known to generate an additional splice whereby 92 bases are removed from the 3'UTR [28]. HLA-G mRNAs having the 92-base deletion are more stable than the complete mRNA forms, and thus determine an increment in HLA-G expression. Therefore, the 14-bp polymorphism is involved in the mechanisms controlling post-transcriptional regulation of HLA-G molecules

A crucial role has been attributed to the ability of these molecules to preserve graft function from the insults caused by recipient alloreactive NK cells and cytotoxic T lymphocytes (CTL). [17] This is well supported by the numerous studies demonstrating that high HLA-G plasma concentrations in heart, liver or kidney transplant patients is associated with better graft survival [18-20].

Recent studies of association between the HLA-G +14-bp /−14-bp polymorphism and the outcome of kidney transplantation have provided interesting, though not always concordant results [21-22].

4. Kydney transplantation outcome

In one cohort, a total of 64 patients (20,4%) lost graft function. The patients were divided into 2 groups according to the presence or absence of HLA-G alleles exhibiting the 14-bp insertion polymorphism. The first group included 210 patients (66.9%) with either HLA-G +14-bp/+14-bp or HLA-G −14/+14-bp whereas the second group included 104 homozygotes (33.1%) for the HLA-G −14-bp polymorphism. The patients had a median age of 49 years (range 18-77) and were prevalently males (66.6%). The donors had a median age of 47 years (range 15-75). Nearly all patients (94,9%) had been given a cadaver donor kidney transplant and for most of them (91.7%) it was their first transplant. The average (±SD) number of mismatches was 3 ± 1 antigens for HLA Class I and 1 ± 0.7 antigens for HLA Class II. Average ±SD cold ischemia time (CIT) was 16 ± 5.6 hours. The percentage of patients hyperimmunized against HLA Class I and II antigens (PRA > 50%) was higher in the group of homozygotes for the HLA-G 14-bp deletion. Pre-transplantation serum levels of interleukin-10 (IL-10) were lower in the group of homozygotes for the 14-bp deletion.

Kidney transplant outcome was evaluated by glomerular filtration rate (GFR), serum creatinine and graft function tests. At one year after transplantation, a stronger progressive decline of the estimated GFR, using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation, was observed in the group of homozygotes for the HLA-G 14-bp deletion in comparison with the group of heterozygotes for the 14-bp insertion. This difference between the 2 groups became statistically significant at two years (5.3 ml/min/1.73 m2; $P<0.01$; 95% CI 1.2 -9.3) and continued to rise at 3 (10.4 ml/min/1.73m2; $P<0.0001$; 95% CI 6.4-14.3) and 6 years (11.4 ml/min/1.73m2; $P<0.0001$; 95% CI 7.7 − 15.1) after transplantation.

5. Logistic regression and neural network training

We compared the prognostic performance of ANNs versus LR for predicting rejection in a group of 353 patients who underwent kidney transplantation. The following clinical and immunogenetic parameters were considered: recipient gender, recipient age, donor gender, donor age, patient/donor compatibility: class I (HLA-A, -B) mismatch (0-4), class II (HLA-DRB1 mismatch; positivity for anti-HLA Class I antibodies >50%; positivity for anti-HLA Class II antibodies >50%; IL-10 pg/mL; first versus second transplant, antithymocyte globulin (ATG) induction therapy; type of immunosoppressive therapy (rapamycin, cyclosporine, corticosteroids, mycophenolate mophetyl, everolimus, tacrolimus); time of cold ischemia, recipients homozygous/heterozygous for the 14-bp insertion (+14-bp/+14-bp and +14-bp/−14-bp) and homozygous for the 14-bp deletion (−14-bp/−14-bp). Graft survival was calculated from the date of transplantation to the date of irreversible graft failure or graft loss or the date of the last follow up or death with a functioning graft.

ANNs have different architectures, which consequently require different types of algorithms. The multilayer perceptron is the most popular network architecture in use today (Figure 2). This type of network requires a desired output in order to learn. The network is trained with historical data so that it can produce the correct output when the output is unknown. Until the network is appropriately trained its responses will be random. Finding appropriate architecture needs trial and error method and this is where backpropagation steps in. Each single neuron is connected to the neurons of the previous layer through adaptable synaptic weights. By adjusting the strengths of these connections, ANNs can approximate a function that computes the proper output for a given input pattern. The training data set includes a number of cases, each containing values for a range of well-matched input and output variables. Once the input is propagated to the output neuron, this neuron compares its activation with the expected training output. The difference is treated as the error of the network which is then backpropagated through the layers, from the output to the input layer, and the weights of each layer are adjusted such that with each backpropagation cycle the network gets closer and closer to producing the desired output [4]. We used the Neural Network Toolbox™ 6 of the software Matlab® 2008, version 7.6 (MathWorks, inc.) to develop a three layer feed forward neural network. [23]. The input layer of 15 neurons was represented by the 15 previously listed clinical and immunogenetic parameters. These input data were then processed in the hidden layer (30 neurons). The output neuron predicted a number between 1 and 0 (goal), representing the event "Kidney rejection yes" [1] or "Kidney rejection no" (0), respectively. For the training procedure, we applied the 'on-line back-propagation' method on 10 data sets of 300 patients previously analyzed by LR. The 10 test phases utilized 63 patients randomly extracted from the entire cohort and not used in the training phase. Mean sensitivity (the ability of predicting rejection) and specificity (the ability of predicting no-rejection) of data sets were determined and compared to LR. (Table 1)

		Rejection	Observed Cases	LR Expected cases (%)	ANN Expected cases (%)
Extraction_1	Test N=63	No	55	40 (73)	48 (87)
		Yes	8	2 (25)	4 (50)
Extraction_2	Test N=63	No	55	38 (69)	48 (87)
		Yes	8	3 (38)	4 (50)
Extraction_3	Test N=63	No	55	30 (55)	48(87)
		Yes	8	3 (38)	5 (63)
Extraction_4	Test N=63	No	55	40 (73)	49 (89)
		Yes	8	3 (38)	5 (63)
Extraction_5	Test N=63	No	7	40 (73)	46 (84)
		Yes	8	4 (50)	6 (75)
Extraction_6	Test N=63	No	55	30 (55)	34 (62)
		Yes	8	4 (50)	6 (75)
Extraction_7	Test N=63	No	55	40 (73)	47 (85)
		Yes	8	3 (38)	5 (63)
Extraction_8	Test N=63	No	55	38 (69)	46 (84)
		Yes	8	4 (50)	5 (63)
Extraction_9	Test N=63	No	55	44 (80)	51 (93)
		Yes	8	2 (25)	4 (50)
Extraction_10	Test N=63	No	55	32 (58)	52 (95)
		Yes	8	2 (25)	5 (63)
Specificity % (mean)	No Rejection			68%	85%
Sensitivity % (mean)	YES Rejection			38%	62%

Table 1. Sensitivity and specificity of Logistic Regression and an Artificial Neural Network in the prediction of Kidney rejection in 10 training and validating datasets of kidney transplant recipients
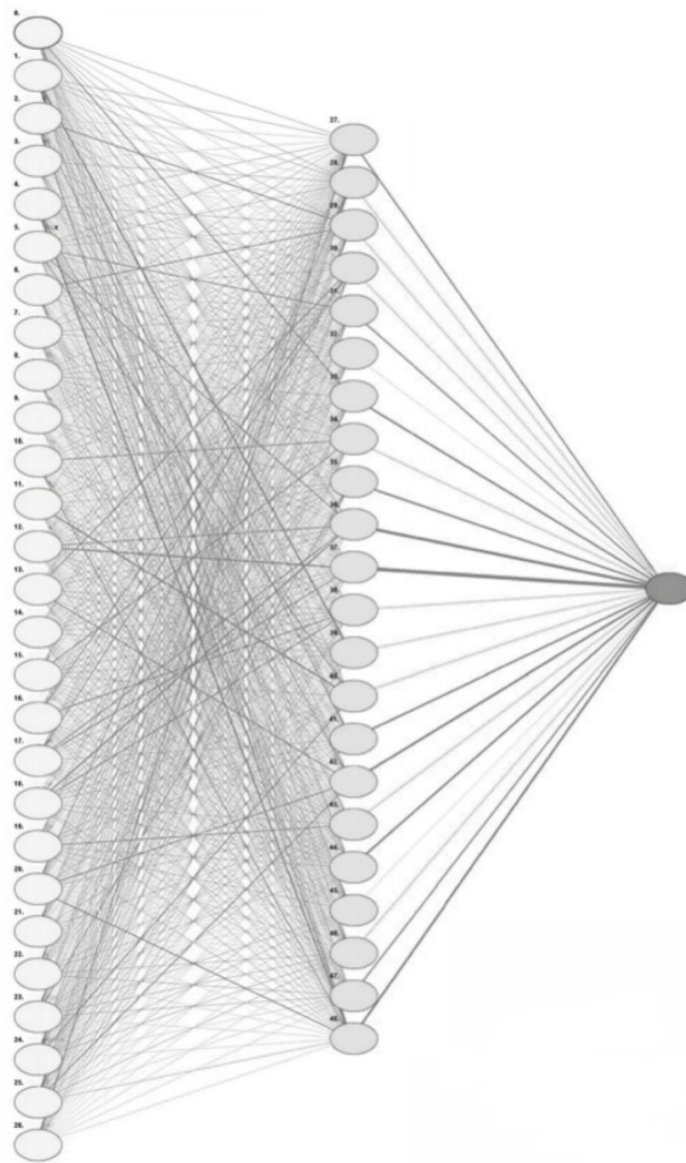
Figure 2. Structure of a three-layered ANN

6. Results and perspectives

ANNs can be considered a useful supportive tool in the prediction of kidney rejection fol-
lowing transplantation. The decision to perform analyses in this particular clinical setting
was motivated by the importance of optimizing transplantation parameters and modifying
factors related to the recipient, donor and transplant procedure. Another motivation was the
need for a simple prognostic tool capable of analyzing the relatively large number of immu-
nogenetic and other variables that have been shown to influence the outcome of transplanta-

tion. When comparing the prognostic performance of LR to ANN, the ability of predicting kidney rejection (sensitivity) was 38% for LR versus 62% for ANN. The ability of predicting no-rejection (specificity) was 68% for LR compared to 85% of ANN.

The advantage of ANNs over LR can theoretically be explained by their ability to evaluate complex nonlinear relations among variables. By contrast, ANNs have been faulted for being unable to assess the relative importance of the single variables while LR determines a relative risk for each variable. In many ways, these two approaches are complementary and their combined use should considerably improve the clinical decision-making process and prognosis of kidney transplantation.

Acknowledgement

Author details

Giovanni Caocci[1], Roberto Baccoli[2], Roberto Littera[3], Sandro Orrù[3], Carlo Carcassi[3] and Giorgio La Nasa[1]

1 Division of Hematology and Hematopoietic Stem Cell Transplantation, Department of Internal Medical Sciences, University of Cagliari, Cagliari, Italy

2 Technical Physics Division, Faculty of Engineering, Department of Engineering of the Territory, University of Cagliari, Cagliari, Italy

3 Medical Genetics, Department of Internal Medical Sciences, University of Cagliari, Cagliari, Italy

References

[1] Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. Stat Med. 2000;19:1831-1847.

[2] Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med.1996;15:361-387.

[3] Schwarzer G, Vach W, Schumacher M. On the misuses of artificial neural networks for prognostic and diagnostic classification in oncology. Stat Med. 2000;19:541-561.

[4] Soteris A. Kalogirou. Artificial neural networks in renewable energy systems applications: a review. Renewable and Sustainable Energy Review. 2001;5:373–401.

[5] 5. Linder R, König IR, Weimar C, Diener HC, Pöppl SJ, Ziegler A. Two models for outcome prediction - a comparison of logistic regression and neural networks. Methods Inf Med. 2006;45:536-540.

[6] Simic-Ogrizovic S, Furuncic D, Lezaic V, Radivojevic D, Blagojevic R, Djukanovic L. Using ANN in selection of the most important variables in prediction of chronic renal allograft rejection progression. Transplant Proc. 1999; 31:368.

[7] Brier ME, Ray PC, Klein JB. Prediction of delayed renal allograft function using an artificial neural network. Nephrol Dial Transplant. 2003; 18:2655-9.

[8] Tang H, Poynton MR, Hurdle JF, Baird BC, Koford JK, Goldfarb-Rumyantzev AS. Predicting three-year kidney graft survival in recipients with systemic lupus erythematosus. ASAIO J. 2011; 57:300-9.

[9] Kazi JI, Furness PN, Nicholson M. Diagnosis of early acute renal allograft rejection by evaluation of multiple histological features using a Bayesian belief network. J Clin Pathol. 1998; 51:108-13.

[10] Furness PN, Kazi J, Levesley J, Taub N, Nicholson M. A neural network approach to the diagnosis of early acute allograft rejection. Transplant Proc. 1999; 31:3151

[11] Furness PN. Advances in the diagnosis of renal transplant rejection. Curr. Diag. Pathol. 1996; 3:81-90.

[12] Rush DN, Henry SF, Jeffery JR, Schroeder TJ, Gough J. Histological findings in early routine biopsies of stable renal allograft recipients. Transplantation 1994; 57:208-211.

[13] Solez K, Axelsen RA, Benediktsson H, et al. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int 1993; 44:411-22.

[14] Kovats S, Main EK, Librach C, Dtubblebine M, Fisher SJ, DeMars R. A class I antigen, HLA-G, expressed in human trophoblasts. Science, 1990; 248:220-223

[15] Carosella ED, Favier B, Rouas-Freiss N, Moreau P, LeMaoult P. Beyond the increasing complexity of the immunomodulatory HLA-G molecule. Blood 2008; 11:4862-4870

[16] Le Rond S, Aze´ma C, Krawice-Radanne I, Durrbach A, Guettier C, Carosella ED, Rouas-Freiss N. Evidence to support the role of HLA-G5 in allograft acceptance through induction of immunosuppressive/ regulatory T cells. Journal of Immunology, 2006; 176:3266–3276.17.

[17] Rouas-Freiss N, Gonçalves RM, Menier C, Dausset J, Carosella ED. Direct evidence to support the role of HLA-G in protecting the fetus from maternal uterine natural killer cytolysis. Proc Natl Acad Sci U S A. 1997; 94:11520-5.

[18] Lila N, Amrein C, Guillemain R, Chevalier P, Fabiani JN, Carpentier A. Soluble human leukocyte antigen-G: a new strategy for monitoring acute and chronic rejections after heart transplantation. J Heart Lung Transplant. 2007; 26:421-2.

[19] Baştürk B, Karakayali F, Emiroğlu R, Sözer O, Haberal A, Bal D, Haberal M. Human leukocyte antigen-G, a new parameter in the follow-up of liver transplantation. Transplant Proc. 2006; 38:571-4.

[20] Qiu J, Terasaki PI, Miller J, Mizutani K, Cai J, Carosella ED. Soluble HLA-G expression and renal graft acceptance. Am J Transplant. 2006; 6:2152-6.

[21] Crispim JC, Duarte RA, Soares CP, Costa R, Silva JS, Mendes-Júnior CT, Wastowski IJ, Faggioni LP, Saber LT, Donadi EA. Human leukocyte antigen-G expression after kidney transplantation is associated with a reduced incidence of rejection. Transpl Immunol. 2008; 18:361-7.

[22] Piancatelli D, Maccarone D, Liberatore G, Parzanese I, Clemente K, Azzarone R, Pisani F, Famulari A, Papola F. HLA-G 14-bp insertion/deletion polymorphism in kidney transplant patients with metabolic complications. Transplant Proc. 2009; 41:1187-8.

[23] Demuth H, Beale M, Hagan M. Neural Network Toolbox™ 6. User's Guide. The MathWorks, Inc. 2008; Natick, MA.