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Comparison of Artificial Neural Networks and Cox Regression Models in Prediction of Kidney Transplant Survival

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ABSTRACT

Cox regression model serves as a statistical method for analyzing the survival data, which requires some options such as hazard proportionality. In recent decades, artificial neural network model has been increasingly applied to predict survival data. This research was conducted to compare Cox regression and artificial neural network models in prediction of kidney transplant survival. The present multi-center retrospective study was conducted on the medical records of 756 kidney transplant recipients undergoing kidney operations at two treatment centers from 2001 through 2012. The data was randomly divided into two educational and experimental (validation) groups. Then, Kaplan-Meier, Cox proportional hazard, and three-layer artificial neural network models were used for analyzing the data. To compare the prediction of both models, the area under the curve in the characteristic function was applied. Post-operative creatinine and relative family are among the factors of influencing kidney transplant survival. Moreover, the survival estimates of the transplanted kidney for periods of six months, one year, three years, and five years were 89, 87.4, 80, and 75 percent, respectively. ROC areas under the curve, for multi-layer perceptron neural network model and Cox regression, were 81.3% and 71%, respectively. If a structure with high prediction ability is obtained in neural network, we may detect risk patients through the method and consider more treatment resources for them.

Key words: Artificial neural network; Survival analysis; Kidney transplant; Cox regression.

INTRODUCTION

Kidney transplant is a proper and the most effective treatment method for the patients suffering from the end stage renal disease (ESRD), which brings about decreasing the death rate and increasing their life

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quality (Meier-Kriesche et al., 2000, Shrestha and Haylor, 2007). Organ transplant was first performed in Germany in 1954. However, the first kidney transplant in Iran was carried out in Shiraz in 1967 (Mahdavi-Mazdeh et al., 2007). The sources for providing the organs included transplant from live relative donors, live non-relative donors, and cadavers, which among them cadaver is one of the most significant sources of transplant (Tan et al., 2000). However, it is necessary to note that transplant from a living donor is much more durable than that from a cadaver(Courtney et al., 2008, Bakr and Ghoneim, 2005) . Similar studies conducted on the rate of kidney transplant in 2009 showed that the survival rates of 1-, 3-, and 5-year kidney transplants were 98.3, 96.4, and 92%, respectively in Shiraz (Hassanzade et al., 2011). Meanwhile, the survival rates of 1- and 5-year kidney transplants were respectively reported as 93 and 75% in Egypt, 2005 (El-Husseini et al., 2005). Selecting a proper model for analyzing the survival data depends on the hypotheses known as model assumptions. For example, in Cox regression model, it is essential that such options as hazard proportionality and independent time of occurrence be working. If the data is complicated, it may make using the models problematic and restricted (Kutner et al., 2004). One way to tackle such problems is to apply artificial neural network (ANN) models that have been increasingly used in recent decades (Warner and Misra, 1996). These models developed due to being distribution-free and requiring no option. Every ANN comprises some layers including simple inter-related processing components called neurons. Generally, neuron is the smallest data processing unit forming the basis of network performance. The neurons existing at the same level form a layer. In addition, each layer has its own weight indicating the rate of interaction between two neurons. A neural network commonly has three input, middle (hidden) and output layers. Each layer is connected to one or more middle layers. Then, middle layers are also linked to the output layer. The network output will be the desired respond. Any neuron has a threshold along with an activation function playing a role in the educational process. Learning occurs in the applicable perceptron network through minimizing the mean square output and using the learning algorithm after the distribution of errors by means of numerical iteration methods (Warner and Misra, 1996). Since ANNs models are known as black box models and, like classical models, do not offer coefficients such as OR and ß to determine the effect of each independent variable in the model, we come to study the Wrapper characteristic selection method. In a study entitled “comparison of ANN and Cox regression models in predicting the survival of the patients with gastric cancer” in 2010, data for 436 patients referring to the Taleghani Hospital in Semnan for surgical operation from 2002 through 2006, was collected. The data was randomly divided into two educational and experimental groups. Cox proportional hazard model, and a three-layer ANN model were used for analyzing the data. The ANN model (81.51%) resulted in a better prediction compared to Cox regression model (72.6%). Moreover, ROC[1] areas under the curve for ANN and Cox regression models were 82.6% and 75.4%, respectively. Therefore, it is suggested that ANN model can be used in the studies for survival prediction (Biglarian et al., 2010). Many studies have been conducted on analyzing the survival of the transplanted kidneys in Iran. Since ANN is not so much considered, we decided to study the prediction of the 5-year survival of transplanted kidneys through the ANN model and its comparison with Cox regression.

MATERIALS AND METHODS

This multi-center retrospective study was carried out on the medical records of 756 kidney-recipient patients undergoing kidney surgical operation at Imam Reza and Chaharomin Shahid-e Mehrab treatment centers from 2001 through 2012. The patients that were followed for less than three months were excluded from the research. The exact time of transplant was considered as the initial event and the time of irreversible transplant rejection was seen as the final event, causing the individual to return to treatment

[1] Receiver Operating Characteristic

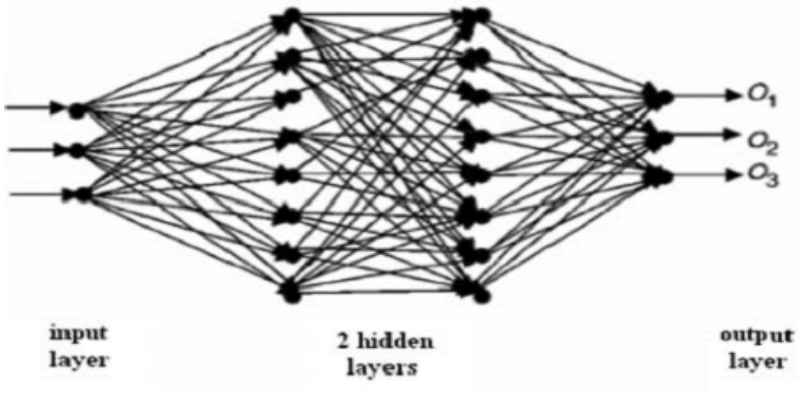
with dialysis and, in some cases, resulting in the patient's death. The cases where the final event has not occurred due to leaving the problem or the patient's death for reasons other than rejecting the transplant are regarded as censored data. Research data was collected from the medical records available at Chaharomin Shahid-e Mehrab and Imam Reza transplant centers. To determine the condition of transplant survival, follow-up medical records at the same centers, medical records available at nephrologists' offices and, in some cases, patients' contact numbers accessible in their medical records were used. Multi-layer perceptron (MLP) ANN model was applied to identify the risk factors of kidney transplant survival. In the Wrapper technique, all the cases where independent variables are introduced into the model (2^n, where *n* denotes the number of independent variables) are considered. As we regarded seven variables, we introduced 128 possible cases into the ANN model, selecting the one with maximum TCR[2] as the superior model. 70% of the observations in the training phase and 30% were allocated to the test. The variables introduced into the study included donor's and recipient's sex, blood group consistence, initial disease, donor's relationship (relative and non-relative), transplanted kidney's position, and the rate of creatine at discharge time. ROC analysis was used for comparing Cox regression and ANN models. This curve means sensitivity in terms of one minus specificity, and the area under it ranges between 0 and 1. It is used as a criterion for measuring the prediction ability of the models. The nearer the number is to 1, the more able it is to predict (13 metabolic syndromes). To analyze the data, MATLAB (ver. 2009) and SPSS (ver. 16) software were used.

Prediction models

Multi-layer perceptron (MLP) artificial neural network

Considering an assumption distribution such as normal distribution for response variables, linearity of the suggested relationship, and variance of errors similarity are among the limitations of classical methods. Moreover, none of these methods has the ability of modeling the complicated nonlinear relationships and high-degree interaction. ANN is used for detection, classification, and prediction of the cases where the relationships are usually nonlinear. Perceptron ANN is a type of neural network based on a computational unit called perceptron. In fact, perceptron takes a vector of inputs with real values and computes a linear combination of them. If the resulting number is greater than a certain threshold, perceptron output equals to 1; otherwise, it equals to -1. Multi-layer perceptron ANN is mainly used for solving complicated problems due to its parallel valuable abilities and learning. Learning process in these networks takes place through certain algorithms that instruct the network by regulating the weights in the relationships among neurons (Quchani and Tahami, 2007). ANN is a type of processing system inspired by biologic neural systems like brain. Data processing system is a key element of the new structure many of which work together, such as brain hormones, to solve certain problems like model identification or data classification through the learning process. Learning in neural networks occurs in two ways: (1) supervised, and (2) unsupervised. It is supervised in common neural networks. Indeed, the task of neural networks is similar to learning process in children. By showing an object, its nature becomes clear for a child.

[2] Text character recognition



Findings

In this cohort retrospective research, 756 patients receiving kidney transplant from 2001 through 2012, were studied. As table 1 shows, 756 kidney transplant recipients included 407 men and 349 women. The donors consisted of 545 men and 211 women. The patients ranged from 4 to 74 years old with a mean age of 39.6±13.4. In addition, the transplant donors had a mean age of 27.4±5.7. Concerning blood groups, O had the highest rate of 272 individuals (36.2%), while AB having the lowest rate of 45 individuals (6%). Moreover, 265 patients (35.1%) underwent a right-kidney transplant, whereas 491 patients (64.9%) received a left-kidney transplant. A number of 722 recipients (95.5%) had received kidneys from non-relative donors. In about 22 percent of cases, the reason for suffering from ESRD was unclear. Otherwise, it was mainly due to hypertension, diabetes, and polycystic, respectively. The patients' pre-operative dialysis time ranged from zero through 72 months, with a mean of 17.8±12.7 months. Their mean follow-up time was 37.8±38.4 months.

Table 1. *Frequency distribution of the transplanted patients based on the variables under study*

Variable	Sub-group	Quantity	Percent
Donor's sex	Man	545	(72.1)
	Woman	211	(27.9)
Recipient's sex	Man	407	(53.8)
	Woman	349	(46.2)
Transplanted Kidney's position	Right	265	(35.1)
	Left	491	(64.9)
Donor's relationship	Non-relative	722	(95.5)
	Relative	34	(4.5)

Blood group	Same	734	(97.1)
	Different	22	(2.9)
Postoperative Creatine	>2	436	(57.7)
	<2	320	(42.3)
initial disease	hypertension	151	(20)
	Diabetes	123	(16.3)
	polycystic	107	(14.2)
	Syndrome nephrotic	97	(12.8)
	glomronphrite	86	(11.4)
	Unknown	167	(22.1)
	Other	25	(3.2)

As shown in figure 1, based on Kaplan-Meier method, the survival rates of 6-month, 3-year, and 5-year transplanted kidneys were 89, 87.4,80, and 75 percent, respectively.

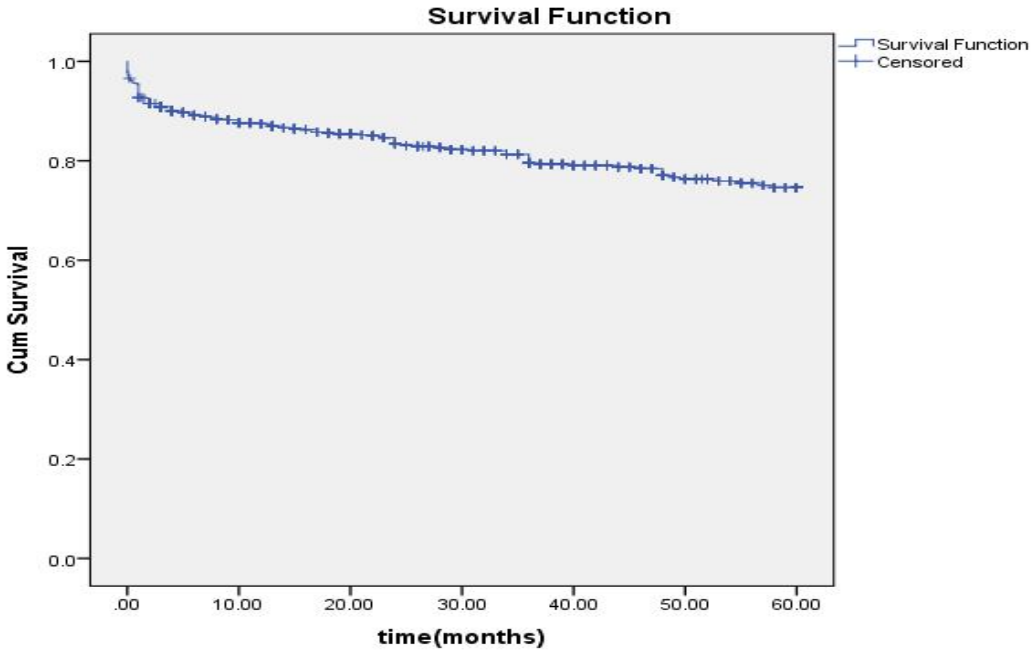


Fig. 1. Kaplan-Meier diagram for the 5-year survival of kidney transplant

For modeling the factors influencing the rate of transplant survival, such variables as donor's and recipient's sex, transplanted kidney's position, blood group consistency, initial disease, family relationship, and the amount of post-operative creatinine were introduced into Cox regression model by means of the Enter method. Among them, family relationship and the amount of post-operative creatinine were significant variables, having the highest RR. In other words, the patients who had received kidneys from their relatives and those with an amount of post-operative creatine lower than two had a more durable transplant survival (table 2).

Table 2 *. RR reject transplanted patients based on the variables under study*

Variable	Exp(coefficient)(RR)	P value
Donor's sex	1.25	0.286
Recipient's sex	1.31	0.182
Donor's relationship	0.212	0.03
Postoperative Creatinine	5.46	0.001
Transplanted Kidney's position	0.73	0.158
initial disease	1.04	0.256
Blood group	0.27	0.067

MLP neural network model provided the highest diagnostic value among 124 possible conditions for a case where donor's and recipient's sex, family relationship, rate of post-operative creatinine, initial disease and blood group consistency are simultaneously introduced into it with the 6.6.6.2 model (i.e., 6 input variables, 6 variables in the first middle layer, 6 variables in the second middle layer, and 2 variables in the output layer), with TCR=88.6. ROC areas under the curve were estimated for MLP neural network and Cox regression models, being 81.3% and 71%, respectively (*See* diagram 2). According to the diagram, ANN model has better prediction ability.

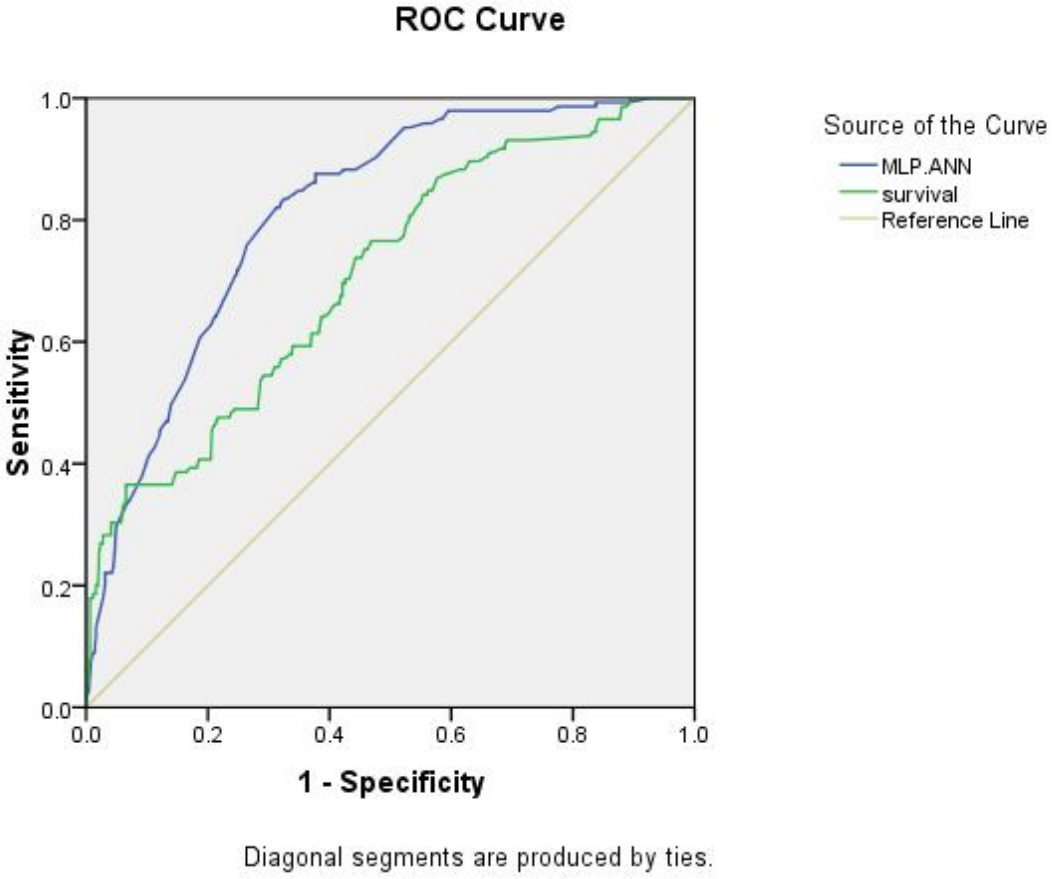


Figure 2: ROC curve for ANN and cox regression(survival)

DISCUSSION

Because of the advances in surgical methods and immunosuppressive therapy, the rate of transplant survival has increased compared to past decades. The results showed that the rates of 6-month, 1-year, 3-year, and 5-year transplanted kidneys were 89, 87.4, 80, and 75 percent, respectively. Ashrafi *et al*. (2008), in their study, reported the rate of the 1-year survival as 96 percent (Ashrafi et al., 2009), being more than that in the present research. This study shows relatively better results for both 1-year and 5-year time sections compared to those obtained from the research conducted in Tehran (Ghods et al., 2000). Rezaei , in their study carried out in Kermanshah, reported that the rates of 1-year and 5-year survivals for the transplants from family relatives were 97.4 and 86.8 percent, respectively. However, in the present research, they were respectively 97 and 91 percent so that we may witness a better condition for the 5-year survival. In their study, Rezaei at al. also reported the rates of 1-year and 5-year survivals for the transplants received from non-relative donors to be 85.6 and 67.6 percent, respectively (Rezaei et al., 2002). These rates were respectively 87 and 47 percent in the present study, being more than those in the previous research conducted in Kermanshah. To compare these results with those of the overseas studies, we can point to a study conducted in Egypt. The rates of 1-year and 5-year survivals were

reported as 93 and 75 percent, respectively (El-Husseini et al., 2005). In this research, the rate of 1-year survival has been lower, but the 5-year one has been similar to that in Egypt. The differences observed between these two centers may be due to the fact that the studies have not been simultaneously conducted. However, other reasons such as the experience of the transplant centers and their physicians may be developed for the differences in the cumulative probability of transplant survival. In this study, the results of semi-parametric Cox regression model were compared with those of ANN model through ROC curve in prediction of kidney survival in the patients receiving kidney transplant. Research findings revealed that ANN model has better prediction ability than that of Cox regression model. Moreover, ANN model possessed acceptable specificity and sensitivity. Many studies have been conducted on the application of ANN for analyzing the survival data, and most of them have evaluated the results of the model to be favorable. For example, the study by Ashrafi at al. reported the network accuracy as 79 percent (Ashrafi et al., 2009), being lower than the 83-percent accuracy of the present research. However, Santori showed a better performance with an accuracy of 87 percent (Santori et al., 2007). In a study by Biglarian *et al*., ROC areas under the curves were reported as 82.6 and 75.4 percent for ANN and Cox regression models, respectively. Like the present study, it also indicates the superiority of the ANN model (Biglarian et al., 2010).

Conclusion

In the ANNs model known as black box, it is difficult to extract data (such as OR and ß). In fact, they offer an overview of the relationships. However, if we properly instruct the network and obtain the best structure for prediction, the network may be able to provide us with a suitable prediction of the new data. This fact is quite important in managing the treatment resources for those who are predicted as risky individuals. Kidney survival was more durable than that in the previous study in Kermanshah. It is common to apply regression methods for analyzing the survival data due to presenting hazard ratios and coefficients. If we obtain a structure with high prediction ability in the neural network, we may identify the high risk patients and consider more treatment resources for them.

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