RESEARCH ARTICLE

Comparison of the Performance of Log-logistic Regression and Artificial Neural Networks for Predicting Breast Cancer Relapse

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Abstract

Background: Breast cancer is the most common cancers in female populations. The exact cause is not known, but is most likely to be a combination of genetic and environmental factors. Log-logistic model (LLM) is applied as a statistical method for predicting survival and it influencing factors. In recent decades, artificial neural network (ANN) models have been increasingly applied to predict survival data. The present research was conducted to compare log-logistic regression and artificial neural network models in prediction of breast cancer (BC) survival. Materials and Methods: A historical cohort study was established with 104 patients suffering from BC from 1997 to 2005. To compare the ANN and LLM in our setting, we used the estimated areas under the receiver-operating characteristic (ROC) curve (AUC) and integrated AUC (iAUC). The data were analyzed using R statistical software. Results: The AUC for the first, second and third years after diagnosis are 0.918, 0.780 and 0.800 in ANN, and 0.834, 0.733 and 0.616 in LLM, respectively. The mean AUC for ANN was statistically higher than that of the LLM (0.845 vs. 0.744). Hence, this study showed a significant difference between the performance in terms of prediction by ANN and LLM. Conclusions: This study demonstrated that the ability of prediction with ANN was higher than with the LLM model. Thus, the use of ANN method for prediction of survival in field of breast cancer is suggested.

Keywords: Breast cancer - log-logistic regression - artificial neural networks - prediction - disease free

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Introduction

Breast cancer (BC) is one of the most common cancers in female population and the most important cause of death due to cancer in female's worldwide (Jemal et al., 2011; National cancer institute, 2012; WHO, 2012). Breast cancer is a malignant tumor that develops from uncontrolled growth of cells in the breast and a malignant tumor is composed of cells that invade or spread to other parts of the body (National Cancer Institute, 2012; WHO, 2012).

The exact cause of breast cancer is not known, but is most likely to be a combination of genetic and environmental factors. However, in general, earlier diagnosis and treatment should increase survival rates, as the disease is much easier to control if it has not spread to other parts of the body (National Cancer Institute, 2012).

About 23% of total new cancer cases and 14% of the cancer death in females in 2008 are due to breast cancer (Jemal et al., 2011). Many risk factors such as family history, age, tumor size, early diagnosis are known to play important a role in pathogenesis of metastasis and death in BC patients (Faradmal et al., 2010). Prediction of survival or disease free time based is one of the most interesting areas in data mining applications (Kurt et al.; 2008; Faradmal et al., 2010).

In addition to traditional survival model such as Cox proportional hazard model and accelerator survival models, artificial neural networks (ANN) are popularly used in medicine. These methods have been widely used as prediction model in censored survival data (Xiang et al., 2000; Jerez et al., 2005; Chi et al., 2007; Eleuteri et al. 2007; Giordano et al, 2011). ANN were applied in different survival analysis studies such as the analysis of circulating tumor cells in metastatic breast cancer patients (Giordano et al., 2011), classification of micro-calcification in mammograms (Deheeba et al., 2011), classification of BC (Naghibi et al., 2011), prediction and classification of

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cancer patients based upon their gene expression profiles (Lancashire et al., 2008).

Many studies have been published on the comparison of ANN with other traditional statistical models. These studies often compare the ANN with classification methods. Kazemnejad et al. (2010) compared binary logistic regression and ANN in their ability to differentiate between disease-free subjects and those with impaired glucose tolerance or diabetes mellitus diagnosed by fasting plasma glucose (Kazemnejad et al., 2010). Kim and et al, also, compared the performance of logistic regression and ANN in differentiation of benign and malignant breast masses (Kim et al., 2012). Kurt et al. (2008) in a retrospective study, compared the performances of classification techniques including multi-layer perceptron (MLP), radial basis function, self-organizing feature maps, logistic regression and classification and regression tree, in order to predict the presence or absence of coronary artery disease in 1245 subjects (Kurt et al., 2008). Rughani and et al used an artificial neural network to predict head injury outcome (Rughani et al., 2010). The authors describe the artificial neural network as an innovative and powerful modeling tool that can be increasingly applied to develop predictive models in neurosurgery. They aimed to demonstrate the utility of an ANN in predicting survival following traumatic brain injury and compare its predictive ability with those of 2 logistic regression models and clinicians (Rughani et al., 2010).

Few papers have been published on the comparison of ANN with other prediction models of hazard or survival times. Gohari et al. (2011) predicted the survival time of colorectal cancer patients using an artificial neural network model. They compared the accuracy of prediction of ANN and Cox model. Biglarian et al. (2012) used an ANN to predict metastasis.

Some studies have compared ANN with Cox Model in chronic disease (Hashemian et al., 2013; Zhu et al., 2013). Tangri and et al designed a study to compare the factors that predict survival on peritoneal dialysis using ANN, logistic and Cox regression methods (Tangri et al., 2011).

Shi and et al designed a study to validate the use of ANN model for predicting in-hospital mortality in HCC surgery patients in Taiwan and to compare the predictive accuracy of ANN with that of LR model. The results is showed In comparison with the conventional LR model, the ANN model in the study was more accurate in predicting in-hospital mortality and had higher overall performance indices (Shi et al., 2012).

Parsaeian and et al compared the empirically predictive ability of an artificial neural network with a logistic regression in prediction of low back pain. They demonstrated that artificial neural network would give better performance than logistic regression. Although, the difference is statistically significant, it does not seem to be clinically significant (Parsaeian et al., 2012).

In addition, some studies compared neural networks model with other techniques including observed survival in patients with colonic cancer (Dolgobrodov et al., 2007), proportional hazards model to predict survival in patients undergoing resection of head and neck squamous cell cancer, and support vector machine to predict survival time for rats with hemorrhagic shocks (Jang et al., 2011).

The purpose of this study is the comparison of performances in two prediction models in order to predict the disease free survival time of women with breast cancer. We have created models using log-logistic model (LLM) and ANN model which are often used to predict free survival (DFS) in patients with breast cancer. LLM is a completely useful parametric model for situations in which the odds ratio of DFS for two cases is constant over time. This model may be used when the PH assumptions are not satisfied for covariates but the hazard of two different persons does not cross (Faradmal et al., 2010). On the other hand, ANNs have been used to model medical and functional outcomes of different disease. They have become a popular tool for prediction, as they are very flexible, not assuming predetermined parametric form for survival time (Chi et al, 2007; Giordano et al., 2011; Naghibi et al., 2011). In the current study, the performances of two above- mentioned prediction techniques were compared using area under the Receiver operating characteristic (ROC) curve (AUC) and integrated AUC (iAUC).

Materials and Methods

Data

A historical cohort study was performed on 104 patients with BC. During our study, 41 (41.5%) cancer patients developed metastasis. These patients had visited three teaching hospitals including Shohadaye Tajrish, Madaen and Shahid Fayyazbakhsh. Inclusion criteria was as follows: (i) undergone modified radical mastectomy or breast conservative surgery, (ii) with no metastasis at the time of surgery, (iii) aged 36-70 years at time of diagnosis of breast cancer, (iv) node positive and (v) undertaken adjuvant chemotherapy for the first time using either CMF, anthracycline-based or Taxane-based regimes. Patients with poor quality data were eliminated from the study.

Independent variables included ''type of surgery, adjuvant chemotherapy regime, histological grade, number of involved lymph node, tumor size, and age at diagnosis''. Tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer (AJCC, 2002) was used to tumors classification and Scarff-Bloom-Richardson was used as the grading system. Three types of adjuvant chemotherapy were considered including (i) CMF regime: cyclophosphamide, methotrexate and 5-fluorouracil (ii) anthracycline-based regimes: chemotherapy regimens containing doxorubicin and (iii) Taxane-based regimes: chemotherapy regimens contain a Taxane agent such as paclitaxel or docetaxel. After chemotherapy, Tamoxifen was given to all positive estrogen receptor patients.

Patients were regularly followed up by clinical examinations, laboratory profiles, serologic markers and imaging evaluations. The dependent variable, DFS, was recorded in the terms of the number of days from surgery to the first recurrence/metastasis. Different methods including biopsy, chest X-ray, ultrasound, bone scan, liver sonography and marker rising with physician confirmation were used for the determination of endpoint. Subjects with missing data on prognosis factors or metastasis status were reached one way or another, mainly through phone calls. Patients who died before the first metastasis or did not experience the metastasis before the data collection ends were considered as censored.

Before building models, the data set was randomly split into two subsets, training and test sets. About 80% (n = 84) of the records was considered for training set and 20% (n = 20) of the records for test set.

Prediction techniques

Multi-layer perceptron: MLP, the most popular static network, consists of three classes of layers of adaptive weights. The first and the last layers are input and output layers, respectively. The layer between these two layers is the hidden layer. Each layer consists of several neurons and every neuron in one layer transmits its output forward to every neuron in the next layer. The mission of neurons is simple. They sum their inputs and compute an appropriate output upon the activation function.

This network can be obtained from a given data set. Learning is based on the definition of a suitable error function, which is optimized with respect to the weights and biases in the network. ANN for k independent variables and m neurons in the hidden layer can be written as follow: $\hat{y} = f[b_0 + \sum_{j=1}^{m} w_j f(\sum_{i=1}^{m} w_{ij} I_i + b_{Hi})]$

Where b_0 and b_H are the biases parameters and ws' are the weights. We use a logistic activation function for both of the hidden and output layers which are given by $f(x) = (1 + e^{-x})^{-1}$.

Log-logistic model: Royston used log-normal as the suitable model for relapse time of patients with BC and ovarian cancer (Royston et al, 2001). Hazard function of log-normal distribution can decrease over time or initially increase to a peak and then decrease (Kleinbaum et al, 2005). While the hazard function of log-normal is similar to hazard function of log-logistic distributions, the latter has the advantage of having constant odds ratio over time (Faradmal et al, 2010; Kleinbaum et al, 2005). LLM for p prognosis factors can be written as: $S_T(t) = \{1 + \exp[(t - (\beta_0 + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_p x_p)) \div \sigma]\}^{-1}$ $\sigma > 0$

Where $S_T(t)$ is the probability that the DFS is bigger than t, some specified time. Also β_0, β_1, ..., β_p are the model coefficients and σ is the shape parameter (Kleinbaum et al., 2005).

Comparison of models: to compare ANN and LLM in our setting, we used the estimated areas under the receiver-operating characteristic (ROC) curve (AUC) and integrated AUC (iAUC) which were proposed by Uno and et.al (Uno et al., 2007). ROC curves are popular tools to evaluate the accuracy of classifiers or the predictive ability of diagnosis tests in clinical medicine. Uno et.al proposed iAUC and estimated the prediction accuracy for time-to-event data when the random censoring assumption holds (Uno et al., 2007). The estimator is based on inverse-probability-of-censoring weights and is not limited to Cox proportional hazard model. Estimated iAUC were compared using the rank sum test method for dependent samples (Haibe-Kains et al., 2008).

Software: the software we used to analyze the database was 'R', Version 2.15.0, which is an open-source computing software freely available from http://www.r-project.org (R Development Core Team, 2011). R packages including 'survnnet' version 7.3-1, 'survival' version 2.36-14, 'survAUC' version 1.0-2 and 'survcomp' version 1.6.0 were used for fitting the feed forward neural network, LLM, iAUC estimation of the two above mentioned models and comparison of two estimated iAUCs, respectively (R Development Core Team, 2011).

Results

Comparison of patients' characteristics

The patients' characteristics are shown in Table 1. The difference in mean of age and age at menarche between the censored and complete response data was examined by the Mann–Whitney–Wilcoxon test. Chi-square test was used to examine the relation between qualitative variables. The results indicated that there is no statistical

Table 1. Comparison of Pathological Characteristics of Patients with Metastasis and No-metastasis Observed

	Metastasis Not observed		Metastasis observed		p values
	N	Mean (SD)	N	Mean (SD)	
Age at diagnosis	61	49.33 (10.160)	43	45.81 (9.725)	0.153
Menarche age	53	13.75 (1.108)	41	13.56 (1.026)	0.929
	N	(%)	N	(%)	
Adjuvant					
CMF	18	48.60	19	51.40	0.053
Chemotherapy					
Anthracycline-based	20	54.10	17	45.90	
Taxane-based	23	76.70	7	23.30	
Tumor Size (cm)					
<2	6	54.5	5	45.5	0.147
2-5	41	66.1	21	33.9	
Lymph Nodes (n)					
1-3	35	63.6	20	36.4	
4-10	13	50	13	50	0.434
>10	11	52.4	10	47.6	
Histological grade					
Well differentiated	14	70	6	30	0.577
Moderately differentiated	25	58.1	18	41.9	
Non-differentiated	22	56.4	17	43.6	

Table 2. Potential Pathological and Clinical Prognostic Factors Under Log-logistic Model

	Value	Std. Error	p value	Adj. OR (95%CI)
Adjuvant chemotherapy				
Anthracycline-based or CMF	Ref			
Taxane-based	0.335	0.259	0.196	1.398 (0.842, 2.323)
Involved Lymph node (n)				
1-3	Ref			
>3	-0.065	0.199	0.745	0.937 (0.635, 1.384)
Histological grade				
Well differentiated	Ref			
Moderately differentiated	-0.46	0.283	0.103	0.631 (0.363, 1.099)
Non-differentiated	-0.734	0.275	0.008	0.480 (0.280, 0.823)
Tumor size (cm)				
<2	Ref			
2-5	-0.142	0.382	0.71	0.867 (0.410, 1.833)
>5	-0.373	0.397	0.347	0.689 (0.316, 1.499)
diagnosis Age (years)				
≥45	Ref			
<45	-0.18	0.199	0.366	0.836 (0.566, 1.234)

*Ref: reference level; **Chi^2=15.54; df=7; p value=0.03

difference between the characteristics of subjects who develop metastasis during the period of the study and the others who do not (p value >0.05).

Prediction of DFS

We used five affective variables (type of chemical treatment, number of involved lymph nodes, grade, tumor size and age) to predict the DFS of BC patients. These variables were the tumor size, histological grade, type of chemotherapy regimens (anthracycline-based or CMF as the reference category and Taxane-based regime), number of involvement lymph node (1-3 lymph nodes involved as the reference category and more than 3) and the patient's age at diagnosis (older than 45 years as the reference category and younger than 45). These variables were selected by backward stepwise method. The estimation of parameters of LLM is presented in Table 2. These estimations are based on data in training set.

With ANN, we used the above mentioned prognosis factors which are obtained for LLM as input variables with a single linear output. This model considers the location parameter of log-logistic distribution as a function of input variables. The neural networks were trained with training set to achieve the convergence. The best performance of ANN was obtained with 5 neurons in hidden layer.

Comparison of DFS predictors

Table 3. Areas Under the ROC Curves in Two Predicting Techniques

	Mean of AUCs	Sd of AUCs	iAUC	p value
Artificial neural network	0.845	0.063	0.847	<0.001
Log logistic model	0.744	0.095	0.749	

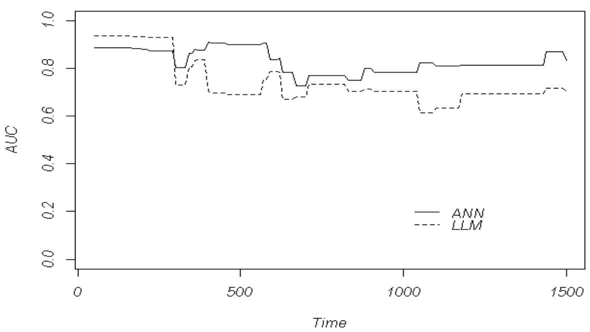

Figure 1. Time Dependent AUCs of ANN and LLM for Predicting of DFS

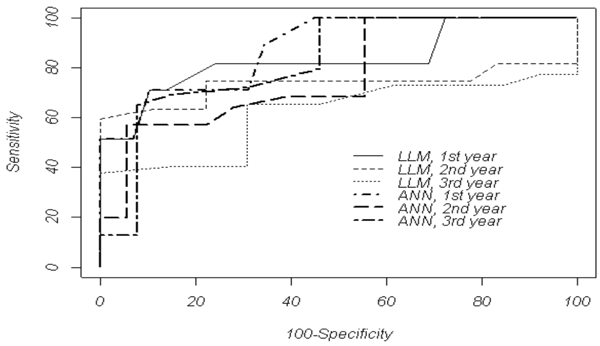

Figure 2. ROC Curves for ANN and LLM at 1, 2 and 3 Years After Diagnosis

We calculated the AUC for 50 to 1500 days after diagnosis for test data. The AUC values for LLM and ANN vary between 0.60 and 0.96. The results are illustrated in Figure 1. During the first 1500 days after diagnosis, the values of AUC in ANN model are greater than LLM ones (Figure 1). Specially, the AUC for the first, second and third years after diagnosis are 0.918, 0.780 and 0.800 in ANN, and 0.834, 0.733 and 0.616 in LLM, respectively (Figure 2).

Table 3 present the mean of AUC and iAUC values in two predicting techniques. A comparison of the ANN and LMM in terms of the iAUC was made using the Wilcoxon rank sum test for dependent samples (Haibe-Kains et al., 2008). The results showed that the performances of ANN and LLM were statistically different (p<0.001) and ANN predict DFS more accurately than LLM do.

Discussion

Breast cancer is the most frequent cancer and the most common cause of mortality due to cancer among women. Various statistical techniques have been developed to study the relation between prognosis variable and DFS/ survival time. Prediction time of the event is one of the main objects of these models. In the current study, we developed the LLM and ANN models to predict DFS of BC patients. The performance of the LLM and ANN models in predicting a subject's DFS was evaluated and compared using the AUC, a measure of concordance and iAUC proposed by Uno et al. (2007).

The LLM results reveals that adjusted on other prognosis factors, patients with Taxane-based therapy have better prognosis compared with non-Taxane-based therapy (Faradmal et al., 2010). However, because of the small sample size, the difference was not statistically significant. Also the results showed that early detection of BC may enlarge the DFS (Faradmal et al., 2010).

Based on Figure 1 and 2, the prediction ability reduces slightly over time. The prediction rule performs very well in both model for short term DFS (AUC about 95%), however, its prediction ability reduces for long term DFS (AUC about 65%). both models reviewed in this study have the potential to be used as predicting tools. Although the mean AUC values for both models were far from 0.5, the mean AUC for ANN (0.845) was statistically higher for the LLM (0.744). Some studies also showed that ANN performs as well as or better than traditional statistical models (Kurt et al., 2008; Kazemnejad et al., 2010; Hashemian et al., 2013; Zhu et al., 2013). However some other studies showed that the traditional model outperforms ANN (Xiang et al., 2000). The main reason for this controversy is related to the data structure. Prediction performance may differ from one data structure to another. If the correct functional form of the relation between prognosis factor and response is known, then it seems that the traditional statistical models perform better than ANNs (Kurt et al., 2008). However, in reality, the pattern of data is unknown and it is difficult to guess the appropriate form of this relationship. Then it is expected that ANN performs better than LLM in terms of prediction (Xiang et al., 2000; Kazemnejad et al., 2010; Parsaeian et al., 2012).

In this study, we assume the linear relationships among different risk factors and the (log) DFS of patients. As mentioned by Jerez et al. (2005) these relationships "may well be non-linear in nature" (Jerez et al., 2005), so, the LLM that assume the linear relationships among variables, cannot detect the probably non-linear relation in biological relationships.

One advantage of ANNs is that these models may rapidly recognize linear, non linear and/or even interaction effects (Zhu et al., 2013).

On the other hand, in the LLM, the exponential of the regression coefficients are interpretable as the odds ratio of DFS. Unlike traditional statistical models, neural networks are not effective in identifying the contribution of each variable on the response variable. Another disadvantage of ANN is that they are "computationally intensive"; convergence and training may take a long time and over learning may occur in such model (Xiang et al., 2000).

Finally, this study showed a significant difference between the performance in terms of prediction of ANN and LLM. Then this study suggests continuing the use of ANN to predict DFS. In addition, this study demonstrated the fact that the predicting ability of both techniques is reduced slightly over time. We conclude that the selection of prediction techniques for predicting DFS depends on our background knowledge on the data pattern and whether we want to determine the contribution of the variable in the model.

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