Comparison between artificial neural network and Cox regression model in predicting the survival rate of gastric cancer patients

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Abstract. The aim of this study was to determine the prognostic factors and their significance in gastric cancer (GC) patients, using the artificial neural network (ANN) and Cox regression hazard (CPH) models. A retrospective analysis was undertaken, including 289 patients with GC who had undergone gastrectomy between 2006 and 2007. According to the CPH analysis, disease stage, peritoneal dissemination, radical surgery and body mass index (BMI) were selected as the significant variables. According to the ANN model, disease stage, radical surgery, serum CA19-9 levels, peritoneal dissemination and BMI were selected as the significant variables. The true prediction of the ANN was 85.3% and of the CPH model 81.9%. In conclusion, the present study demonstrated that the ANN model is a more powerful tool in determining the significant prognostic variables for GC patients, compared to the CPH model. Therefore, this model is recommended for determining the risk factors of such patients.

Introduction

Although the global incidence of gastric cancer (GC) is on the decrease, it remains high in eastern Asia (1). GC remains one of the leading causes of cancer-related mortality worldwide, being the second most common type of cancer and the second most common cause of cancer-related mortality in China (2). It is the most frequently diagnosed cancer in rural areas and the incidence of GC among males and females is estimated to be 49.6 and 22.5, respectively, per 100,000 individuals (2).

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The determination of prognostic factors and survival rate of patients is crucial. Over the last decades, data analysts have used various survival methods, such as the Cox regression hazard (CPH) or the parametric regression models, for analyzing survival data sets. However, the human body is a complex biological system and the majority of the clinical characteristics exhibit a multidimensional and non-linear relationship. Thus, it is difficult to predict the prognosis of gastric carcinomas with a conventional statistical technique. The artificial neural network (ANN) is a novel computer model inspired by the function of the human brain. It is able to build non-linear statistical models to assess complex biological systems. Over the last few years, ANN models have been introduced in clinical medicine for clinical validations (3-6).

In this study, we developed an ANN model to determine the risk factors for GC patients.

Materials and methods

Patients. A total of 289 patients, including 218 men and 71 women, with a mean age of 63.20±10.75 years, with histologically proven gastric carcinoma who underwent surgery between March, 2006 and December, 2007 were enrolled in this study. Of these 289 patients, radical total gastrectomy was performed in 76 (26.3%), radical subtotal gastrectomy in 168 (58.1%) and palliative gastrectomy in 41 patients (14.2%). According to the American Joint Committee on Cancer TNM classification (7), 56 patients had stage I, 86 had stage II, 116 had stage III and 31 had stage IV disease. Peripheral blood samples were obtained from each patient within 1 week prior to surgery. The cut-off values for serum CEA and CA19-9 were 5 ng/ml and 37 U/ml, respectively. In this historical cohort study, the required information for each patient, including age at diagnosis, serum CEA and CA19-9 levels, ascites, peritoneal dissemination, curability of surgery, body mass index (BMI), histological grade and disease stage, was gathered from the registered patient documents of the First Affiliated Hospital of Wenzhou Medical College. The survival time of each patient (in months) following surgery was also registered.

This study was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical College,

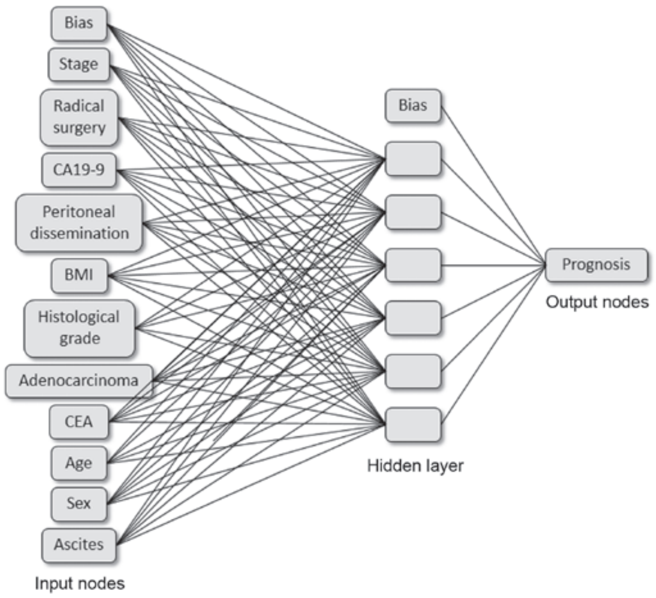

Figure 1. Schematic diagram of the artificial neural network model developed to predict the 5-year survival of gastric cancer. For data analysis, the SPSS software version 20.0 and the MATLAB software version 8.0 were used.

Wenzhou, China. Prior to this study, written informed consent was obtained from patients and their families.

Statistical analysis and neural network analysis. In the first step of data analysis, due to the survival nature of the outcome data, preliminary analyses such as the Kaplan-Meier and log-rank tests were performed. Subsequently, we utilized more complex statistical methods, including CPH and ANN models, for predicting patient survival rate. In the modeling process, we randomly divided data into two subsets: 173 patients were used for constructing the models (training subset) and the remaining 116 patients for assessing the validation of the models (testing subset). After evaluating the validation, the receiver operation characteristic (ROC) curve and the concordance index were applied to compare the prediction power of the described models. Of note, in fitting the ANN model we used a three-layer back-propagation neural network with 11 nodes in the input layer, 6 nodes in the hidden layer and 1 node in the output layer (Fig. 1). Since each patient's status was a binary response variable (deceased or censored), the sigmoid function was utilized as the activation function in the hidden and output layers. For net training, a back-propagation learning algorithm with a learning rate of 0.05 and a momentum of 0.9 was utilized. The learning process was discontinued when the average error (mean square error) in the training set decreased to 0.0001. We also applied the backward selection method (with a significant level of entry of 0.10 and a significant level of removal of 0.15) to fit the CPH model.

Results

Patient characteristics. The study sample comprised 289 GC patients, including 218 men (75.4%) and 71 women (24.6%). The mean age of the patients was 63.20±10.75 years. The characteristics of the patients under study are provided in Table I.

Table I. Patient characteristics.

Variables	No.	%
Age (years)		
≤65	148	51.2
>65	141	48.8
Gender		
Male	218	75.4
Female	71	24.6
BMI		
<18.5	34	11.8
18.5-23.9	199	68.9
27-29.9	47	16.3
≥30	9	3.1
Stage[a]		
IA	33	11.4
IB	23	8.0
IIA	37	12.8
IIB	49	17.0
IIIA	34	11.8
IIIB	46	15.9
IIIC	36	12.5
IV	31	10.7
Peritoneal dissemination		
Absent	268	92.7
Present	21	7.3
Ascites		
Absent	242	83.7
Present	47	16.3
Histological grade		
G1	7	2.4
G2	55	19.0
G3	205	70.9
G4	22	7.6
Histological type		
Adenocarcinoma	224	77.5
Other	65	22.5
Radical surgery		
No	41	14.2
Yes	248	85.8
CEA level		
Normal	240	83.0
Elevated	49	17.0
CA19-9 level		
Normal	226	78.2
Elevated	63	21.8

[a]AJCC Cancer Staging Manual Seventh Edition. BMI, body mass index; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

Modeling process. In the first step of the modeling process, data were divided in training (~60% of patients) and testing (~40% of patients) subsets. The Mantel-Cox test demonstrated

Table II. CPH and ANN modeling results of prognostic factors on gastric cancer patient survival.

CPH model	
Ordered factors	P-value
Stage	<0.001
Peritoneal dissemination	0.004
Radical surgery	0.022
BMI	0.092
Age	0.134
Histological grade	0.176
CEA	0.275
CA19-9	0.401
Ascites	0.738
Gender	0.758
Adenocarcinoma	0.814
ANN model	
Ordered factors	Normalized importance
Stage	0.241
Radical surgery	0.222
CA19-9	0.115
Peritoneal dissemination	0.074
BMI	0.073
Histological grade	0.067
Adenocarcinoma	0.062
CEA	0.043
Age	0.042
Gender	0.032
Ascites	0.029

CPH, Cox proportional hazard; ANN, artificial neural network; BMI, body mass index; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

Table III. Classification accuracy of ANN and CPH models in the testing subset.

Groups	Observed (no.)	True prediction by ANN no. (%)	True prediction by CPH no. (%)
Deceased	57	50 (87.7)	48 (84.2)
Survived	59	48 (81.4)	47 (79.7)
Total	116	98 (85.3)	95 (81.9)

ANN, artificial neural network; CPH, Cox proportional hazard.

that the estimated survival curves using the training and testing subsets exhibited no significant differences (P=0.650). In the following step, based on the validation set, the CPH and ANN models were used to determine the risk factors. The results are shown in Table II. To compare the accuracy of prediction between the models, we used true classification (the proportion of patients that were accurately classified in the 'deceased' and 'survived' groups) of the patients in the testing subset. The obtained results are shown in Table III. The ANN model led to more accurate predictions compared to the CPH model (true prediction of 85.3 vs. 81.9%). The area under the ROC curve, calculated from testing data, was 0.891 for the ANN model and 0.824 for the CPH model.

Discussion

GC is the most prevalent malignancy in China and worldwide. The aim of this study was to identify the most significant prognostic factors of GC and compare the ability of CPH and ANN models in predicting the survival of GC patients.

ANN models exhibit several advantages over conventional statistical methods. They may rapidly recognize linear patterns, non-linear patterns with threshold impacts, categorical and stepwise linear patterns, or even contingency effects (8). ANN analyses need not start with a hypothesis or *a priori* identification of potential key variables. Therefore, undocumented or quantified potential prognostic factors may be determined if they already exist in the various datasets, although they may have been overlooked in the past.

In this study, the CPH analysis demonstrated that the survival time of the patients was associated with disease stage, peritoneal dissemination, radical surgery, BMI, age at diagnosis, histological grade, serum CEA level, serum CA19-9 level, ascites, gender and adenocarcinoma, in that order of importance. In this analysis, disease stage, peritoneal dissemination, radical surgery and BMI were significantly associated with survival time. Based on the ANN model, disease stage, radical surgery, serum CA19-9 level, peritoneal dissemination, BMI, histological grade, adenocarcinoma, serum CEA level, age at diagnosis, gender and ascites were identified as the significant variables, in that order of importance. Of these variables, disease stage, radical surgery, serum CA19-9 level, peritoneal dissemination and BMI were the most significant. This result may be attributed to the interaction terms between the variables considered in the ANN model.

Previously published studies reported that disease stage is the most important prognostic factor in GC patients (9-11). Additional studies identified other risk indicators, such as gender, number of involved lymph nodes, histological type and type of complementary treatment, as the significant effective factors for survival of GC patients (12-17). Lai *et al* (18) conducted an ANN-based study for the prediction of tumor staging in GC patients. They reported an accuracy of 81.8% in predicting tumor stage in primary GC patients. In another study conducted by Chien *et al* (19), the ordinary logistic regression, ANN and decision tree methods were used for predicting postoperative complications of GC patients. The results of that study indicated that the ANN was a more accurate technique for predicting postoperative complications, compared to the logistic regression and decision tree methods.

In the present study, we compared the results of the CPH and ANN models in determining significant risk factors and true prediction of GC patients. Our findings indicated that the ANN is an appropriate technique for this purpose.

In conclusion, the ANN model appears to be more efficient in determining the prognostic factors of GC patients compared to the CPH model. Therefore, it is recommended for determining the significant risk factors and survival of GC patients.

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