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AIMS AND SCOPE

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Application of preoperative artificial neural network based on blood biomarkers and clinicopathological parameters for predicting long-term survival of patients with gastric cancer

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Abstract

BACKGROUND
Because of the powerful abilities of self-learning and handling complex biological information, artificial neural network (ANN) models have been widely applied to disease diagnosis, imaging analysis, and prognosis prediction. However, there has been no trained preoperative ANN (preope-ANN) model to preoperatively predict the prognosis of patients with gastric cancer (GC).

AIM
To establish a neural network model that can predict long-term survival of GC patients before surgery to evaluate the tumor condition before the operation.

METHODS
The clinicopathological data of 1608 GC patients treated from January 2011 to

April 2015 at the Department of Gastric Surgery, Fujian Medical University Union Hospital were analyzed retrospectively. The patients were randomly divided into a training set (70%) for establishing a preope-ANN model and a testing set (30%). The prognostic evaluation ability of the preope-ANN model was compared with that of the American Joint Commission on Cancer (8th edition) clinical TNM (cTNM) and pathological TNM (pTNM) staging through the receiver operating characteristic curve, Akaike information criterion index, Harrell's C index, and likelihood ratio chi-square.

RESULTS
We used the variables that were statistically significant factors for the 3-year overall survival as input-layer variables to develop a preope-ANN in the training set. The survival curves within each score of the preope-ANN had good discrimination ($P < 0.05$). Comparing the preope-ANN model, cTNM, and pTNM in both the training and testing sets, the preope-ANN model was superior to cTNM in predictive discrimination (C index), predictive homogeneity (likelihood ratio chi-square), and prediction accuracy (area under the curve). The prediction efficiency of the preope-ANN model is similar to that of pTNM.

CONCLUSION
The preope-ANN model can accurately predict the long-term survival of GC patients, and its predictive efficiency is not inferior to that of pTNM stage.

Key words: Gastric cancer; Artificial neural network model; Prognostic model; Preoperative; Blood biomarkers; Long-term survival

Core tip: We established an artificial neural network model before surgery that can predict the long-term survival of patients with gastric cancer, and its predictive efficiency is not inferior to that of pathological TNM stage.

INTRODUCTION

Gastric cancer (GC) is one of the five most common malignant tumors in the world, and it is the third leading cause of death in cancer patients[1]. Despite the progress in the diagnosis and treatment of GC, the prognosis of GC patients is still very poor, especially the long-term survival of advanced GC patients, for which the 5-year survival rate is only 10%[2]. Most scholars have focused on how to accurately distinguish the stages of GC in patients. The improved postoperative American Joint Commission on Cancer (AJCC) TNM staging system based on pathological examination is currently the most important and recognized prognostic staging system for GC[3-5]. However, this scoring system needs to be performed based on the pathological analysis of tumor specimens and examination of lymph nodes after surgery, which cannot provide a reference for preoperative treatment and consultation. Recently, the treatment for GC has gradually changed from simple surgical treatment to comprehensive treatment with the core being surgical treatment. Accurate preoperative tumor assessment providing a reasonable individualized treatment for GC patients is the key to improving the prognosis of patients with GC. However, the single traditional index, namely, the clinical TNM (cTNM) staging system based on the imaging examination, does not show the ideal accuracy of preoperative tumor assessment. Therefore, it has been a challenge in clinical work to explore the markers and methods for preoperative accurate tumor assessment.

In recent years, increasingly more scholars have believed that the inflammation indexes are relevant to the survival of cancer patients[6,7]. Some scholars have reported that inflammatory cells may promote tumor growth and progression of the disease, rather than produce an effective host antitumor response. Consequently, the inflammatory biomarkers in peripheral blood are potential predictors of cancer prognosis[8-11]. It has been reported that several indexes from peripheral blood, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and albumin-globulin ratio (AGR), have a powerful impact on the prognosis of GC[8,11-14]. The prognostic nutrition index (PNI) based on lymphocyte and albumin levels is a feasible parameter to reflect the immune and nutritional status of patients with a malignant tumor and is regarded as a good index to evaluate the prognosis of patients with GC[3,15]. Although the previously established inflammatory models could predict the prognosis of patients with GC, their accuracy was still not satisfactory. Furthermore, many pathophysiological processes of malignant tumors are nonlinear processes, which cannot be well reflected through traditional linear analysis methods. Many studies have shown that artificial neural networks (ANNs) can deal with the nonlinear statistical relationship better than the traditional analysis methods, including studies on the prognosis of various cancers[16-18]. It has been reported that ANNs had a more accurate prognostic ability than TNM staging in patients with breast and rectal cancers[19]. However, there is no study on the relationship between a preoperative ANN (preope-ANN) and the prognosis in GC patients. Therefore, this study combined the preoperative blood biomarkers and preoperative tumor data to establish an ANN model in order to build a reliable preoperative prediction system that can achieve the same effect of postoperative TNM staging. The aim of this study was to evaluate the prognosis of patients with GC and to provide a reasonable individualized treatment plan for patients.

MATERIALS AND METHODS

Patients

The clinicopathological data of 1860 GC patients treated at the Department of Gastric Surgery, Fujian Medical University Union Hospital from January 2011 to April 2015 were analyzed retrospectively. The inclusion criteria were that all patients were diagnosed with GC and accepted radical surgery at our center. The exclusion criteria were as follows: (1) The general clinical data were incomplete, including age, sex, body mass index (BMI), American society of anesthesiologists (ASA) score, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA199), alpha fetoprotein (AFP), NLR, PLR, AGR, PNI, preoperative complications, tumor size, primary site, clinical T stage (cT), and clinical N stage (cN); (2) The follow-up data were missing; and (3) Patients receiving neoadjuvant chemotherapy. A total of 1608 patients were included (Supplementary Figure 1). The study was approved by the Ethics Committee of Fujian Medical University Union Hospital.

Data

All patients underwent routine preoperative examinations, including upper gastrointestinal endoscopy and upper gastrointestinal angiography, to assess tumor location. Preoperative clinical staging was assessed using chest radiography, total abdominal computed tomography (CT), abdominal ultrasound, and, if necessary, PET-CT, and bone scans. The 8th edition of the AJCC tumor staging system was used for cTNM and pathological TNM (pTNM) staging (Supplementary Figure 1). The overall survival (OS) time was the time from the operation to the last follow-up time or death.

All patients were randomly divided into a training set (n = 1104, 70%) and a testing set (n = 504, 30%), and the testing set was separated for evaluation of the final model. The training data were used five times for cross-validation to optimize the neural network. Finally, the separated data of the testing set were used to evaluate the model.

Blood sample analysis

Routine blood biochemistry and tumor markers were assessed within 1 wk before the operation. Using X-tile software, the optimal critical values of the NLR for OS were 1.91 and 3.87 ($P < 0.05$). According to optimal critical values, the patients were divided into three groups as follows: Low NLR group (NLR ≤ 1.91, n = 632), middle NLR group (1.91 < NLR ≤ 3.87, n = 753), and high NLR group (NLR > 3.87, n = 223). Similarly, the patients were divided into a low PLR group (PLR ≤ 89.5, n = 258), middle PLR group (89.5 < PLR ≤ 162.3, n = 777), and high PLR group (PLR > 162.3, n =

573). According to the AGR, the patients were divided into a low AGR group (AGR ≤ 6.59, *n* = 474), middle AGR group (6.59 < AGR ≤ 7.81, *n* = 612), and high AGR group (AGR > 7.81, *n* = 522). Furthermore, according to the PNI, the patients were divided into a low PNI group (PNI ≤ 371.01, *n* = 495), middle PNI group (371.0 < PNI ≤ 430.0, *n* = 771), and high PNI group (PNI > 430.0, *n* = 342).

Preope-ANN model

First, logistic univariate analysis was used to analyze 1104 cases in the training set to screen the variables that affected the 3-year survival and to determine these variable items as the input nodes of the ANN.

We used the multilayer perceptron to develop the preope-ANN (Figure 1). The input layer of the preope-ANN model consisted of the screened general clinicopathological data and preoperative blood biomarkers using logistic analysis and the 3-year survival condition. The ANN intelligently analyzed the 3-year survival of the patients according to the input data and generated the outcome compared with the real value. The output layer consisted of two values: (1) The patient's 3-year survival (death or survival); and (2) The continuous variables from 0 to 1, which represent the predictive probability of the outcome of the patient's 3-year survival. The network architecture of the preope-ANN model was composed of seven hidden layers, and the input layer was composed of 16 nodes (including 14 general clinical data and blood biomarkers and two survival conditions related to the 3-year OS). The hidden layer was activated by the hyperbolic tangent function, and the output layer was composed of two nodes activated by the softmax function, including the survival condition and survival probability. According to the survival probability predicted by the preope-ANN model, the patients were divided into seven subgroups: The survival probability was 0%-30% for group A, 30%-50% for group B, 50%-65% for group C, 65%-80% for group D, 80%-90% for group E, 90%-97% for group F, and 97%-100% for group G.

Statistical analysis

All data were analyzed using SPSS 20.0 (SPSS Inc. Chicago, IL, United States) and R software (version 3.5.4). The classified variables were tested using the χ^2 test or Fisher's exact test. The X-tile software was used to determine the best cut-off point of the counting data. Mann-Whitney *U* test was used to test the receiver operating characteristic (ROC) curve and the area under the curve (AUC), and the Z test was used to compare the AUCs (MedCal software). We used Harrell's C index to measure the discriminatory ability of the different models[4,20]. The likelihood ratio chi-square was calculated by Cox regression to measure homogeneity; a higher score means better homogeneity[21]. The Akaike information criterion (AIC) within the Cox regression model was used to compare performances between two prognostic models; smaller AIC values represent better optimistic prognostic stratification[22]. We calculated the relative likelihood of two models using the following formula: Exp {[AIC (model A) - AIC (model B)]/2}. The relative likelihood represents the probability that model A minimizes information as effectively as model B and could thus be interpreted as a *P* value for the comparison of both AIC values[23]. *P* < 0.05 was considered statistically significant.

RESULTS

General information

Table 1 shows the clinical data of 1608 patients with GC. Among them, 1104 cases were in the training set, and 504 cases were in the testing set. The average age of all patients diagnosed was 60.72 years (range, 12-101 years), and the male to female ratio was 2.84:1. The proportion of patients diagnosed with stages I, II, III, and IVA disease in the cTNM system was 11.6%, 38.2%, 45.6%, and 4.6%, respectively. The proportion of patients diagnosed with stage I, II, and III disease in the pTNM system was 22.6%, 24.9%, and 52.5%, respectively.

Univariate logistic analysis of the survival of patients in the training set

In the training set, the univariate logistics regression analysis (Table 2) showed that age, sex, BMI, CEA, CA199, AFP, NLR, PLR, AGR, PNI, ASA score, tumor location, tumor size, cT stage, and cN stage were significant factors for the 3-year OS of the patients (*P* < 0.05 for all).

Performance evaluation of the preope-ANN model

The accuracy, sensitivity, and specificity of the preope-ANN model in the training set were 77.3%, 88.5%, and 50.1%, respectively. For the preope-ANN model in the testing
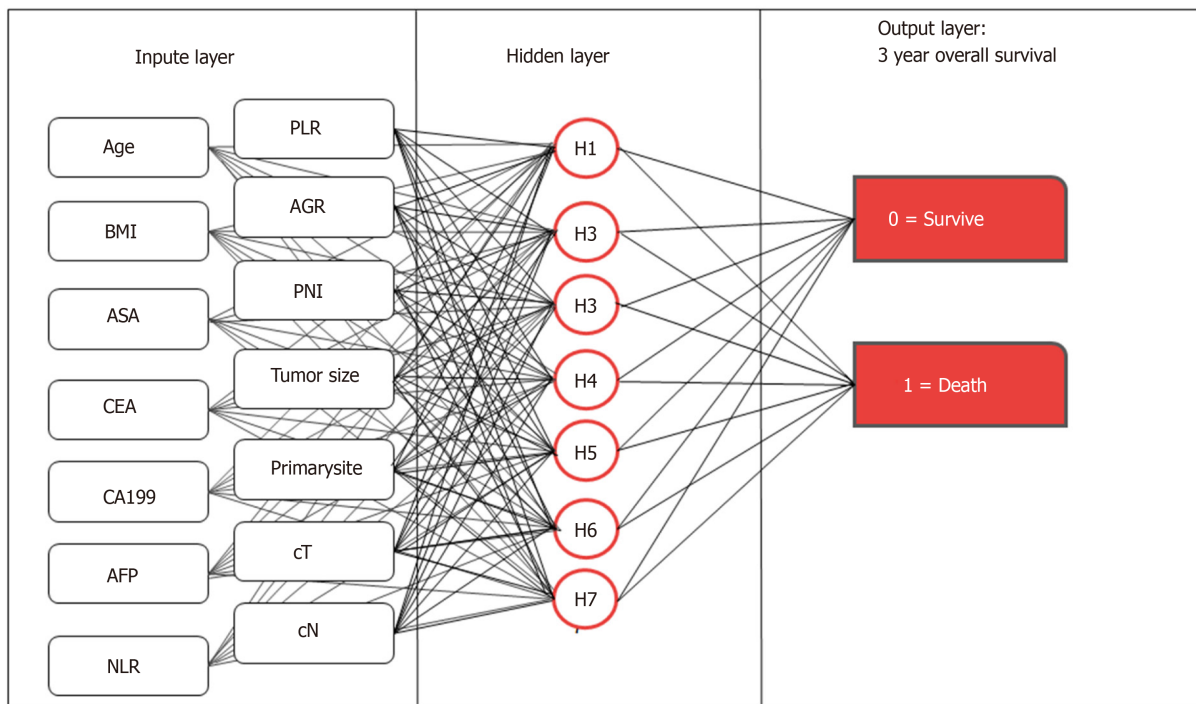
Figure 1 Structure diagram of the preoperative artificial neural network model. Age, sex, body mass index, American society of anesthesiologists score, tumor location, tumor size, prognostic nutrition index, albumin-globulin ratio, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, clinical T stage, clinical N stage, carcinoembryonic antigen, carbohydrate antigen 19-9, and alpha fetoprotein are the input variables. All weighted values passed to the hidden layer node are summed on the hidden layer node and passed to the output node through the sigmoid function. All weighted values entering the output node are summed again and passed through the sigmoid function. For each patient, the probability of output is 0-1.0. In the training of the artificial neural network, the output values are compared with the real results of each patient. The weight is adjusted so that the next time the patient appears on the network, the network output is closer to the real result. NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; AGR: Albumin-globulin ratio; PNI: Prognostic nutrition index; BMI: Body mass index; ASA: American society of anesthesiologists score; cT: Clinical T stage; cN: Clinical N stage; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 19-9; AFP: Alpha fetoprotein.

set, the accuracy was 75.2%, the sensitivity was 86.5%, and the specificity was 43.8% (Figure 2).

Subgroups of the preope-ANN model for Kaplan-Meier survival analysis

In Figure 3, the prediction results of the preope-ANN model were divided into seven subgroups. The Kaplan-Meier survival curve showed that the survival curve of each subgroup within the preope-ANN model had good discrimination in both the training and testing sets ($P < 0.05$). For cTNM staging, the survival curve in the training set showed (Figure 4) that the substages of the TNM system were well differentiated ($P < 0.05$). However, the survival curve of the testing set showed that the curve of stage III was close to that of stage IVA ($P = 0.335$). Figure 5 shows the survival analysis of the pTNM staging. In the training set, the survival curve discrimination between stages IA and IB was poor ($P = 0.240$), and there was no significant difference between stages IIA and IIB and stages IIB and IIIA ($P < 0.05$). In the testing set, there was no significant difference in survival curves between stages IA and IB, IIA and IIB, and IIIA and IIIB ($P > 0.05$).

Accuracy of each model

Figure 6 shows the ROC curves of the preope-ANN model, cTNM stage, and pTNM stage in both the training set and the testing set. In the training set, the AUC values of the preope-ANN model, cTNM stage, and pTNM stage were 0.820 (0.800-0.838), 0.740 (0.718-0.762), and 0.803 (0.782-0.822), respectively. The predictive performance of the preope-ANN was better than that of the cTNM stage ($P < 0.05$) and was similar to that of the pTNM stage ($P = 0.130$). In the testing set, the AUC values of the preope-ANN model, cTNM stage, and pTNM stage were 0.790 (0.752- 0.825), 0.687 (0.644-0.727), and 0.786 (0.748-0.821), respectively. Comparison of the AUC showed that the prediction performance of the preope-ANN was better than that of the cTNM stage ($P < 0.05$), and was similar to that of the pTNM ($P = 0.858$).

Comparison of the three models

As shown in Table 3, for Harrell's C index, the preope-ANN model was superior to

Table 1 General clinicopathological data, *n* (%)			
Variable	All patients (*n* = 1608)	Training set (*n* = 1104)	Testing set (*n* = 504)
Age (yr)			
< 57	593 (36.9)	413 (37.4)	180 (35.7)
57-74	838 (52.1)	565 (51.2)	273 (54.2)
> 74	177 (11.0)	126 (11.4)	51 (10.1)
Sex			
Female	412 (25.6)	299 (27.1)	113 (22.4)
Male	1196 (74.4)	805 (72.9)	391 (77.6)
BMI			
< 18.5	156 (9.7)	98 (8.9)	58 (11.5)
18.5-23.5	960 (59.7)	670 (60.7)	290 (57.5)
> 23.5	492 (30.6)	336 (30.4)	156 (31.0)
CEA			
< 2.8	932 (58.0)	626 (56.7)	306 (60.7)
2.8-4.8	328 (20.4)	226 (20.5)	102 (20.2)
> 4.8	348 (21.6)	252 (22.8)	96 (19.0)
CA199			
< 15.0	1043 (64.9)	696 (63.0)	347 (68.8)
15.0-39.2	348 (21.6)	255 (23.1)	93 (18.5)
> 39.2	217 (13.5)	153 (13.9)	64 (12.7)
AFP			
< 2	496 (30.8)	344 (31.2)	152 (30.2)
2-5.29	916 (57.0)	631 (57.2)	285 (56.5)
> 5.3	196 (12.2)	129 (11.7)	67 (13.3)
NLR			
< 1.91	632 (39.3)	422 (38.2)	210 (41.7)
1.91-3.87	753 (46.8)	525 (47.6)	228 (45.2)
> 3.87	223 (13.9)	157 (14.2)	66 (13.1)
PLR			
< 89.5	258 (16.0)	177 (16.0)	81 (16.1)
89.5-162.3	777 (48.3)	540 (48.9)	237 (47.0)
>162.3	573 (35.6)	387 (35.1)	186 (36.9)
AGR			
< 6.59	474 (29.5)	332 (30.1)	142 (28.2)
6.59-7.81	612 (38.1)	426 (38.6)	186 (36.9)
> 7.81	522 (32.5)	346 (31.3)	176 (34.9)
PNI			
< 371	495 (30.8)	347 (31.4)	148 (29.4)
371-430	771 (47.9)	531 (48.1)	240 (47.6)
> 430	342 (21.3)	226 (20.5)	116 (23.0)
ASA			
I	983 (61.1)	677 (61.3)	306 (60.7)
II	561 (34.9)	379 (34.3)	182 (36.1)
III-IV	64 (4.0)	48 (4.3)	16 (3.2)
Comorbidity			
No	1133 (70.5)	779 (70.6)	354 (70.2)
Yes	475 (29.5)	325 (29.4)	150 (29.8)
Primary site			
Lower	671 (41.7)	476 (43.1)	195 (38.7)
Middle	350 (21.8)	231 (20.9)	119 (23.6)
Upper	401 (24.9)	257 (23.3)	144 (28.6)
Overlapping	186 (11.6)	140 (12.7)	46 (9.1)
Tumor size (mm)			

< 30	578 (35.9)	404 (36.6)	174 (34.5)
30-60	711 (44.2)	477 (43.2)	234 (46.4)
> 60	319 (19.8)	223 (20.2)	96 (19.0)
cT			
T1	167 (10.4)	108 (9.8)	59 (11.7)
T2	185 (11.5)	135 (12.2)	50 (9.9)
T3	429 (26.7)	292 (26.4)	137 (27.2)
T4	827 (51.4)	569 (51.5)	258 (51.2)
cN			
N0	662 (41.2)	457 (41.4)	205 (40.7)
N1	376 (23.4)	257 (23.3)	119 (23.6)
N2	362 (22.5)	245 (22.2)	117 (23.2)
N3	208 (12.9)	145 (13.1)	63 (12.5)
Follow-up duration (mo)	48 (3-91)	48 (3-91)	50 (3-89)

BMI: Body mass index; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 19-9; AFP: Alpha fetoprotein; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; AGR: Albumin-globulin ratio; PNI: Prognostic nutrition index; ASA: American society of anesthesiologists; cT: Clinical T stage; cN: Clinical N stage.

the cTNM staging model and had the same performance as the pTNM staging model in both the training and testing sets. (In the training set: Preope-ANN *vs* cTNM = 0.773 *vs* 0.663, respectively, $P < 0.001$; preope-ANN *vs* pTNM = 0.773 *vs* 0.757, respectively, $P = 0.120$; in the testing set: Preope-ANN *vs* cTNM = 0.752 *vs* 0.652, respectively, $P < 0.001$; preope-ANN *vs* pTNM =0.752 *vs* 0.740, respectively, $P = 0.539$). The AIC analysis showed that the preope-ANN model of the training set had a better fitting degree than both the cTNM staging and pTNM staging (preope-ANN *vs* cTNM = 4977.83 *vs* 5176.70, respectively, relative likelihood < 0.001; preope-ANN *vs* pTNM = 4977.83 *vs* 4999.80, respectively, relative likelihood < 0.001). The fitting degree of the preope-ANN model in the testing set was better than that of the cTNM staging (preope-ANN *vs* cTNM = 1952.94 *vs* 2020.37, respectively, relative likelihood < 0.001), and the fitting degree of the preope-ANN model was not inferior to that of the pTNM staging (preope-ANN 1952.94 *vs* pTNM 1951.84, respectively, relative likelihood = 1.733). Therefore, the performance of the preope-ANN was better than that of the cTNM staging and was similar to that of the pTNM staging.

DISCUSSION

Presently, GC remains a common malignant tumor worldwide and the third leading cancer cause of death. As is known, it is very important to develop a GC prognostic model in order to provide valuable prognosis information for the patients and help clinicians formulate reasonable treatment regimens for the patients[19]. The TNM staging system proposed by the AJCC is the most important prognostic evaluation system for GC, and it has served as the main instruction for clinicians to choose the treatment plan. However, pTNM staging needs both grouping information and prognostic information from the postoperative histopathology results of the tumor specimen, which prevents the approach from guiding the preoperative treatment decision[24]. The exact pretreatment clinical stage is essential to customize the treatment strategy for each patient. Park *et al*[25] suggested that the clinical staging based on endoscopy and the CT scan has predictive value, where cTNM staging can be used to guide the treatment of GC patients; however, its accuracy depends on the imaging experience of the physician. Some scholars found that this method had limitations in evaluating the cT stage of large tumors, while the accuracy of cN was only 20%; and over 80% of pN0 patients are overestimated[26,27]. Thus, there is an urgent need for a more accurate preoperative prognostic model to guide the choice of treatment options.

In recent years, increasingly more studies have shown that blood inflammatory markers are associated with a poor prognosis in cancer patients[28]. The NLR, PLR, and PNI in cancer patients have been proven to be prognostic markers for various malignant tumors[29-32]. In our study, logistic analysis confirmed that the preoperative NLR, PLR, PNI, and AGR were significant prognostic factors for the 3-year survival, which is consistent with previous studies. However, because of the nonlinearity of biological information in the human body, the traditional model inevitably has had

Table 2 Univariate logistics regression analysis of risk factors for the 3-year survival

Variable	Training set			
	OR	95CI		*P* value
Age (yr)				
< 57	REF			
57-74	0.38	0.25	0.58	< 0.001
> 74	0.63	0.42	0.93	0.020
Sex				
Male	REF			
Female	0.96	0.72	1.29	0.782
BMI				
< 18.5	REF			
18.5-23.5	3.04	1.90	4.85	< 0.001
> 23.5	1.28 357	0.95	1.73	0.111
CEA				
< 2.8	REF			
2.8-4.8	0.33	0.24	0.45	< 0.001
> 4.8	0.46	0.31	0.67	< 0.001
CA199				
< 15.0	REF			
15.0-39.2	0.20	0.14	0.29	< 0.001
> 39.2	0.33	0.22	0.50	< 0.001
AFP				
< 2	REF			< 0.001
2-5.29	0.78	0.51	1.18	0.240
> 5.3	0.50	0.33	0.74	0.001
NLR				
< 1.91	REF			
1.91-3.87	0.32	0.22	0.48	< 0.001
> 3.87	0.48	0.33	0.69	< 0.001
PLR				
< 89.5	REF			
89.5-162.3	0.26	0.16	0.42	< 0.001
> 162.3	0.59	0.45	0.78	< 0.001
AGR				
< 6.59	REF			
6.59-7.81	2.11	1.50	2.98	< 0.001
> 7.81	1.58	1.13	2.20	0.007
PNI				
< 371	REF			
371-430	3.98	2.62	6.06	< 0.001
> 430	1.94	1.29	2.92	0.002
ASA				
I	REF			
II	0.44	0.24	0.79	0.006
III-IV	0.53	0.29	0.97	0.041
Comorbidity				
No	REF			
Yes	0.99	0.74	1.31	0.933
Primary site				
Lower	REF			
Middle	0.30	0.20	0.45	< 0.001
Upper	0.54	0.35	0.83	0.001
Overlapping lesion of the stomach	0.47	0.31	0.73	< 0.001

Tumor size (mm)				
< 30	REF			
30-60	0.08	0.06	0.13	< 0.001
> 60	0.43	0.31	0.60	< 0.001
cT				
T1	REF			
T2	0.05	0.02	0.13	< 0.001
T3	0.18	0.11	0.32	< 0.001
T4	0.24	0.17	0.34	< 0.001
cN				
N0	REF			
N1	0.18	0.12	0.27	< 0.001
N2	0.28	0.18	0.43	< 0.001
N3	0.67	0.44	1.007	0.054

BMI: Body mass index; CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen 19-9; AFP: Alpha fetoprotein; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; AGR: Albumin-globulin ratio; PNI: Prognostic nutrition index; ASA: American society of anesthesiologists; cT: Clinical T stage; cN: Clinical N stage; OR: Odds ratio; CI: Confidence interval.

some limitations when the traditional linear analysis method was used to construct the prognostic model in previous studies. At the same time, the growth of a tumor is a process of interaction between the human body and the tumor, which depends on the nutritional status of the body, the immune system, and the tumor malignancy; thus, the application of a single index for forecasting may lack accuracy[18]. Consequently, we need a new statistical model that can synthesize the biological indicators and better address the nonlinear relationship among the indicators.
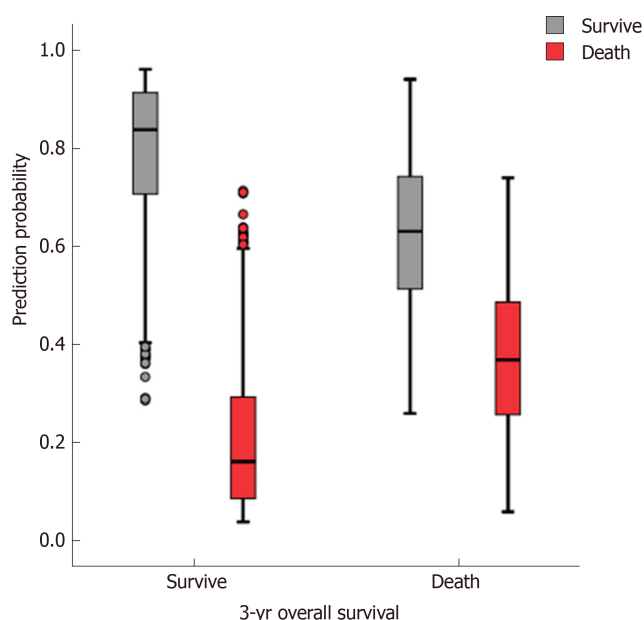
The ANN is a new computational model developed by simulating the function of human brain; this method can establish a nonlinear statistical model to evaluate complex biological systems and address the relationship between complex biological indicators more flexibly[33]. In recent years, ANNs have been successfully applied to the field for the identification of lesions in pathological specimens, automatic detection of breast X-ray injury, and disease diagnosis and treatment[33,34].

We synthesized preoperative blood biomarkers (the inflammatory indicators and PNI) and preoperative clinical data to establish the preope-ANN, which are easily available compared with the need for postoperative pathological results. At the same time, we used the ANN to reduce the error of human interference, ensuring the objectivity and accuracy of the results. The verification results showed that the accuracy of the preope-ANN model in predicting the 3-year survival rate was 91.7%. In addition, the comparison of Harrell's C index and AIC analysis showed that the accuracy and the fitting degree of the preope-ANN model were better than those of cTNM staging, and the preope-ANN model could achieve the same prediction effect as pTNM staging. The TNM staging system divides the patients into different risk groups, and our preope-ANN model can provide an even more detailed prediction for each patient, which is better than grouping the predictions. The preope-ANN model can be used to predict the long-term survival of patients before surgery and to choose a reasonable individualized treatment according to the prognosis. We can obtain the possible poor prognosis information of those patients with a low score before surgery and improve the prognosis by adopting neoadjuvant radiotherapy and chemotherapy.

This study still has some limitations. First, some patients had a follow-up period less than 5 years, and we only conducted the study for the 3-year survival outcome, not for the longer-term survival outcome. Second, this was a retrospective study, and some potential biases were still unavoidable. Moreover, this study included all postoperative patients, and the results are not suitable for the evaluation of the prognosis of patients with unresectable advanced GC. Nevertheless, this study first confirmed that the preope-ANN is a novel and convenient prognostic model through the use of a large sample data size, which can effectively predict the prognosis of GC patients. In the clinic, the preope-ANN model can be considered as part of preoperative risk stratification to guide the individualized treatment of patients with GC. The next challenge is to establish a web version of the preope-ANN model that can be dynamically adjusted for the input of different sample data; with this approach, the model accuracy would be closer to the real value and more flexibly applied to the evaluation of clinical patients.

Table 3 Comparison of the area under the curve values and Harrell's C index between the pathological TNM stage, clinical TNM stage, and preoperative artificial neural network

	Training set			Testing set			Bio-ANN	Cli-ANN
	Preope-ANN	cTNM	pTNM	Preope-ANN	cTNM	pTNM		
Harrell's C index	0.773 (0.753-0.795)	0.663 (0.640-0.687)	0.757 (0.735-0.779)	0.752 (0.719-0.785)	0.652 (0.615-0.688)	0.740 (0.707-0.775)	0.722 (0.698-0.746)	0.760 (0.738-0.782)
P value		< 0.001	0.120		< 0.001	0.539	[a]$P < 0.001$; [b]$P = 0.000$; [c]$P = 0.018$	[d]$P < 0.001$ [e]$P < 0.000$; [f]$P = 0.827$
AIC	4977.83	5176.70	4999.80	1952.94	2020.37	1951.84	5115.9	5011.9
Relative likelihood		< 0.001	< 0.001		<0.001	1.733	[a]$P < 0.001$; [b]$P > 1$ [c]$P < 0.001$	[d]$P = 0.001$ E > 1 [f]$P = 0.06$

[a]P, Bio-artificial neural network (ANN) *vs* preoperative ANN (preope-ANN);
[b]P, Bio-ANN *vs* clinical TNM (cTNM);
[c]P, Bio-ANN *vs* pathological TNM (pTNM).
[d]P, cli-ANN *vs* preope-ANN;
[e]P, cli-ANN *vs* cTNM;
[f]P, cli-ANN *vs* pTNM. pTNM: Pathological TNM; cTNM: Clinical TNM; preope-ANN: Preoperative artificial neural network; AIC: Akaike information criterion.

Figure 2 Prediction of the 3-year survival of patients using the preoperative artificial neural network. In the training set, the predictive accuracy rate was 77.3%. The sensitivity and specificity of the centralized training model were 88.5% and 50.1%, respectively. The accuracy of the testing set model for survival prediction was 75.2%. The sensitivity and specificity of the test set model were 86.5% and 43.1%, respectively.
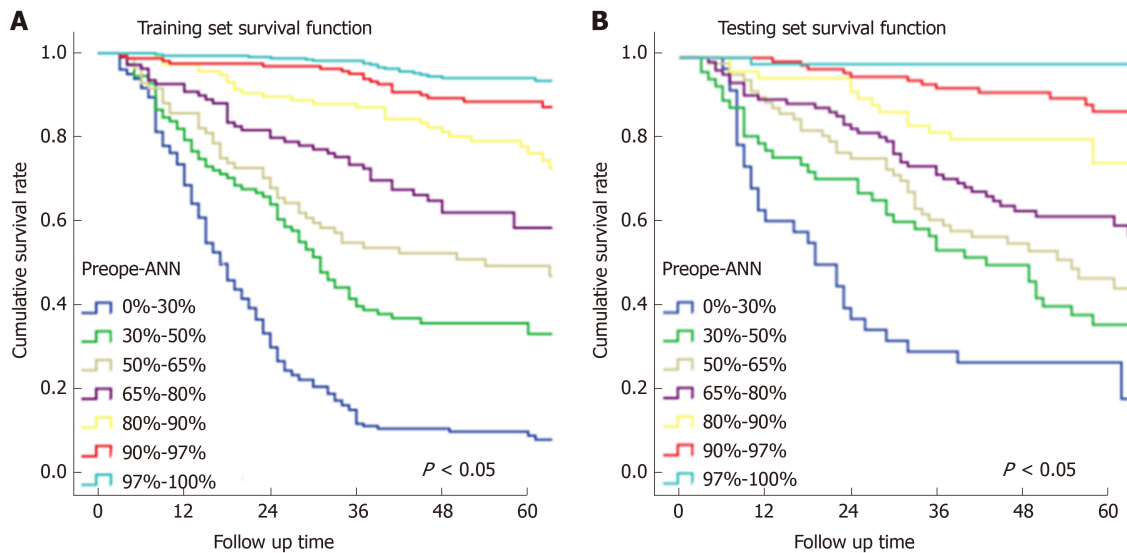
Figure 3 Subgroup survival curves of the preoperative artificial neural network. A: The survival curve of each subgroup of the preoperative artificial neural network model showed good discrimination in the training and testing sets ($P < 0.05$). B: The survival analysis of the training set showed that the substages of the TNM system were well differentiated ($P < 0.05$). Preope-ANN: Preoperative artificial neural network.
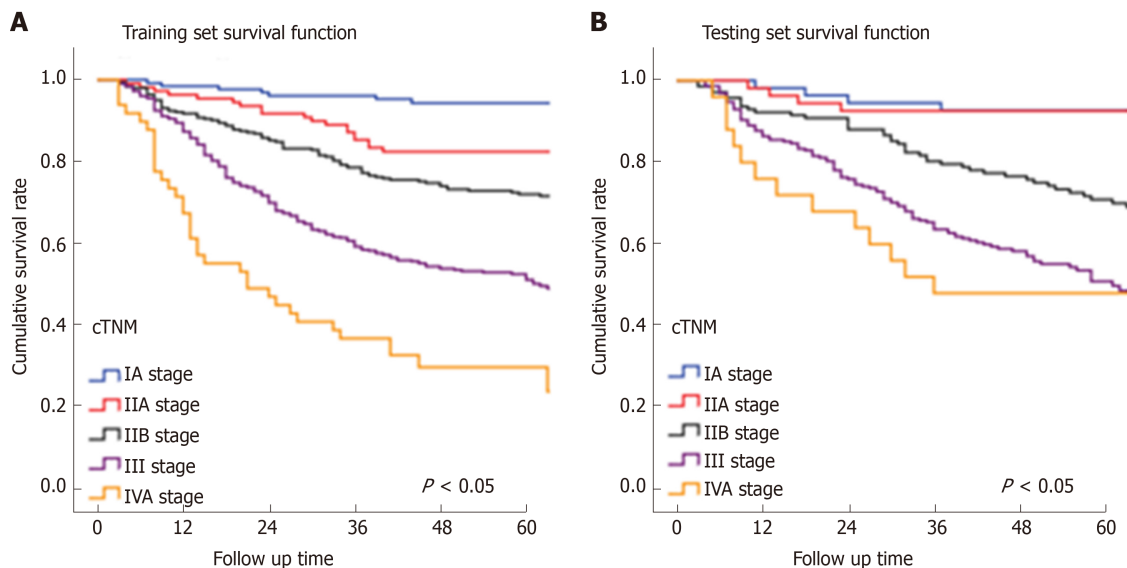

Figure 4 Survival curves of the clinical TNM staging. A: The discrimination between the survival curves of each stage of the clinical TNM (cTNM) system in the training set was good ($P < 0.05$). B: There was no significant difference in the survival curves between the cTNM stages I and II A ($P = 0.935$), and between stages III and IVA ($P = 0.355$). cTNM: Clinical TNM.
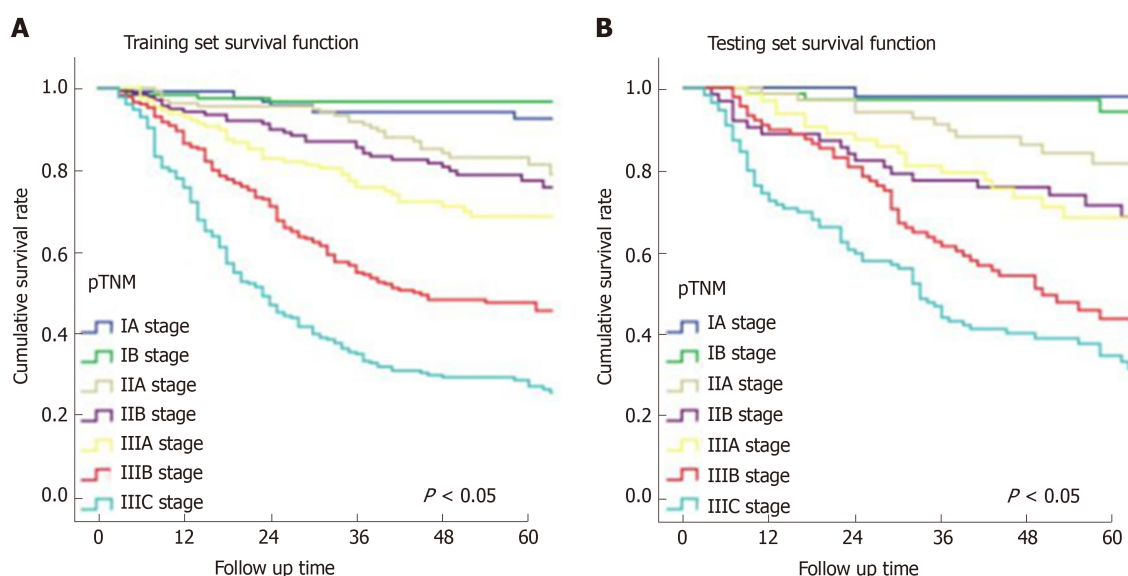
Figure 5 Survival curves of the pathological TNM staging. A: In the training set, the survival curve discrimination between stages IA and IB was poor (*P* = 0.240), and there was no significant difference in the survival curves between stages IIA and IIB and IIB and IIIA (*P* < 0.05). B: In the testing set, there was no significant difference in survival curves between stages IA and IB, IIA and IIB, and IIIA and IIIB of the pathological TNM staging (*P* > 0.05). pTNM: Pathological TNM.
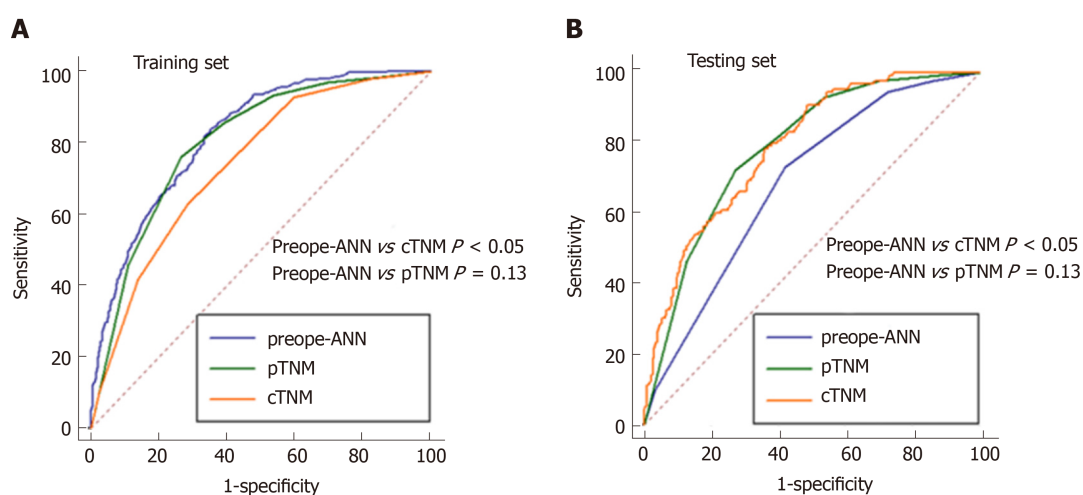

Figure 6 Comparison of the receiver operating characteristic curves among the preope-ANN model, clinical TNM stage, and pathological TNM stage. A: In the training set, the area under the curve (AUC) values of the preoperative artificial neural network (preope-ANN) model, clinical TNM (cTNM) staging, and pathological TNM (pTNM) staging were 0.820 (0.800-0.838), 0.740 (0.718-0.762), and 0.803 (0.782-0.822), respectively. The comparison of the AUC values in the training set showed that the predictive performance of the preope-ANN was better than that of the cTNM stage (*P* < 0.05), and similar to that of pTNM stage (*P* = 0.130). B: In the testing set, the AUC values of the preope-ANN model, cTNM staging, and pTNM staging were 0.790 (0.752-0.825), 0.687 (0.644-0.727), and 0.786 (0.748-0.821), respectively. The comparison of the AUC values in the testing set showed that the prediction performance of the preope-ANN and the pTNM stage was better than that of the cTNM stage (*P* < 0.05), and the prediction performance of the preope-ANN was similar to that of the pTNM stage (*P* = 0.858). pTNM: Pathological TNM; cTNM: Clinical TNM; preope-ANN: Preoperative artificial neural network.

ARTICLE HIGHLIGHTS

Research background

Because of the powerful abilities of self-learning and handling complex biological information, artificial neural network (ANN) models have been widely applied to disease diagnosis, imaging analysis, and prognosis prediction. However, there has been no trained preoperative ANN (preope-ANN) model to preoperatively predict the prognosis of patients with gastric cancer (GC).

Research motivation

This study combined the preoperative blood biomarkers and preoperative tumor data to establish an ANN model in order to build a reliable preoperative prediction system that can achieve the same effect as postoperative TNM staging. The aim of this study was to evaluate the

prognosis of patients with GC and to provide a reasonable individualized treatment plan for patients.

Research objectives
We aimed to establish a neural network model that can predict long-term survival of GC patients before surgery to evaluate the tumor condition before the operation.

Research methods
The clinicopathological data of 1608 GC patients treated from January 2011 to April 2015 at the Department of Gastric Surgery, Fujian Medical University Union Hospital were analyzed retrospectively. Patients were randomly divided into a training set (70%) for establishing a preope-ANN model and a testing set (30%). The prognostic evaluation ability of the preope-ANN model was compared with that of the American Joint Commission on Cancer (8th edition) clinical TNM stage (cTNM) and pathological TNM stage (pTNM) through the receiver operating characteristic curve, Akaike information criterion index, Harrell's C index, and likelihood ratio chi-square.

Research results
We used the variables that were statistically significant factors for the 3-year overall survival as input-layer variables to develop a preope-ANN in the training set. The survival curves within each score of the preope-ANN had good discrimination ($P < 0.05$). Comparing the preope-ANN model, cTNM, and pTNM in both the training and testing sets, the preope-ANN model was superior to cTNM in predictive discrimination (C index), predictive homogeneity (likelihood ratio chi-square), and prediction accuracy (area under the curve). The prediction efficiency of the preope-ANN model was similar to that of pTNM.

Research conclusions
The preope-ANN model can accurately predict the long-term survival of GC patients, and its predictive efficiency is not inferior to pTNM staging.

Research perspectives
This study for the first time confirmed that the preope-ANN is a novel and convenient prognostic model through the use of a large sample data size, which can effectively predict the prognosis of GC patients. In the clinic, preope-ANN can be considered as part of preoperative risk stratification to guide the individualized treatment of patients with GC. The next challenge is to establish a web version of the preope-ANN model that can be dynamically adjusted for the input of different sample data; with this approach, the model accuracy would be closer to the real value and more flexibly applied to the evaluation of clinical patients.

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