Development of an Artificial Neural Network Model and Comparison with Nomogram for Prediction of Pathological Complete Response After Neoadjuvant Chemotherapy in Breast Cancer

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Abstract

Identifying breast cancer patients who may benefit from neoadjuvant chemotherapy will facilitate personalized treatment regarding chemotherapy and surgery. In our work, we developed two predictive models, nomogram and a machine learning model based on artificial neural network (ANN), to anticipate pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) in breast cancer. We demonstrated that high level of estrogen receptor (ER) positivity, positive human epidermal growth factor receptor 2 (HER2) status, complete response on magnetic resonance imaging (MRI), abnormal CEA level after NAC, and abnormal CA15-3 level after NAC were significant predictors of pCR. A nomogram and ANN model trained to predict pCR were developed using these five predictors. The performance of the two models were tested using a fully independent test set. Validation test showed the area under the receiver operating characteristic curve (AUC) of 0.789 (95% confidence interval (CI), 0.707-0.871) for the nomogram and 0.876 (95% CI, 0.808-0.943) for the ANN model. Both models showed excellent performance, but the ANN model performed better in terms of accuracy and discrimination. Machine-learning algorithms hold promise in medical application and provide better prediction than nomogram.

Introduction

Neoadjuvant chemotherapy (NAC) has become the standard treatment for locally advanced or unresectable breast cancer. NAC allows unresectable tumor to become operable while downstaging operable tumor to allow breast conservation^{1,2}. Pathologic complete response (pCR) of breast cancer after NAC is a well-known outcome that correlates with better prognosis, higher event-free survival and overall survival^{3,4}.

Studies have tried to find useful molecular, clinical or radiologic predictors of pCR to NAC. Imaging studies, such as magnetic resonance imaging (MRI) and sonography are often used to demonstrate change in tumor extent and predict response to NAC⁵. Human epidermal growth factor receptor 2 (HER2) overexpression and lack of estrogen receptor (ER) and progesterone receptor (PR) expression have been identified as potential predictors of pCR^{6,7}. High level of serum tumor marker CA 15 – 3 was predictive of poor pathological response⁸. Therefore, development of a method to combine multiple prognostic factors to predict a pCR would allow patient stratification and more appropriate treatment regimens. Patients with high probability of complete response could benefit from early resection, while non-responders to NAC could be further treated with hormonal therapy or alternative regimens.

Nomogram is one of the most popular statistical tool to provide overall probability of certain outcome and several nomograms were developed to predict residual tumor size or pathologic response following NAC⁹⁻¹². However, a nomogram assumes a linear relationship between predictors and outcome, and a transformation is needed when the relationship is non-linear. Alternatively, a variety of machine learning algorithms, such as decision trees and artificial neural network (ANN), have been recently applied in cancer prognosis^{13,14}. Machine learning allows inclusion of larger number of input variables and complex data with non-linear relationship can be handled more comprehensively. Moreover, some

algorithms even perform feature selection as part of their overall operation, and this reduces the risk of omitting some covariates as required in many predictive models.

In this study, we developed a machine learning method based on ANN algorithm to predict pCR after NAC in patients with advanced breast cancer. Moreover, we built a nomogram with the same dataset and further compared predictive accuracy of the two models for breast cancer prognosis.

Methods

Patients

Patients with histology-proven invasive breast carcinoma and who met the selection criteria were included in this study. The inclusion criteria were patients who (1) received breast conserving surgery or total mastectomy between January 2017 and December 2019; (2) received NAC prior to surgical resection. The exclusion criteria were patients who were diagnosed with recurred tumor. In total, 359 patients were included and their clinical data from electronic medical system were obtained, retrospectively. All methods were carried out in accordance with relevant guidelines and regulations. The Institutional Review Board (IRB) of Seoul National University Bundang Hospital waived the need of informed consent from patients because this was retrospective study based on medical records and had minimal risk to included patients even if the informed consent was waived. This study was approved by the IRB of Seoul National University Bundang Hospital (IRB No. B-2105/682 – 102).

Statistical Analysis

Univariate analyses were performed to determine whether clinicopathologic characteristics including age, body mean index, multiplicity, palpability, family history, clinical tumor stage, clinical node stage, histologic grade, nuclear grade, ER, PR, HER2 status, size of tumor at MRI, tumor-associated antigens (carcinoembryonic antigen (CEA) and carbohydrate antigen 15–3 (CA15-3)) were associated with pCR after NAC. Continuous variables were examined by student's t-test and presented as mean and standard deviation. Categorical variables were examined by chi-square test and expressed as number and percentage. For multivariate analyses, only variables with a significant association with pCR in the univariate analyses were used. Backward elimination method was carried out using logistic regression analyses and predictors were expressed by the odds ratio (OR) and 95% confidence interval (CI). Before developing predictive models, pCR group and non-pCR group were balanced using Synthetic Minority Over-sampling Technique (SMOTE) ¹⁵. The balanced dataset was randomly split into training and test sets with a ratio of 7:3. R software version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses.

Model Construction and Evaluation

Predictive models were built using status of pCR as the outcome variable. The training set was used to build predictive models and test set was used to assess the models. Significant variables from multivariate logistic regression analysis were included as predictors. For nomogram, continuous variables with a wide range, i.e. CA15-3 and CEA, were converted into categorical variable because range observed in the training set may not fully represent real world data. For machine learning model, a widely used neural network package, neuralnet, was used with multiple hidden layers and nodes. Discrimination power of each model was quantified by the area under the receiver–operating characteristics curve (AUC).

Results

Patient Characteristics

A total of 359 breast cancer patients who received NAC prior to surgical resection were included in this study. Patient demographics and clinical features are summarized in Table 1. Among the patients, 106 (29.5%) patients achieved pCR after NAC. Univariate analyses showed that negative ER (74.5 vs. 47.0%, $p < 0.001$), negative PR (90.6 vs. 64.0%, $p < 0.001$), positive HER2 (66.7 vs. 30.6%, $p < 0.001$), smaller tumor size on initial MRI (3.6 vs. 4.2 cm, $p = 0.005$), higher level of pre-NAC Ki-67 (43.0 vs. 36.7%, $p = 0.004$), lower level of pre-NAC CA15-3 (11.1 vs. 16.2 ng/mL, $p = 0.030$), lower level of pre-NAC CEA (2.0 vs. 2.8 ng/mL, $p = 0.030$), complete response on post-NAC MRI (67.0 vs. 13.4%, $p < 0.001$), lower level of post-NAC CA15-3 (14.4 vs. 16.7 ng/mL, $p = 0.004$), and lower level of post-NAC CEA (2.3 vs. 3.0 ng/mL, $p = 0.001$) were independent predictors of pCR.

Table 1
Clinical features and their correlation with pCR

	Total	pCR (n = 106)	Non-pCR (n = 253)	<i>p</i>
Age	49.5 ± 10.3	50.3 ± 10.1	49.2 ± 10.4	0.338
BMI	23.8 ± 3.7	23.4 ± 3.0	24.0 ± 3.9	0.175
Multiplicity				0.306
No	321 (89.4%)	98 (92.5%)	223 (88.1%)	
Yes	38 (10.6%)	8 (7.5%)	30 (11.9%)	
Palpability				1.000
No	79 (22.0%)	23 (21.7%)	56 (22.1%)	
Yes	280 (78.0%)	83 (78.3%)	197 (77.9%)	
Family history				1.000
No	287 (83.4%)	84 (83.2%)	203 (83.5%)	
Yes	57 (16.6%)	17 (16.8%)	40 (16.5%)	
Clinical tumor stage				0.163
cT1	29 (8.1%)	11 (10.4%)	18 (7.1%)	
cT2	227 (63.2%)	73 (68.9%)	154 (60.9%)	
cT3	77 (21.4%)	17 (16.0%)	60 (23.7%)	
cT4	26 (7.2%)	5 (4.7%)	21 (8.3%)	
Clinical node stage				0.720
cN0	85 (23.7%)	25 (23.6%)	60 (23.7%)	
cN1	158 (44.0%)	47 (44.3%)	111 (43.9%)	
cN2	62 (17.3%)	21 (19.8%)	41 (16.2%)	
cN3	54 (15.0%)	13 (12.3%)	41 (16.2%)	

pCR: pathologic complete response, BMI: body mass index, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, NAC: neoadjuvant chemotherapy, MRI: magnetic resonance image

	Total	pCR (n = 106)	Non-pCR (n = 253)	<i>p</i>
Histologic grade				0.059
G1	7 (1.9%)	1 (0.9%)	6 (2.4%)	
G2	129 (35.9%)	29 (27.4%)	100 (39.5%)	
G3	216 (60.2%)	75 (70.8%)	141 (55.7%)	
Missing	7 (1.9%)	1 (0.9%)	6 (2.4%)	
Nuclear grade				0.083
G1	2 (0.6%)	0 (0.0%)	2 (0.8%)	
G2	100 (27.9%)	21 (19.8%)	79 (31.2%)	
G3	251 (69.9%)	84 (79.2%)	167 (66.0%)	
Missing	6 (1.7%)	1 (0.9%)	5 (2.0%)	
ER status				< 0.001
High positive	133 (37.0%)	15 (14.2%)	118 (46.6%)	
Low positive	21 (5.8%)	8 (7.5%)	13 (5.1%)	
Negative	198 (55.2%)	79 (74.5%)	119 (47.0%)	
Missing	7 (1.9%)	4 (3.8%)	3 (1.2%)	
PR status				< 0.001
Positive	101 (28.1%)	10 (9.4%)	91 (36.0%)	
Negative	258 (71.9%)	96 (90.6%)	162 (64.0%)	
HER2 status				< 0.001
Positive	146 (41.4%)	70 (66.7%)	76 (30.6%)	
pCR: pathologic complete response, BMI: body mass index, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, NAC: neoadjuvant chemotherapy, MRI: magnetic resonance image				

	Total	pCR (n = 106)	Non-pCR (n = 253)	<i>p</i>
Negative	207 (58.6%)	35 (33.3%)	172 (69.4%)	
Longest tumor diameter before NAC, MRI (cm)	4.0 ± 2.1	3.6 ± 1.8	4.2 ± 2.2	0.005
Pre-NAC Ki-67 (%)	38.6 ± 18.8	43.0 ± 19.4	36.7 ± 18.2	0.004
Pre-NAC CA15-3 (U/mL)	14.7 ± 15.5	11.1 ± 5.5	16.2 ± 17.8	< 0.001
Pre-NAC CA15-3				0.012
Normal (< 25)	327 (91.1%)	100 (94.3%)	227 (89.7%)	
Abnormal (≥ 25)	28 (7.8%)	3 (2.8%)	25 (9.9%)	
Missing	4 (1.1%)	3 (2.8%)	1 (0.4%)	
Pre-NAC CEA (ng/mL)	2.6 ± 3.7	2.0 ± 2.5	2.8 ± 4.1	0.030
Pre-NAC CEA				0.056
Normal (< 5)	324 (90.3%)	98 (92.5%)	226 (89.3%)	
Abnormal (≥ 5)	28 (7.8%)	4 (3.8%)	24 (9.5%)	
Missing	7 (1.9%)	4 (3.8%)	3 (1.2%)	
Longest tumor diameter after NAC, MRI (cm)	1.7 ± 1.8	0.6 ± 1.3	2.2 ± 1.8	< 0.001
Complete response on MRI				< 0.001
No	248 (69.1%)	34 (32.1%)	214 (84.6%)	
Yes	105 (29.2%)	71 (67.0%)	34 (13.4%)	
Missing	6 (1.7%)	1 (0.9%)	5 (2.0%)	
Post-NAC CA15-3 (U/mL)	16.0 ± 8.1	14.4 ± 5.6	16.7 ± 8.8	0.004
Post-NAC CA15-3				0.016

pCR: pathologic complete response, BMI: body mass index, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, NAC: neoadjuvant chemotherapy, MRI: magnetic resonance image

	Total	pCR (n = 106)	Non-pCR (n = 253)	<i>p</i>
Normal (< 25)	327 (91.1%)	103 (97.2%)	224 (88.5%)	
Abnormal ($\geq$ 25)	32 (8.9%)	3 (2.8%)	29 (11.5%)	
Post-NAC CEA (ng/mL)	2.8 $\pm$ 2.7	2.3 $\pm$ 1.3	3.0 $\pm$ 3.1	0.001
Post-NAC CEA				0.039
Normal (< 5)	324 (90.3%)	102 (96.2%)	222 (87.7%)	
Abnormal ($\geq$ 5)	31 (8.6%)	3 (2.8%)	28 (11.1%)	
Missing	4 (1.1%)	1 (0.9%)	3 (1.2%)	
pCR: pathologic complete response, BMI: body mass index, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, NAC: neoadjuvant chemotherapy, MRI: magnetic resonance image				

Significant Risk Factors Associated with pCR after NAC

Multivariate logistic regression analysis showed that factors which significantly affected possibility of pCR were: high level of ER positivity (OR 0.84, $p < 0.001$), positive HER2 status (OR 1.25, $p < 0.001$), complete response on post-NAC MRI (OR 1.62, $p < 0.001$), abnormal CEA level after NAC (OR 0.86, $p = 0.051$), and abnormal CA15-3 level after NAC (OR 0.87, $p = 0.074$) (Table 2).

Table 2

Predictive factor for pCR, estimated by univariate and multivariate logistic regression analyses

	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age	1.00	1.00–1.01	0.903			
BMI	0.99	0.98–1.01	0.213			
Multiplicity (yes)	0.89	0.75–1.06	0.193			
Palpability (yes)	1.00	0.88–1.15	0.972			
Family history (yes)	1.00	0.87–1.15	0.995			
Clinical tumor stage						
cT1	Ref					
cT2	0.88	0.72–1.07	0.193			
cT3	0.84	0.67–1.05	0.132			
cT4	0.74	0.56–0.97	0.031			
Clinical node stage						
cN0	Ref					
cN1	0.90	0.79–1.03	0.143			
cN2	0.93	0.79–1.10	0.379			
cN3	0.80	0.67–0.95	0.012			
Histologic grade						
G1	Ref					
G2	1.21	0.83–1.74	0.320			
G3	1.31	0.91–1.89	0.147			

	Univariate analysis			Multivariate analysis		
Nuclear grade						
G1	Ref					
G2	1.31	0.67– 2.58	0.429			
G3	1.52	0.78– 2.97	0.220			
ER status (Level)						
Negative	Ref			Ref		
Low positive	0.98	0.79– 1.23	0.892	0.98	0.82– 1.17	0.809
High positive	0.75	0.67– 0.83	< 0.001	0.82	0.75– 0.90	< 0.001
PR status (positive)	0.77	0.68– 0.86	< 0.001			
HER2 status (positive)	1.40	1.27– 1.55	< 0.001	1.25	1.15– 1.36	< 0.001
Longest tumor diameter before NAC, MRI (cm)	0.97	0.95- 1.00	0.048			
Pre-NAC Ki-67 (%)	1.00	1.00– 1.00	0.295			
Pre-NAC CA15-3 (U/mL)	0.99	0.99- 1.00	0.001			
Pre-NAC CA15-3						
Normal (< 25)	Ref					
Abnormal (≥ 25)	0.76	0.62– 0.93	0.008			
Pre-NAC CEA (ng/mL)	0.99	0.97- 1.00	0.078			
Pre-NAC CEA						
Normal (< 5)	Ref					
Abnormal (≥ 5)	0.85	0.70– 1.04	0.109			
Longest tumor diameter after NAC, MRI (cm)	0.91	0.88– 0.94	< 0.001			

	Univariate analysis			Multivariate analysis		
Complete response on MRI						
No	Ref			Ref		
Yes	1.79	1.62– 1.97	< 0.001	1.63	1.48– 1.79	< 0.001
Post-NAC CA15-3 (U/mL)	0.99	0.99- 1.00	0.011			
Post-NAC CA15-3						
Normal (< 25)	Ref			Ref		
Abnormal (≥ 25)	0.75	0.62– 0.91	0.004	0.86	0.74- 1.00	0.051
Post-NAC CEA (ng/mL)	0.95	0.93– 0.98	0.001			
Post-NAC CEA						
Normal (< 5)	Ref			Ref		
Abnormal (≥ 5)	0.77	0.64– 0.93	0.007	0.87	0.75– 1.01	0.074

Development and Validation of the Nomogram and the ANN Model

Using the training set and five independent variables identified by the multivariate logistic regression analyses, a nomogram was developed to predict pCR after NAC (Fig. 1). Total point calculated by sum of the points for each variable is used to identify the probability of pCR after NAC. Similarly, we developed an ANN model (Fig. 2). First input layer consists of the five independent variables as used in the nomogram, and number of layers and nodes were determined based on systematic experimentation that worked best for our dataset. The prediction rate was best when hidden layers were set to three and each node to two.

The two prediction models were internally validated using the test set and receiver operating characteristic (ROC) curves are depicted in Fig. 3–4. The AUC of the machine learning model and nomogram were 0.876 (95% CI, 0.808–0.943) and 0.789 (95% CI, 0.707–0.871), respectively. Discriminative power of the machine learning model was higher than that of the nomogram.

Discussion

The present study developed two independent predictive models to predict pCR after NAC in breast cancer patients based on clinicopathologic indicators. Multivariate analysis showed that breast cancer with

lower level of ER expression, HER2 positivity, complete response on post-NAC MRI, normal CEA and CA 15 – 3 levels after NAC were more likely to achieve a pCR after NAC. With an AUC of 0.789 [95% CI, 0.707–0.871] for the nomogram and 0.876 [95% CI, 0.808–0.943] for the ANN model, the two models both exhibited sufficient power to predict pCR after NAC in breast cancer, however, the ANN model outperformed nomogram in terms of accuracy and precision.

Various models have been developed to predict pathologic response after NAC. Several researchers proposed nomograms using preoperative clinicopathological variables (e.g. age, NAC cycles, ER, HER2, status of lymphovascular invasion) or just simple laboratory indexes (clinical tumor stage, lymphocyte to monocyte ratio, fibrinogen level, and D-dimer level) to predict pCR after NAC^{12,16}. These nomograms were helpful in stratifying patient who would experience more or less benefit from NAC, but small patient size (less than 200) limited its validation power and result of external validation was not as good when tested in other institutions. Moreover, each nomogram consisted of different variables as researchers intended and implication of excluded or unknown covariates were neglected.

Recent studies have evaluated the significance of machine learning in classification of breast cancer. For example, Asri et al. compared different machine learning algorithms (Support Vector Machine, Decision Tree, Naive Bayes and k Nearest Neighbors) on the Wisconsin Breast Cancer datasets to assess which algorithm is the best in breast cancer risk prediction and diagnosis¹⁷. Although support vector machine was the best in terms of precision and low error rate, all four types of algorithms showed accuracy above 90%. Delen et al. compared two data mining methods (ANN and decision trees) along with a statistical method (logistic regression) to develop a prediction model for breast cancer survivability and demonstrated that artificial neural network and decision trees performed better than logistic regression model¹⁸. These studies showed that machine-learning algorithms have promise in medical application and may provide better prediction than any other models developed before.

In this study, we compared ANN algorithm along with one of the most commonly used analytic method, nomogram, to develop a predictive model for pCR after NAC. Nomogram is a graphical tool that is designed for quick and simple determination. However, its accuracy is limited due to small number of variables that could be included in the model. Before developing a nomogram, statistical-based feature selection process must be performed to select significant factors and many potentially important clinical, radiological, or pathological factors could be dropped out during this feature reduction process. On the other hand, machine learning algorithms allow unlimited number of input variables and an optimal set of variables could be improved with training methods. Although the ANN model and nomogram were built based on the same factors for comparative purpose, we believe predictive performance of machine learning model could be improved by including extensive clinicopathologic variables. Development of a new ANN model without feature selection procedure is worthy of consideration in further study.

Nonetheless, artificial neural network has a fundamental problem regarding interpretability and lack of understanding. Despite of extreme efficiency and accuracy in dealing with large data sets, researchers are unable to explain how the algorithm uses input variables to make the output. Interpretability is crucial in

healthcare fields and inexplicability may prevent its widespread in clinical settings. Recently, researchers are trying to develop an explainable neural networks by discriminating functions the model has built on¹⁹. Adoption of such model will certainly improve its applicability in medical fields.

To the best of our knowledge, this is the first study to compare an ANN and nomogram in prediction of pCR after NAC in breast cancer. Nomograms have provided simple and intuitive visual explanation for prediction of patients' outcome and helped clinicians in decision-making. On the other hand, machine learning algorithms are complicated in nature but their ability to learn without being explicitly programmed provide much more opportunities as data becomes complex and larger in size. Our study suggests potential of machine learning algorithms to aid clinicians in more accurate decision making for breast cancer patients.

We acknowledge that there are some limitations to our study. The main weakness is that our models were validated with internal data only. Moreover, neural network does not provide relative importance among input variables and we cannot explain which variable is more important compare with others. Lastly, machine learning has advantage in handling large size of data, but our data is limited in number. If we could further investigate using explainable neural network in large dataset, we would be able to improve its generalizability and reproducibility.

Conclusions

The comparative study of prediction models for breast cancer prognosis provide insight into the importance of machine learning algorithm in medical predictive study. The artificial neural network model demonstrated superior discrimination (AUC 0.876 [95 % CI, 0.808–0.943]) compared with the nomogram (AUC 0.789 [95% CI, 0.707–0.871]). With advancement in prediction of pCR after NAC, surgeons would be able to stratify patients who would benefit from early surgical resection while non-responders to NAC may be further treated with more extensive surgery, hormonal therapy or alternative chemotherapy regimens.

Declarations

Authors' contributions

JJ performed study design, statistical analysis, and was a major contributor in writing the manuscript. EK and EK made significant contributions to the conception. JHK, SHK, and KJS executed neoadjuvant chemotherapy. SMK, MJ, and BLY performed radiologic examination before and after neoadjuvant chemotherapy. SYP performed histological examination of breast. HS performed study design and substantially revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Nomogram model to predict pathologic complete response after neoadjuvant chemotherapy

Figure 2

Artificial neural network model to predict pathologic complete response after neoadjuvant chemotherapy

Figure 3

ROC curve showing the predictive accuracy of the nomogram

Figure 4

ROC curve showing the predictive accuracy of the artificial neural network model