Nomogram predicted overall survival of patients with neuroendocrine carcinoma of the breast

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Abstract

Background For primary neuroendocrine carcinoma of breast was a very rare subtype in breast cancers, its prognosis was still controversial and there was no independent standard for its treatment. The purpose of our retrospective study was to construct a nomogram to predict the overall survival (OS) of patients with neuroendocrine carcinoma of the breast.

Methods 150 patients of training cohort were collected from Surveillance, Epidemiology, and End Results (SEER) database diagnosed between 2003 and 2015, and 93 patients of verification cohort were enrolled from Sun Yat-sen University Cancer Center (Guangzhou, China) diagnosed between 2004 and 2018. The nomogram was constructed uniting three significantly risk factors of overall survival identified by univariate and multivariate analysis and then validated using receiver operating characteristic (ROC) curves for discrimination, calibration plots and the decision curves analysis (DCA).

Results Age, N stage and PR status were closely and significantly related to overall survival in patients with breast neuroendocrine carcinoma. The C-index of nomogram in the training and verification cohorts are 0.775 (95% CI, 0.784 to 0.615) and 0.760 (95% CI, 0.705 to 0.800) respectively. Calibration plots of practical and predicted possibility for the nomogram demonstrated that the predictive 5-year overall survival rate was in accordance with the actual overall survival probability in both sets. Moreover, the decision curves (DCA) also expressed pretty clinical benefit of the nomogram across a range of high-risk threshold.

Conclusion This novel population-based nomogram may help with treatment decisions in patients with neuroendocrine carcinoma of the breast (NEBC).

Background

Breast cancer was the number one multifactorial cancer in women worldwide, composed of many different subtypes with various clinicopathologic features. Neuroendocrine carcinoma of the breast is a rare special subtype, endorsed by the WHO for the first time in 2003[1]. Neuroendocrine tumors of the breast (NEBC) are very uncommon malignant tumors having a proportion of less than one percent in breast cancers[2]. Exactly as a result of its scarce, the existing learning of NECB is confined to clinical case reports and some small series analysis[3–18]. And most of the current knowledge concerning the disease was obtained from these studies. For specific recommendations regarding treatment do not exist so far, surgical management, similar to conventional breast cancer, was performed with NEBC patients[19]. Although curative surgical treatment has been performed, the long-term postoperative prognosis of NECB is still controversial.

On the prognosis, no consensus has been reached for NEBC. Contradictory research results appeared in the previous studies, very likely thanks to the limited reported number of patients, and different selection criteria[20]. Thus, identification of prognostic factors of NEBC has long been receiving much attention. And to get to know more about mammary NEC, we have made full use of a relatively complete and large

cancer database collected over the past two decades from Surveillance, Epidemiology, and End Results (SEER) registries and Sun Yat-sen University Cancer Center (Guangzhou, China). Using these data, we assessed the onset and clinical prognosis of NEBC.

There were three goals of our present study. First, our aim is to assess the prognostic value of clinicopathological characteristics in NEBC patients. Secondly, we designed to establish a predictive nomogram which has been widely used in many other cancer diseases to accomplish overall survival estimation for NEBC patients[21–27]. Finally, we aimed to evaluate the clinical applicability of the nomogram in predicting prognosis.

Methods

Patients

Two independent groups of NEBC patients after radically surgical resection were selected for this study. The training cohort patients (n = 150) were from Surveillance, Epidemiology, and End Results (SEER) registries diagnosed with NEBC between 2003 to 2015 and the verification cohort were collected from patients (n = 93) who received curative surgery in Sun Yat-sen University Cancer Center (Guangzhou, China) between 2004 and 2018. All patients had survived at least 3 months after radical surgery. Criteria for the inclusion and exclusion of patients analyzed in both cohorts are as follows: (a) confirmed pathological diagnosis of NEBC; (b) radically surgical resection of tumors with axillary lymph node dissection or intraoperative sentinel lymph node biopsy as well as no residual cancer; (c) the entire clinicopathologic and follow-up data were recorded; (d) the patients, who had no regional lymph node status and tumor size records were excluded from the analysis. Data announced from the SEER database hasn't demanded any patient consent because cancer was a disease that could be reported everywhere in the United States. For patients used for verification in the study, we have got informed consent from themselves and the research program has been approved by the Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center. Clinicopathologic features analyzed included age, primary site, laterality, grade, axillary lymph node metastasis, T stage, N stage, ER status, PR status and HER2 status. In addition, we reviewed the outpatient visit records or contacted the patients by phone to determine the overall survival time, which was defined as the period between the time of surgery and time of either death or last follow-up,

Statistical Analysis

SPSS software (version 24.0) and R (version 3.4.4) were applied to statistical analyses of data. According to conventional clinical findings, the grouping of categorical variables was shown in Table 1. Univariate analysis was carried out to evaluate the statistical significance of clinical and pathological features. Multivariate analysis results were obtained by Cox proportional hazard regression. All the analyzed variables with P values less than 0.05 in the multivariate analysis were used to create a predictive nomogram. The nomogram was established in the training set and then verified in the other validation set. The discrimination was quantified by the area under the receiver operating characteristic (ROC)

curves (AUC or C-index). Graphically evaluation of calibration was executed by using the Hosmer fitting optimization test to draw the relationship between actually observed probabilities and predictive probabilities[28]. The Decision Curve Analysis (DCA) was applied to assess the clinical effectiveness of nomogram for the prognosis prediction. All tests were performed in both sets of queues and $P < 0.05$ was considered significant.

Table 1
Basal clinicopathologic characteristics in training and verification cohort.

Characteristics	Training set n = 150 (%)	Verification set n = 93(%)
Age		
≤ 50	33(22.0%)	39(41.9%)
> 50	117(78.0%)	54(58.1%)
Primary Site		
Central portion	4(2.7%)	2(2.2%)
UIQ	17(11.3%)	29(31.2%)
LIQ	9(6.0%)	13(14.0%)
UOQ	49(32.7%)	13(14.0%)
LOQ	14(9.7%)	9(9.7%)
Others	57(38.0%)	27(29.0%)
Laterality		
Left	63(42.0%)	46(49.5%)
Right	87(58.0%)	47(50.5%)
Grade		
I	23(15.3%)	3(3.2%)
II	51(34.0%)	31(33.3%)
III	76(50.7%)	12(12.9%)
Unknown	-	47(50.5%)
T Stage		
T1	63(42.0%)	40(43.0%)
T2	70(46.7%)	51(54.8%)
T3	17(11.3%)	2(2.2%)
Regional lymph nodes		

UIQ, upper-inner quadrant; LIQ, lower-inner quadrant; UOQ, upper- outer quadrant; LOQ, lower-outer quadrant; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Characteristics	Training set n = 150 (%)	Verification set n = 93(%)
Positive	54(36.0%)	24(25.8%)
Negative	96(64.0%)	69(74.2%)
N Stage		
N0	95(63.3%)	69(74.2%)
N1	38(25.3%)	17(18.3%)
N2	8(5.3%)	5(5.4%)
N3	8(5.3%)	2(2.2%)
ER status		
Positive	114(76.0%)	89(95.7%)
Negative	35(23.3%)	2(2.2%)
Unknown	1(0.7%)	2(2.2%)
PR status		
Positive	92(61.3%)	84(90.3%)
Negative	57(38.0%)	9(9.7%)
Unknown	1(0.7%)	-
Her 2 status		
Positive	2(1.3%)	5(5.4%)
Negative	76(50.7%)	81(87.1%)
Unknown	72(48.0%)	7(7.5%)
UIQ, upper-inner quadrant; LIQ, lower-inner quadrant; UOQ, upper- outer quadrant; LOQ, lower-outer quadrant; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.		

Results

Clinicopathological characteristics

The comprehensive characteristics of all enrolled patients in the training and verification cohorts were shown in Table 1; the median survival time for the two groups were 35.5 months and 30 months, respectively. The median age of onset in the two sets were 63 years (range, 34–99 years) and 54 years (range, 25–85 years), respectively. The location of neuroendocrine breast carcinoma lesions were on the left breast in 109 cases (44.86%) and on the right breast in 134 cases (55.14%). For typical immune

indicators, most patients were negative for axillary lymph node metastasis, positive for ER and PR status and negative for HER2 status in both sets. No significant differences were found between the training and verification groups with regard to the above-mentioned clinicopathologic characteristics.

Identification of prognostic factors in patients with NEBC

To identify potential prognostic factors, we performed univariate analysis on the training group with the result indicating in Table 2. Univariate analysis revealed that age ($p < 0.001$), axillary lymph node metastasis (N stage) ($p < 0.001$) and PR status ($p = 0.009$) were confirmed as the most important prognostic factors for OS. In multivariate analysis, age (hazard ratio [HR], 1.052; 95% confidence interval [CI], 1.024–1.082; $p < .001$), N stage (HR, 1.842; 95% CI, 1.270–2.673; $p = .001$), and PR status (HR, 5.157; 95% CI, 2.514–10.577; $p < .001$) were still significantly predictive factors of OS (Table 2). According to the above analysis results, we determined that age, N stage and PR status were independent factors affecting the OS of patients with NEBC, and then were integrated in the construction of nomogram.

Table 2
Independent prognostic factors predicting OS in the training cohort.

Variables	Univariate analysis for OS	Multivariate analysis for OS
	HR 95%CI p value	HR 95%CI p value
Age, years	1.053 1.024–1.083 0.000	1.052 1.024–1.082 0.000
Primary Site	1.051 0.929–1.189 0.431	NA
Laterality (left vs right)	1.244 0.658–2.348 0.502	NA
Grade (I, II vs III)	1.750 0.920–3.327 0.088	NA
T Stage	0.065	NA
T1	1.00	
T2	1.472 0.737–2.938 0.273	
T3	2.450 0.941–6.380 0.067	
Regional lymph nodes (positive vs negative)	1.011 0.982–1.040 0.462	NA
N Stage		
N0	1.00 0.001	1 0.001
N1	0.856 0.366–2.004 0.720	1.042 0.444–2.446 0.925
N2	3.416 1.163–10.029 0.025	2.019 0.656–6.778 0.210
N3	6.332 2.314–17.326 0.000	9.801 3.179–30.217 0.000
ER status (positive vs negative)	1.859 0.960–3.602 0.066	NA
PR status (positive vs negative)	2.376 1.241–4.549 0.009	5.157 2.514–10.577 0.000
Her 2 (positive vs negative)	1.052 0.940–1.176 0.377	NA
P < 0.05 was considered significant and marked in bold. NA, not applicable; OS, overall survival.		

Construction and verification of prognostic nomogram for OS

All the three independently predictive factors of OS in multivariate cox proportional hazards regression analysis derived from the training cohort were integrated into the prediction nomogram model which is

shown in Fig. 1. The nomogram demonstrated good accuracy with an unadjusted concordance index (C-index) of 0.775 (95% CI, 0.784 to 0.615) (Fig. 2A). The calibration curve of survival probability for 5 years after operation also showed pretty good consistency between the nomogram model and actual observation prediction (Fig. 2C).

In the verification cohort, the median follow-up time was 30 months (range, 3-169 months). The C-index of the constructed nomogram for predicting 5-year OS was 0.760 (95% CI, 0.705 to 0.800) (Fig. 2B), and good calibration was observed for predicting the probability of 5-year OS (Fig. 2D).

Clinical usefulness of the nomogram as evaluated by DCA

Given that the established nomogram demonstrated good predictive capabilities in terms of C-index, DCA was needed to determine the clinical validity of the nomogram. On DCA, the nomogram showed great net benefit with a wide range of threshold probability (Fig. 3A). Then we performed DCA in the verification cohort which also presents a similar wide range of threshold probability (Fig. 3B). This result further demonstrated fairly good estimation of clinical decision making at high net benefit levels.

Discussion

Mammary NEC has always been a controversial disease. Different studies have conveyed different clinical results owing to inconsistent diagnostic criteria in part. Some have revealed that the prognosis of neuroendocrine carcinomas was better than that of patients without specific types of aggressive cancer, whereas a worse prognosis has recently been observed in more larger series[9, 14, 16, 29]. To study more about prognosis of NEBC, we collected total 243 NEBC patients who underwent curative surgery both from the SEER and Sun Yat-sen University Cancer Center (Guangzhou, China) database and constructed two groups, the training cohort and verification cohort, respectively. On the basis of the two separate queues, novel and effective nomogram have been developed to project the individual probability of overall survival at 5 years. With integration of the independent prognostic factors that reflect clinical points and postoperative pathological results, the nomogram was expected to be an effective and reliable tool.

Most population-based results showed that NECB is often positive for hormone receptors, whereas HER2 is almost always negative. In agreement with these previous series of study, our results also showed that the positive rate of ER, PR and HER2 are 83.5%, 72.4% and 2.9% respectively. Meanwhile, the study also presented that NEBC tended to occur in elderly patients (mean age 59 years), showing a higher pathological grade, a larger tumor (mean 27 mm) and less local lymph node metastasis.

The advantage of our present study was that two cohorts of NEBC patients were enrolled for analysis, and they all underwent radically surgical treatment. Then major confounding factors for clinical outcomes of NEBC, including age, N stage and PR status, were eliminated. The nomogram possessed C-indices of 0.775 and 0.760 for 5-year OS in the training and verification cohort separately; although not perfect, the widely used nomogram was first applied in mammary neuroendocrine carcinoma to predict postoperative survival. Besides, the nomogram was developed in the training set and then validated in the

other verification set to get more reliability. This tool could further promote individualized clinical decisions by applying clinically pathological factors that were readily available to estimate the overall survival in patients with NEBC.

Although the nomogram showed good accuracy for predicting postoperative overall survival, we must consider some limitations of this study. First of all, due to the lack of postoperative recurrence follow-up, we did not incorporate DFS into the study. Hence, postoperative disease-free survival of NEBC patients couldn't be predicted via the nomogram. Secondly, the nomogram was clinically suitable for postoperative decision-making, but not for preoperative decision making. Thirdly, tumor stage and grade should be considered as risk factors; however, in univariate analysis, they both showed no statistical difference. This may hinder the ability of the nomogram to predict prognosis. Finally, the possibility of selective bias was introduced because of the use of retrospective data. And patients of the training cohort were white, so estimation for non-white patients might not be as accurate as prediction. Given these above, we should conduct a larger sample size and longer follow-up study to further confirm the accuracy of the nomogram.

Conclusion

The novel population-based nomogram, developed from retrospectively collected data, could precisely predict 5-year OS of patients with neuroendocrine carcinoma of breast and thus help to make individualized treatment decisions. Definitely, larger queues or forward-looking studies were expected to further confirm our findings.

Abbreviations

NEBC
neuroendocrine carcinoma of the breast
C-index
concordance index
SEER
Surveillance, Epidemiology, and End Results
OS
overall survival
ROC
receiver operating characteristic
DCA
decision curves analysis

Declarations

Ethics approval and consent to participate

Data announced from the SEER database hasn't demanded any patient consent because cancer was a disease that could be reported everywhere in the United States. For patients used for verification in the study, we have got informed consent from themselves and the research program has been approved by the Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center (the committee approval number GZR2016-076).

Patient consent for publication

Not applicable.

Availability of data and materials

The datasets used in our study are available from the author on reasonable request.

Competing interests

No potential conflict of interest.

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Authors' contributions

WT and XX designed the study and performed statistical analysis of the data. XX, YK and PL conducted the data analysis and interpretation. WT wrote the manuscript. Xiao. X and Wei. Tan edited and revised the manuscript. All authors discussed the results.

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Not applicable.

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Figures

Figure 1

Figure 1

Five-year overall survival nomogram for patients with NEBC. In order to use the nomogram, the value of each single patient is situated on each variable axis, and a line is drawn up to calculate the number of points received for every variable value. To use the nomogram, the value of an individual patient is located on each variable axis, and a line is drawn up-ward to calculate the number of points received for

each variable value. The points were summed up together to obtain the total points and 5-year OS can be estimated the total points of each patient.

Figure 2

Figure 2

Discrimination and calibration of the nomogram in training and verification cohorts. Great prediction performance was observed in receiver operating characteristic (ROC) curves for discrimination of both the training(A) and verification sets(B). Calibration plots of survival probability for 5 years also suggested

pretty good consistency between the predicted 5-year OS and actual observed OS in the training(C) and verification cohort(D).

Figure 3

Figure 3

Decision curve analysis (DCA) for 5-year survival in training (A) and verification cohorts (B). The clinical net benefit, expressed by the Y-axis, was calculated by adding the benefits (true positive) and subtracting the harm (false positive). The hypothesis that no patient will experience the event is represented by

horizontal solid black lines, while the solid blue lines represent the hypothesis that all patients will die or relapse. The solid red lines in both sets indicate good net benefit of nomogram across a range of high risk threshold.