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Original Research

A high-quality model for predicting the prognosis of breast neuroendocrine carcinoma to help clinicians decide on appropriate treatment methods: A population-based analysis

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ABSTRACT

Background: Breast neuroendocrine carcinoma (NEC) is a rare malignancy with unclear treatment options and prognoses. This study aimed to construct a high-quality model to predict overall survival (OS) and breast cancer-specific survival (BCSS) and help clinicians choose appropriate breast NEC treatments.
Patients and methods: A total of 378 patients with breast NEC and 349,736 patients with breast invasive ductal carcinoma (IDC) were enrolled in the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2018. Propensity score matching (PSM) was performed to balance the clinical baseline. Prognostic factors determined by multivariate Cox analysis were included in the nomogram. C-index and calibration curves were used to verify the performance of the nomogram.
Results: Nomograms were constructed for the breast NEC and breast IDC groups after PSM. The C–index of the nomograms ranged from 0.834 to 0.880 in the internal validation and 0.818–0.876 in the external validation, indicating that the nomogram had good discrimination. The risk stratification system showed that patients with breast NEC had worse prognoses than those with breast IDC in the low-risk and intermediate-risk groups but had a similar prognosis that those in the high-risk group. Moreover, patients with breast NEC may have a better prognosis when undergoing surgery plus chemotherapy than when undergoing surgery alone or chemotherapy alone.
Conclusions: We established nomograms with a risk stratification system to predict OS and BCSS in patients with breast NEC. This model could help clinicians evaluate prognosis and provide individualized treatment recommendations for patients with breast NEC.

Introduction

Neuroendocrine carcinoma (NEC) of the breast is a rare tumor type, accounting for only 2%–5% of breast cancers [1]. Neuroendocrine breast neoplasms in the 5th Edition of the World Health Organization (WHO) classification of breast tumors were classified as “neuroendocrine tumors” and “neuroendocrine carcinomas”. Key changes were the exclusion of special histologic types (solid papillary carcinoma and hypercellular variant of mucinous carcinoma) and the inclusion of large cell neuroendocrine carcinoma [2]. There have been few clinical studies on breast NEC, and the number of cases investigated has always been small owing to its rarity.

Current guidelines do not provide clear recommendations for the treatment of breast NEC. Clinicians have limited knowledge of NEC and

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Table 1
Clinicopathological factors in different subgroups in breast neuroendocrine carcinoma (NEC).

	Neuroendocrine tumor, well-differentiated (n=161) (%)	Small cell carcinoma (n=60) (%)	Large cell neuroendocrine carcinoma (n=14) (%)	Carcinoma with neuroendocrine differentiation (n=143) (%)	*P* value
Age (years)					0.765
≤50	34 (21.1)	13 (21.6)	3 (21.5)	24 (16.8)	
>50	127 (78.9)	47 (78.4)	11 (78.5)	119 (83.2)	
Sex					0.715
Female	158 (98.1)	60 (100)	14 (100.0)	141 (98.6)	
Male	3 (1.9)	0 (0)	0 (0.0)	2 (1.4)	
Race					0.173
White	129 (80.1)	46 (76.7)	13 (92.9)	117 (81.8)	
Black	22 (13.7)	10 (16.7)	1 (7.1)	10 (7.0)	
Other	10 (6.2)	4 (6.6)	0 (0)	16 (11.2)	
Grade					0.001
1	18 (11.1)	1 (1.7)	0 (0.0)	15 (10.5)	
2	142 (88.1)	52 (86.6)	14 (100.0)	125 (87.4)	
3	1 (0.6)	7 (11.7)	0 (0)	3 (2.1)	
Laterality					0.129
Left	77 (47.9)	22 (36.6)	6 (42.8)	78 (54.5)	
Right	84 (52.1)	38 (63.4)	8 (57.2)	65 (45.5)	
Marital status					0.250
Married	83 (51.6)	35 (58.4)	4 (28.6)	76 (53.1)	
Other	78 (48.4)	25 (41.6)	10 (71.4)	67 (46.9)	
T stage					0.772
I–II	127 (78.9)	44 (73.4)	12 (85.7)	112 (78.3)	
III–IV	34 (21.1)	16 (26.6)	2 (14.3)	31 (21.7)	
N stage					0.001
0	98 (60.9)	32 (53.3)	11 (78.5)	119 (83.2)	
I–III	63 (39.1)	28 (46.7)	3 (21.5)	24 (16.8)	
M stage					0.001
0	135 (83.9)	49 (81.7)	10 (71.4)	87 (60.8)	
1	26 (16.1)	11 (18.3)	4 (28.6)	56 (39.2)	
Stage					0.001
I–II	114 (70.8)	35 (58.3)	10 (71.5)	128 (89.5)	
III–IV	47 (29.2)	25 (41.7)	4 (28.5)	15 (10.5)	
Bone					0.068
Yes	19 (11.8)	6 (10.0)	4 (28.5)	10 (7.0)	
No	142 (88.2)	54 (90.0)	10 (71.5)	133 (93.0)	
Brain					0.619
Yes	4 (2.5)	1 (1.6)	0 (0.0)	1 (0.7)	
No	157 (97.5)	59 (98.4)	14 (100.0)	142 (99.3)	
Liver					0.317
Yes	8 (5.0)	5 (8.4)	2 (14.3)	6 (4.2)	
No	153 (95.0)	55 (91.6)	12 (85.7)	137 (95.8)	
Lung					0.025
Yes	6 (3.7)	6 (10.0)	0 (0.0)	2 (1.4)	
No	155 (96.3)	54 (90.0)	14 (100.0)	141 (98.6)	
Subtype					0.001
HR+/ HER2–	118 (73.3)	26 (43.4)	11 (78.6)	118 (82.5)	
HR+/ HER2+	3 (1.9)	0 (0.0)	1 (7.1)	10 (7.0)	
HR–/ HER2+	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	
HR–/ HER2–	40 (24.8)	33 (55.0)	2 (14.3)	15 (10.5)	
ER					0.001
Positive	116 (72.1)	22 (36.7)	12 (85.7)	126 (88.1)	
Negative	45 (27.9)	38 (63.3)	2 (14.3)	17 (11.9)	
PR					0.001
Positive	101 (62.7)	17 (28.4)	10 (71.5)	113 (79.0)	
Negative	60 (37.3)	43 (71.6)	4 (28.5)	30 (21.0)	
HER2					0.089
Positive	3 (1.8)	1 (1.6)	1 (7.1)	10 (7.0)	
Negative	158 (98.2)	59 (98.4)	13 (92.9)	133 (93.0)	
Surgery					0.050
Yes	125 (77.6)	48 (80.0)	10 (71.5)	127 (88.8)	
No	36 (22.4)	12 (20.0)	4 (28.5)	16 (11.2)	
Radiation					0.012
Yes	61 (37.8)	27 (45.0)	3 (21.5)	77 (53.8)	
No	100 (62.2)	33 (55.0)	11 (78.5)	66 (46.2)	
Chemotherapy					0.001
Yes	71 (44.0)	46 (76.6)	6 (42.8)	61 (42.7)	
No	90 (56.0)	14 (23.4)	8 (57.2)	82 (57.3)	
Systemic therapy					0.201
Yes	99 (61.5)	42 (70.0)	9 (64.3)	104 (72.7)	
No	62 (38.5)	18 (30.0)	5 (35.7)	39 (27.3)	

ER: estrogen receptor, HER2: human epidermal growth factor receptor-2, HR: hormone receptors, PR: progesterone receptor.

Table 2
Comparison of the clinical baseline between the neuroendocrine carcinoma (NEC) and invasive ductal carcinoma (IDC) groups before and after propensity score matching (PSM).

	Before PSM			After PSM		
	NEC (%) n=378	IDC (%) n=349736	*P* value	NEC (%) n=327	IDC (%) n=1280	*P* value
Age (years)			0.511			0.854
≤50	74 (19.6)	73284 (21.0)		62 (19.0)	237 (18.5)	
>50	304 (80.4)	276452 (79.0)		265 (81.0)	1043 (81.5)	
Sex			0.315			0.447
Female	373 (98.7)	346769 (99.1)		324 (99.1)	1273 (99.5)	
Male	5 (1.3)	2967 (0.9)		3 (0.9)	7 (0.5)	
Race			0.389			1.000
White	305 (80.7)	275509 (78.8)		264 (80.8)	1034 (80.8)	
Black	43 (11.4)	39028 (11.2)		39 (11.9)	152 (11.9)	
Other	30 (7.9)	35199 (10.0)		24 (7.3)	94 (7.3)	
Grade			0.001			0.259
1	34 (9.0)	76721 (21.9)		29 (8.9)	118 (9.2)	
2	333 (88.1)	272393 (77.9)		291 (89.0)	1149 (89.8)	
3	11 (2.9)	622 (0.2)		7 (2.1)	13 (1.0)	
Laterality			0.401			0.704
Left	183 (48.4)	176876 (50.5)		152 (46.5)	580 (45.3)	
Right	195 (51.6)	172860 (49.5)		175 (53.5)	700 (54.7)	
Marital status			0.029			0.695
Married	198 (52.4)	202611 (57.9)		169 (51.7)	646 (50.5)	
Other	180 (47.6)	147125 (42.1)		158 (48.3)	634 (49.5)	
T stage			0.001			0.073
I–II	295 (78.1)	321279 (91.8)		263 (80.4)	1082 (84.5)	
III–IV	83 (21.9)	28457 (8.2)		64 (19.6)	198 (15.5)	
N stage			0.710			0.961
0	260 (68.7)	243631 (69.6)		224 (68.5)	875 (68.4)	
I–III	118 (31.3)	106105 (30.4)		103 (31.5)	405 (31.6)	
M stage			0.001			0.784
0	281 (74.4)	337121 (96.4)		277 (84.7)	1092 (85.3)	
1	97 (25.6)	12615 (3.6)		50 (15.3)	188 (14.7)	
Stage			0.001			0.122
I–II	287 (75.9)	304255 (86.9)		241 (73.7)	995 (77.7)	
III–IV	91 (24.1)	45481 (13.1)		86 (26.3)	285 (22.3)	
Bone			0.001			0.199
Yes	39 (10.3)	7873 (2.3)		37 (11.3)	115 (9.0)	
No	339 (89.7)	341863 (97.7)		290 (88.7)	1165 (91.0)	
Brain			0.001			0.346
Yes	6 (1.6)	781 (0.2)		6 (1.8)	15 (1.2)	
No	372 (98.4)	348955 (99.8)		321 (98.2)	1265 (98.8)	
Liver			0.001			0.082
Yes	21 (5.6)	3205 (0.9)		19 (5.8)	47 (3.7)	
No	357 (94.4)	346531 (99.1)		308 (94.2)	1233 (96.3)	
Lung			0.001			0.255
Yes	14 (3.7)	4088 (1.2)		13 (4.0)	71 (5.5)	
No	364 (96.3)	345648 (98.8)		314 (96.0)	1209 (94.5)	
Subtype			0.001			0.182
HR+/HER2–	273 (72.2)	249076 (71.3)		230 (70.3)	905 (70.7)	
HR+/HER2+	14 (3.7)	40803 (11.6)		12 (3.7)	77 (6.0)	
HR–/HER2+	1 (0.3)	16904 (4.8)		1 (0.3)	11 (0.9)	
HR–/HER2–	90 (23.8)	42953 (12.3)		84 (25.7)	287 (22.4)	
ER			0.001			0.167
Positive	276 (73.1)	286007 (81.7)		233 (71.2)	960 (75.0)	
Negative	102 (26.9)	63729 (18.3)		94 (28.8)	320 (25.0)	
PR			0.001			0.677
Positive	241 (63.8)	250601 (71.6)		199 (60.9)	795 (62.1)	
Negative	137 (36.2)	99135 (28.4)		128 (39.1)	485 (37.9)	
HER2			0.001			0.054
Positive	15 (4.0)	57707 (16.5)		13(4.0)	88 (6.9)	
Negative	363 (96.0)	292029 (83.5)		314(96.0)	1192 (93.1)	
Surgery			0.001			0.520
Yes	310 (82.1)	329303 (94.1)		264 (80.7)	1053 (82.3)	
No	68 (17.9)	20433 (5.9)		63 (19.3)	227 (17.7)	
Radiation			0.003			0.393
Yes	168 (44.4)	182312 (52.2)		135 (41.3)	562 (44.0)	
No	210 (55.6)	167424 (47.8)		192 (58.7)	718 (56.0)	
Chemotherapy			0.011			0.863
Yes	184 (48.6)	147655 (42.3)		150 (45.9)	594 (46.4)	
No	194 (51.4)	202081 (57.7)		177 (54.1)	686 (53.6)	
Systemic therapy			0.001			0.965
Yes	254 (67.2)	265330 (75.8)		214 (65.4)	836 (65.3)	
No	124 (32.8)	84406 (24.2)		113 (34.6)	444 (34.7)	

ER: estrogen receptor, HER2: human epidermal growth factor receptor-2, HR: hormone receptors, PR: progesterone receptor.

usually treat it the same way as breast invasive ductal carcinoma (IDC). Several clinical studies have suggested that the prognosis of patients with breast NEC is better than that of patients with breast IDC, but there was no significant difference in prognoses between the two groups [3–6]. In contrast, other studies have shown that compared with breast IDC, breast NEC is a more aggressive tumor with a worse prognosis [7–11]. The factors affecting the prognosis of breast NEC were contradictory in several studies, and the treatment method was controversial [12,13]. Further research is needed to study the prognosis of breast NEC and to explore suitable treatment options for breast NEC.

Data of patients with breast NEC and breast IDC were collected from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2018. The aim of this study was to compare the clinicopathological features and outcomes between breast NEC and breast IDC and to construct nomograms for breast NEC. A high-quality model for predicting the prognosis of breast neuroendocrine carcinoma was constructed to help clinicians decide on appropriate treatment methods in this study.

Methods

Data source and patient selection

Patients' clinicopathological features and survival data were collected from the SEER database. Since human epidermal growth factor receptor 2 (HER2) was available after 2010, the SEER database 8.3.8 was queried for patients who were diagnosed with breast IDC and breast NEC with complete data from 2010 to 2018. The selection criteria were based on international classification of diseases (ICD) codes: the study cohort of breast NEC included patients who had the codes ICD–0–3 8246/3, ICD–0–3 8041/3, ICD–0–3 8013/3, or ICD–0–3 8574/3, and while patients with IDC had the code ICD–0–3 8500/3. Patients with unknown or unspecified variable information were excluded.

Patient and clinicopathological characteristics

The variables analyzed in this study included demographic characteristics (age at diagnosis, race, and marital status), disease characteristics (laterality, histological grade, molecular type, and stage), treatment characteristics (breast surgery type, chemotherapy, and radiotherapy), and survival status (survival time and cause of death). Marital status was categorized into married and unmarried.

Statistical analyses

Propensity score matching (PSM) was performed using logistic regression with a caliper width of 0.01, without replacement, to balance the clinical baseline. Age, sex, race, grade, laterality, stage, T stage, N stage, M stage, surgery, radiation, chemotherapy, subtype, and marital status were included in the 1:4 PSM analysis. Pearson's chi-squared test was used for categorical feature comparisons, and Student's t-test was used for continuous feature comparisons. The results of this study were breast cancer-specific survival (BCSS) and overall survival (OS). According to the cause of death classification in the SEER database, BCSS

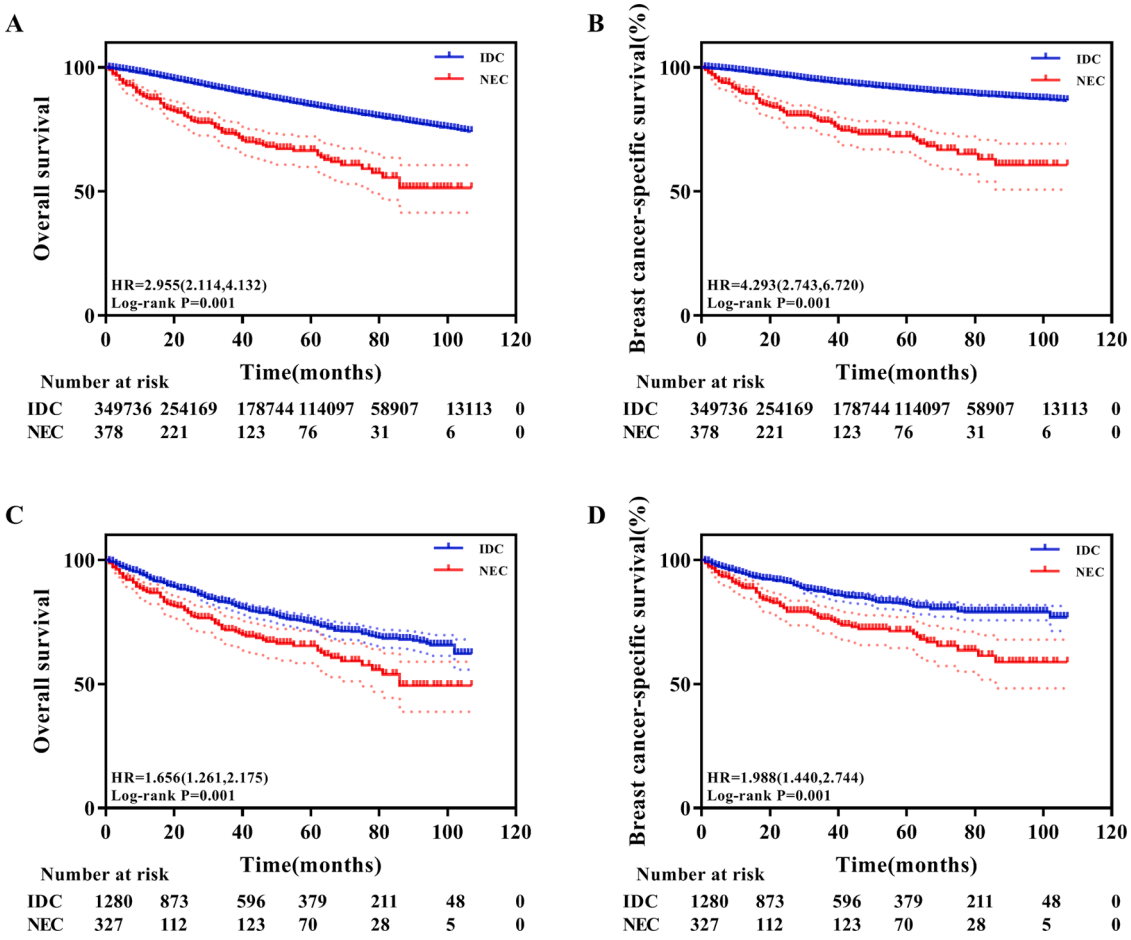

Fig. 1. (A) Overall survival (OS). (B) Breast cancer-specific survival (BCSS) curves plotted using the Kaplan–Meier method for patients diagnosed with breast neuroendocrine carcinoma (NEC) and invasive ductal carcinoma (IDC) after propensity score matching (PSM). (C) OS (D) BCSS curves plotted using the Kaplan–Meier method for patients diagnosed with breast NEC and IDC after PSM.

Table 3
Prognostic factors for overall survival (OS) and breast cancer-specific survival (BCSS) in breast neuroendocrine carcinoma by multivariate analyses.

	NEC					IDC			
	OS		BCSS			OS		BCSS	
Race	HR (95%CI)	*P* value	HR (95%CI)	*P* value	Race	HR (95%CI)	*P* value	HR (95%CI)	*P* value
White	—	—	Reference	0.020	White	—	—	Reference	0.050
Black	—	—	0.488 (0.219,1.087)	0.079	Black	—	—	1.590 (1.032,2.449)	0.035
Other	—	—	3.286 (1.123,9.617)	0.030	Other	—	—	1.784 (0.809,3.935)	0.151
M stage					Marital				
0	Reference		—	—	Married	Reference		—	—
1	2.617 (1.378,4.970)	0.003	—	—	Other	1.543 (1.154,2.064)	0.003	—	—
Stage					T				
I–II	—	—	Reference		I–II	Reference		—	—
III–IV	—	—	3.151 (1.777,5.589)	0.000	III–IV	1.367 (0.949,1.969)	0.093	—	—
Brain					Stage				
Yes	Reference		Reference		I–II	Reference		Reference	
No	0.297 (0.101,0.874)	0.027	0.124 (0.040,0.384)	0.000	III–IV	3.353 (2.247,5.004)	0.000	5.759 (3.755,8.832)	0.000
Liver					Liver				
Yes	Reference		—	—	Yes	Reference		Reference	
No	0.416 (0.189,0.915)	0.029	—	—	No	0.461(0.28,0.761)	0.002	0.512 (0.304,0.863)	0.012
ER					Lung				
Positive	Reference		Reference		Yes	Reference		Reference	
Negative	3.412 (2.088,5.574)	0.000	4.032 (2.142,7.592)	0.000	No	0.500 (0.324,0.771)	0.002	0.502 (0.319,0.790)	0.003
HER2					ER				
Positive	Reference		—	—	Positive	Reference		Reference	
Negative	0.332 (0.115,0.959)	0.042	—	—	Negative	2.208 (1.471,3.314)	0.000	2.318 (1.419,3.785)	0.001
Surgery					PR				
Yes	Reference		Reference		Positive	Reference		Reference	
No	3.409 (1.915,6.067)	0.000	3.748 (2.038,6.893)	0.000	Negative	1.631 (1.104,2.410)	0.014	1.765 (1.083,2.874)	0.022
Chemotherapy					Surgery				
Yes	—	—	Reference		Yes	Reference		Reference	
No	—	—	2.172 (1.191,3.960)	0.011	No	2.810 (1.996,3.955)	0.000	3.744 (2.458,5.703)	0.000
ICDO				0.006	Chemotherapy				
Neuroendocrine tumor, well-differentiated	—	—	Reference		Yes	Reference		Reference	
Small cell carcinoma	—	—	0.795 (0.374,1.691)	0.551	No	2.433 (1.766,3.351)	0.000	1.668 (1.131,2.461)	0.010
Large cell neuroendocrine carcinoma	—	—	1.304 (0.495,3.436)	0.591					
Carcinoma with neuroendocrine differentiation	—	—	4.36 (1.505,12.628)	0.007					

CI: confidence interval, HER2: human epidermal growth factor receptor-2, HR: hazard ratio, ICDO: International Classification of Disease for Oncology, OR: odds ratio.

was defined as the time from the date of diagnosis to the date of death due to breast cancer. The OS was defined as the time from the date of diagnosis to death from any cause. The survival prognoses of the different groups were analyzed using Kaplan–Meier plots and log–rank tests. Patients with breast NEC and IDC after PSM were randomly divided into training and validation cohorts at a ratio of 3:1. Univariate and multivariate Cox analyses were used to identify independent prognostic risk factors. All independent risk factors were included in the nomogram. Internal validation was performed on the training set, and external validation was performed on the validation set to evaluate the accuracy of the nomograms. The concordance index (C–index) was used to measure the model discrimination. Based on nomograms, breast NEC was classified into low-, intermediate-, and high-risk groups to predict prognosis.

Analyses were conducted using SPSS statistical software (version 22.0; IBM Corp., Armonk, NY, USA) and packages (including rms, hmisc, and survival) in R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). The X-tile software was used to select the threshold for risk stratification. A two-tailed $P < 0.05$ was considered statistically significant.

Results

The incidence and patient characteristics in breast NEC

From 2010 to 2018, the annual incidence of breast NEC was approximately 1.96–2.37% of the total breast cancer in the SEER database. After excluding patients with unknown factors, 378 were diagnosed with breast NEC. According to the WHO, the NEC group can be divided into four subgroups: neuroendocrine tumor with well-differentiated, small cell carcinoma, large cell neuroendocrine carcinoma, and carcinoma with neuroendocrine differentiation) There were significant differences in clinicopathological factors among the four subgroups (Table 1). Patients diagnosed with small cell carcinoma usually had higher rates of lymph node metastasis (46.6%), higher stage (41.6%), more lung metastasis (10%), and higher rates of hormone receptors (HR)–/ human epidermal growth factor receptor 2 (HER2)– (55%), whereas other patients in the NEC group usually had lower rates

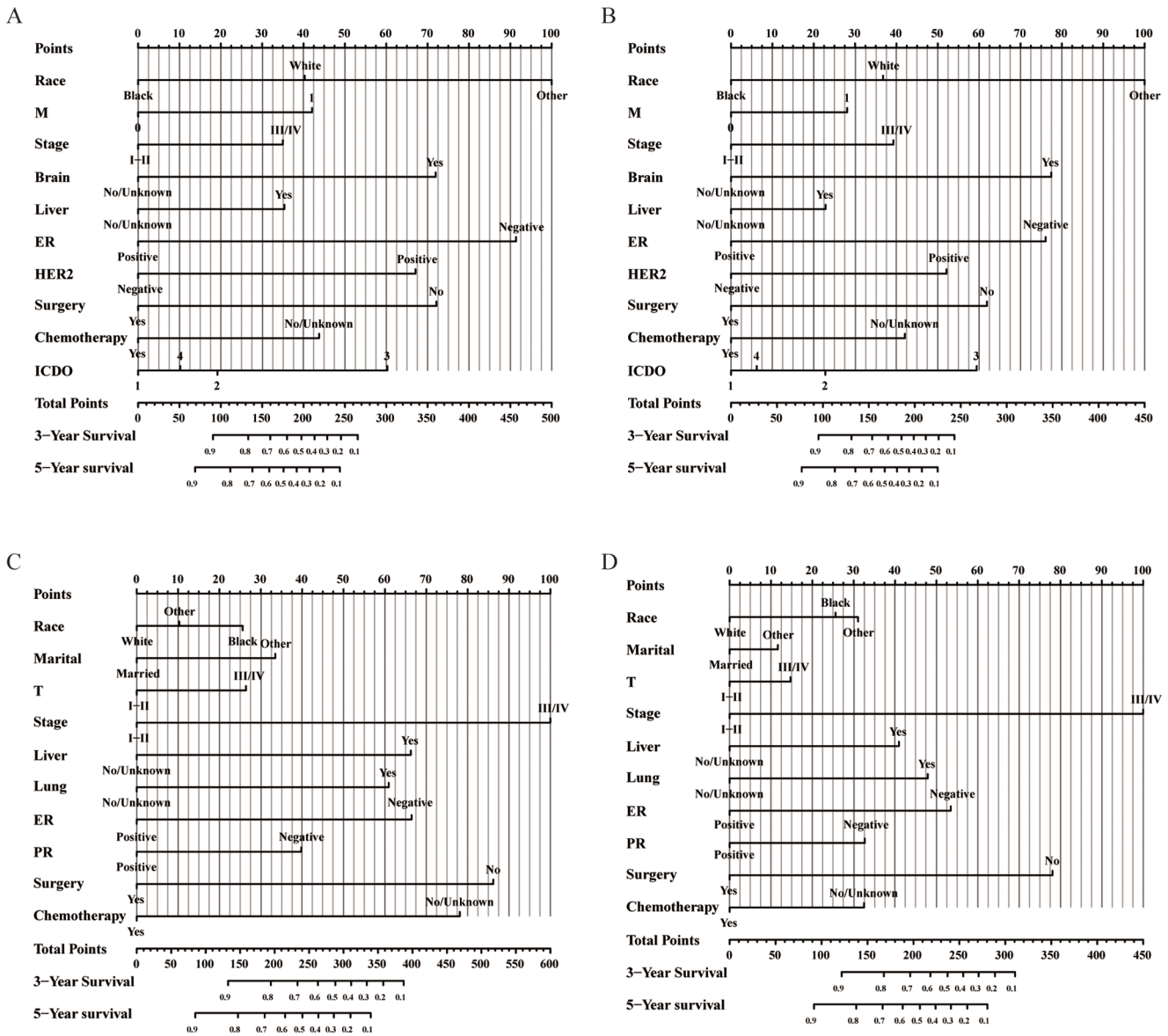

Fig. 2. Nomograms for predicting 3- and 5-year (A) overall survival (OS) and (B) breast cancer-specific survival (BCSS) in patients diagnosed with breast neuroendocrine carcinoma. Nomograms for predicting 3– and 5–year (C) OS and (D) BCSS in patients diagnosed with breast invasive ductal carcinoma after PSM.

of HR–/HER2– (10.5–24.8%).

Clinicopathologic features among breast NEC and breast IDC

Data from 378 patients with breast NEC and 349,736 patients with breast IDC were collected from the SEER database between 2010 and 2018 in this study. The clinicopathological differences in patients diagnosed with breast NEC and IDC are shown in Table 2. Patients diagnosed with breast NEC had a higher stage, larger tumor size, more metastases, and a lower rate of HER2+ (all $P < 0.05$). The mean breast NEC size was 26 mm, whereas the mean breast IDC size was 14 mm. Fewer patients diagnosed with breast NEC underwent surgery (82.1% vs. 94.1%) than those with breast IDC. Compared with patients who were diagnosed with breast IDC, those with breast NEC were more likely to choose chemotherapy (48.6% vs. 42.3%) and less likely to receive radiotherapy (44.4% vs. 54.2%).

Survival analyses

A total of 327 patients with breast NEC and 1280 patients with breast IDC were included after PSM. There was no significant difference in the clinical baseline between the breast NEC and IDC groups after PSM (Table 2). The median follow-up time was 25 months in the breast NEC group (interquartile range [IQR], 10–51 months) and 37.5 months in the breast IDC group (interquartile range [IQR], 15–66 months) after PSM.

Patients diagnosed with breast NEC had worse OS (hazard ratio [HR] = 2.955, 95% confidence interval [CI] 2.114–4.132, $P < 0.001$) and BCSS (HR = 4.293, 95% CI 2.743–6.720, $P < 0.001$) than those diagnosed with breast IDC before PSM (Fig. 1A and B). The 60-month OS rates in the breast NEC and breast IDC groups were 65.9% and 84.4%, respectively, while the 60-month BCSS rates were 71.6% and 90.9%, respectively. Patients diagnosed with breast NEC still showed poorer clinical outcomes (OS, HR = 1.656, 95% CI 1.261–2.175, $P = 0.002$; BCSS, HR = 1.988, 95% CI 1.440–2.744, $P = 0.001$) than patients diagnosed with breast IDC after PSM (Fig. 1C and D). The 60-month OS rates in breast NEC and IDC were 64.8% and 74.2%, respectively, after PSM. The 60-month BCSS rates in breast NEC and IDC were 70.6% and 81.6%, respectively, after PSM.

Table 4
Clinical variable scores in each nomogram.

	NEC			IDC	
	OS	BCSS		OS	BCSS
Race			Race		
White	40	37	White	0	0
Black	0	0	Black	26	26
Other	100	100	Other	10	31
M			Marital		
0	0	0	Married	0	0
1	42	28	Other	33	12
Stage			T		
I–II	0	0	I–II	0	0
III–IV	35	39	III–IV	26	15
Brain			Stage		
Yes	72	77	I–II	0	0
No	0	0	III–IV	100	100
Liver			Liver		
Yes	35	23	Yes	66	41
No	0	0	No	0	0
ER			Lung		
Positive	0	0	Yes	61	48
Negative	92	76	No	0	0
HER2			ER		
Positive	72	52	Positive	0	0
Negative	0	0	Negative	67	53
Surgery			PR		
Yes	0	0	Positive	0	0
No	72	62	Negative	40	33
Chemotherapy			Surgery		
Yes	0	0	Yes	0	0
No	44	42	No	86	78
ICDO			Chemotherapy		
Neuroendocrine tumor, well-differentiated	0	0	Yes	0	0
Small cell carcinoma	19	23	No	78	33
Large cell neuroendocrine carcinoma	60	60			
Carcinoma with neuroendocrine differentiation	10	6			

BCSS: breast cancer-specific survival, HER2: human epidermal growth factor receptor-2, ICDO: International Classification of Disease for Oncology, IDC: invasive ductal carcinoma, NEC: neuroendocrine carcinoma, OS: overall survival.

Prognostic factors

After PSM, the patients were randomly divided into training and validation groups (3:1). Multivariate COX was used to explore the prognostic risk factors (Table 3). In the breast NEC group, M stage, brain metastases, liver metastases, estrogen receptor (ER) status, human epidermal growth factor receptor-2 (HER2) status, and surgery were prognostic risk factors for OS, whereas race, stage, brain metastases, ER status, surgery, chemotherapy, and International Classification of Disease for Oncology (ICDO) were prognostic risk factors for BCSS. In the breast IDC group with pathological factors similar to those in the breast NEC group, race, marital status, T status, stage, liver metastases, lung metastases, ER status, progesterone receptor (PR) status, surgery, and chemotherapy were prognostic risk factors for OS. Race, stage, liver metastases, lung metastases, ER status, PR status, surgery, and chemotherapy were prognostic risk factors for BCSS.

Construction of nomograms and validation

According to the results of the multivariate Cox analysis (Table 3), 10 variables were incorporated into nomograms to predict the 3-and 5-year OS and BCSS for patients who were diagnosed with breast NEC (Fig. 2A and B). In addition, 10 variables were incorporated into nomograms to predict the 3-and 5-year OS and BCSS for patients who were diagnosed with breast IDC (Fig. 2C and D). Scores were assigned to each variable according to the point scale of each nomogram (Table 4). By evaluating the clinical factors of the patients, the sum of the scores could predict the 3- or 5-year OS and BCSS.

The credibility of the nomograms was judged through internal and external verifications of the training and verification sets. The C–index of the four nomograms ranged from 0.834 to 0.880 in the internal validation and from 0.818 to 0.876 in the external validation (Supplementary Table 1). Calibration curves for the 3-and 5-year OS and BCSS predictions showed good coordination between the predictions of the model and the observed outcomes (Fig. 3). Both internal and external validations demonstrated sufficient accuracy of the models.

Prognosis in risk stratification group

To better study the prognosis of breast NEC and IDC patients with similar clinicopathological factors, a risk classification was constructed using nomograms. After PSM, 327 patients diagnosed with breast NEC and 1280 patients diagnosed with breast IDC were divided into different risk stratification groups based on nomogram scores (Table 2). The score range in the risk stratification model was defined as low-risk (total score 0–154), intermediate-risk (total score 155–230), and high-risk (total score >230) in the NEC group. In the breast IDC group, the score range in the risk stratification model was defined as low-risk (total score 0–140), intermediate-risk (total score 141–315), and high-risk (total score >315). The prognoses of the three risk groups for breast NEC and breast IDC could be distinguished significantly by the model (Supplementary Fig. 1). As shown in the Kaplan–Meier plots (Fig. 4), there were no significant differences in OS (HR = 1.427, 95% CI 0.881–2.314, P = 0.104) and BCSS (HR = 1.387, 95% CI 0.827–2.326, P = 0.140) between patients diagnosed with breast NEC and breast IDC in the high-risk group. Patients diagnosed with breast NEC had worse prognoses than patients diagnosed with breast IDC in both the low- and intermediate-risk groups (all $P < 0.05$).

Choice of treatment

According to the nomograms, it was difficult to change the clinicopathological factors (race, M stage, T stage, stage, brain metastases, liver metastases, lung metastases, ER status, HER2 status, ICDO, and marital status). The only factors that can be modified by clinicians are surgery and chemotherapy. Clinicians usually treat patients diagnosed with breast NEC according to guidelines for breast IDC. According to the risk stratification, we found that the prognostic relationship of each group was as follows (Fig. 5): IDC low-risk > NEC low-risk > IDC intermediate-risk > NEC intermediate-risk > IDC high-risk ≈ NEC high-risk (>: $P < 0.05$, ≈:$P > 0.05$). Surgery or chemotherapy can be changed to change the risk group for patients diagnosed with breast NEC to obtain a better prognosis. After adjusting for pathological factors other than surgery and chemotherapy, we found that different treatment modalities could affect the outcomes in patients with breast NEC (Fig. 6). Patients diagnosed with breast NEC who underwent surgery and chemotherapy could have better OS than patients diagnosed with breast NEC who chose other treatments (Supplementary Table 2, all $P < 0.05$).

Discussion

Neuroendocrine carcinoma of the breast is a rare type of cancer. In recent years, the study with the largest number of NEC cases included 361 patients between 2003 and 2016, but it lacked data on the expression of HER2 [14]. Due to the small number of NEC cases and few available reports in the literature, clinicians have limited knowledge of breast NEC and may may misdiagnose as IDC. However, several studies have reported that the pathological features and prognosis of breast NEC and IDC are different. Large cell neuroendocrine carcinoma was added to neuroendocrine breast neoplasms in the 5th Edition of the World Health Organization (WHO) in 2019 [2]. Only seven cases of large-cell neuroendocrine carcinoma of the breast have been reported [15–21]. There are few recent reports on breast NEC including large sample sizes.

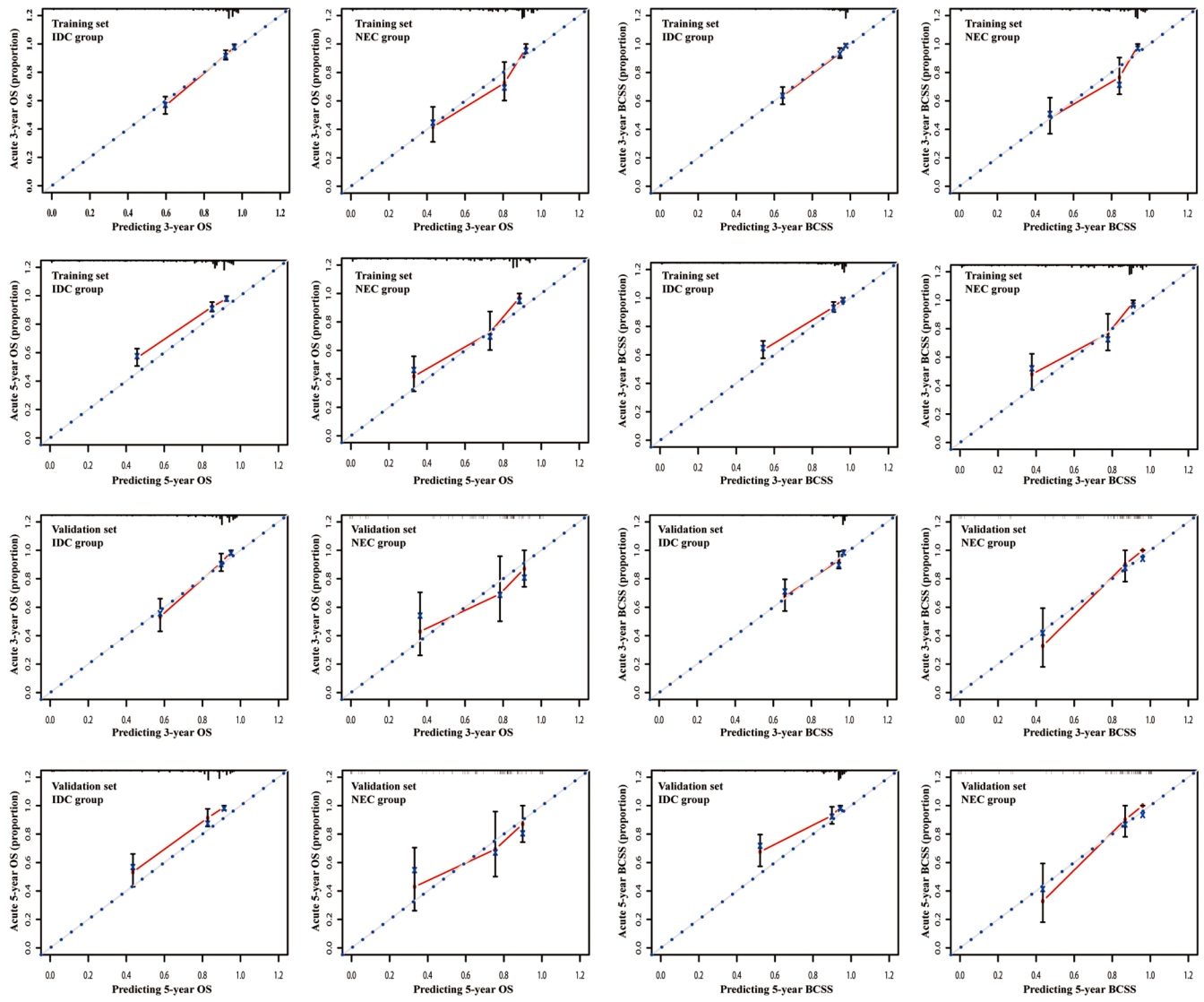

Fig. 3. Calibration curves for nomograms in the training set and validation set. The 45° blue dotted line represents the ideal reference, which means the nomogram-predicted survival probabilities (x-axis) exactly match the actual survival proportions (y-axis). Red dots represent nomogram-predicted probabilities for each group, and blue error bars represent the 95% confidence intervals of these estimates.

Also, large cell NEC has been newly added, which makes it necessary to re-study breast NEC. In this study, the clinicopathological features and outcomes between breast NEC and breast IDC, 378 patients with breast NEC and 349,736 cases with breast IDC were identified from the SEER database between 2010 and 2018 and described.

Compared with patients diagnosed with breast IDC, patients diagnosed with breast NEC had higher stages, larger tumor sizes, and more metastases in this study, which was consistent with previous research [22]. Here, the mean age of NEC patients was 63 years, which was consistent with previous studies which showed that most patients were postmenopausal [23–25]. Patients diagnosed with small cell carcinoma had higher rates of HR–/HER2– compared with the other subgroups (neuroendocrine tumor with well-differentiated, large cell neuroendocrine carcinoma, and carcinoma with neuroendocrine differentiation). Overall, patients with breast NEC had a higher HR+/HER2- ratio than patients with breast IDC, which was similar to previous findings [6,26, 27]. Patients with breast NEC and IDC had different treatment choices. Patients with breast NEC preferred chemotherapy to surgery, which may be related to the high stage of breast NEC.

Patients diagnosed with breast NEC showed poorer clinical outcomes than patients diagnosed with breast IDC both before. The poor prognosis of NEC may be due to its more aggressive clinicopathological factors, which is similar to the results of several studies [7–11]. A retrospective analysis including 43 NEC cases from Oulu and Helsinki University Hospitals in 2007–2015 reported that the relapse-free survival, disease-free survival, and OS of breast NEC were worse than those of breast IDC [7]. A retrospective analysis from China that studied 107 patients with breast NEC found that patients with breast NEC were more likely to have a local recurrence and poor OS [9]. A retrospective analysis that included 68 NEC patients from the University of Texas M. D. Anderson Cancer Center found that NEC showed a more aggressive course than IDC, with a higher propensity for local and distant recurrence, and poorer OS [9]. However, several studies have reported conflicting results. A study reported 12 cases of breast NEC, and none of them died from breast cancer after a median follow-up period of 51 months [3]. A retrospective analysis of 89 patients with breast NEC from 1985 to 2010 reported that breast NEC showed less aggressive clinical behavior [4]. A retrospective analysis that included 96 NEC patients from 1992 to 2013 found that the 10-year OS was 87% [5], which was significantly different from our study. In addition, a retrospective analysis that included 128 patients with breast cancer from Sacro Cuore Hospital between 2000 and 2012 reported that the outcome of breast

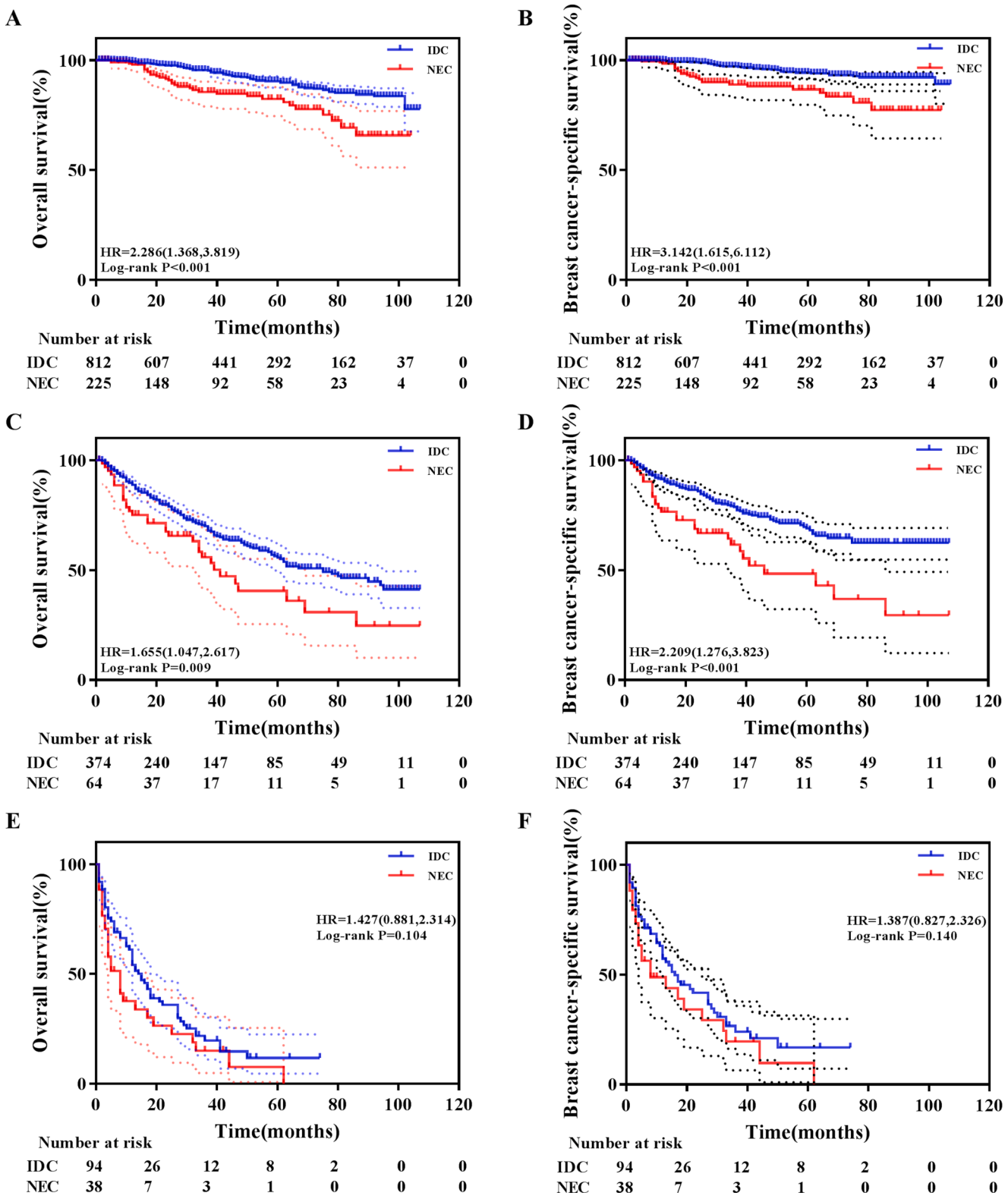

Fig. 4. The prognosis of patients in the risk stratification groups. (A) breast cancer-specific survival (BCSS) in the low-risk group. (B) BCSS in the intermediate-risk group. (C) BCSS in the high-risk group. (D) overall survival (OS) in the low-risk group. (E) OS in the intermediate-risk group. (F) OS in the high-risk group.

NEC was similar to that of IDC. The prognosis of breast NEC remains controversial according to several studies, which may be due to small sample sizes and inconsistent clinical factors in the population included in analyses. Several patient and clinical factors (including age, grade, tumor size, stage, chemotherapy, surgery, and Ki-67) and social factors (medical level and economic situation) would affect the prognosis of breast NEC [13].

Moreover, current guidelines do not clearly stipulate the treatment of patients with breast NEC. Clinicians may treat breast NEC based on their experience, which may lead to different treatment methods for patients

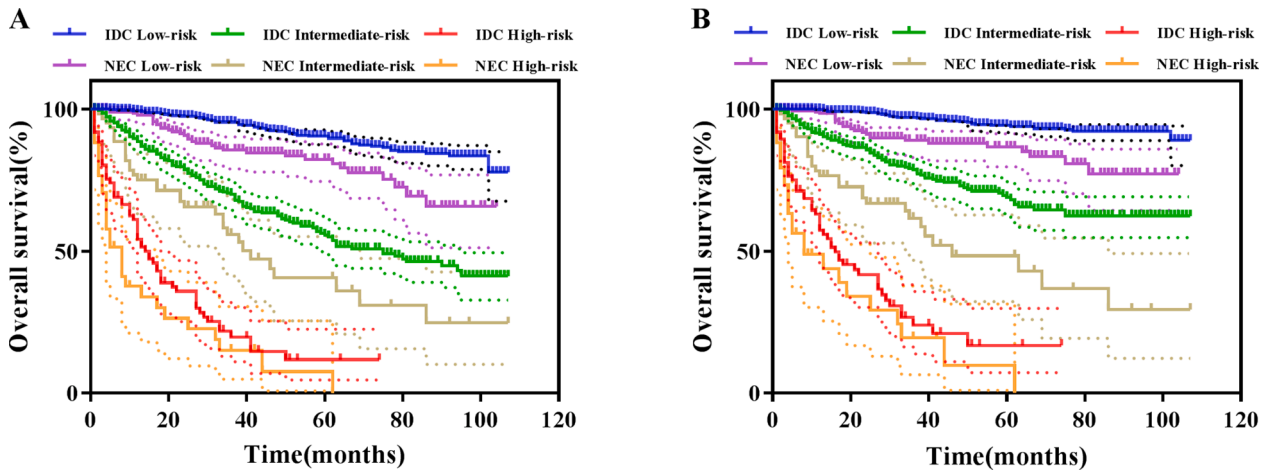

Fig. 5. (A). Overall survival and (B) breast cancer-specific survival of patients in the different groups.

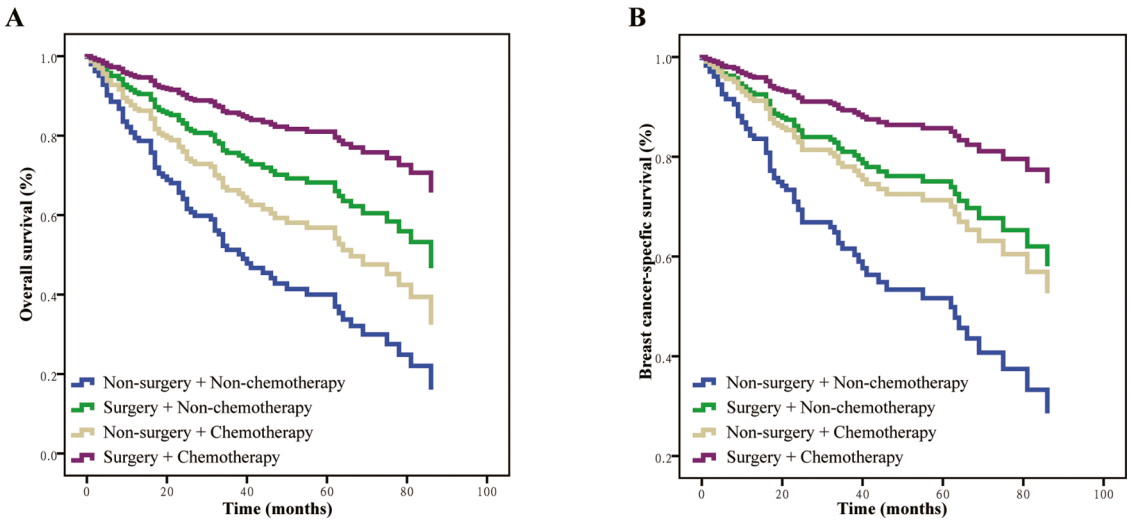

Fig. 6. (A). Overall survival and (B) breast cancer-specific survival of patients diagnosed with breast neuroendocrine carcinoma who underwent different treatments after adjusting for all the pathological factors other than surgery and chemotherapy.

with breast NEC in different regions. The suitable treatment for breast NEC is currently controversial, and clinicians usually refer to treatment plans for breast IDC to treat breast NEC according to age, subtype, stage, and 21 genes [26,28]. In this study, we constructed high-quality nomograms to predict the prognosis of patients diagnosed with breast NEC. In addition, we constructed nomograms for patients diagnosed with breast IDC who had similar clinicopathological factors to breast NEC to predict whether it was suitable for clinicians to treat breast NEC, similar to breast IDC. We divided the patients into low-, intermediate-, and high-risk groups based on the total score. The only factors that could have been changed were surgery and chemotherapy. For example, in a female patient who was white, T4N0M1, lung metastases, unmarried, ER+, PR+, HER2–, neuroendocrine tumor with well-differentiated, clinicians may not be able to administer chemotherapy according to the treatment for breast IDC. The score of this patient in the breast IDC group was 298 (intermediate-risk), and 189 in breast NEC (intermediate-risk). The prognosis of patients diagnosed with breast NEC was worse than that of patients diagnosed with breast IDC, even if they had the same clinicopathological factors. If we chose chemotherapy and surgery, the score of the patient was 117 (low-risk), which may be better than simply treating them as breast IDC. In this study, we found that patients with NEC who received surgery and chemotherapy had better outcomes than those who received surgery or chemotherapy alone.

This study had several limitations that may have influenced the results. Although the annual incidence of breast NEC was approximately 1.96–2.37% of the total breast cancer cases in the SEER database, most of these patients lacked key information such as TNM stage, molecular type, and treatment options. Our study included only 327 patients with complete information, which may have affected our results. Ki-67 could influence the clinical outcome and is an important clinicopathological feature for clinicians to choose suitable treatment [26], which was not recorded in the SEER database. The recurrence-free survival rate is important for evaluating tumor invasiveness. However, due to the lack of recurrence information in the SEER database, our study did not analyze the recurrence-free survival rate. The SEER database also lacks information on endocrine therapy and specific chemotherapy regimens. According to the literature, small cell carcinoma is treated using the same chemotherapy regimen as small cell lung carcinomas, which are similar in terms of clinical, histological, and morphological features. However, this is different from the chemotherapy regimen used in non-small cell carcinomas [26]. The existence of these shortcomings may lead to limitations in the research results, highlighting the need for high-quality prospective studies.

Conclusion

Patients with breast NEC have a worse prognosis than patients with breast IDC. Nomograms were constructed to predict the 3- and 5-year OS and BCSS in patients with breast NEC, which had a good predictive performance. This could help clinicians evaluate the prognosis of patients and choose appropriate treatment methods. Patients diagnosed with breast NEC who undergo surgery and chemotherapy may have a better prognosis than those who undergo surgery or chemotherapy alone.

CRediT authorship contribution statement

Yu-Qiu Chen: Visualization. **Xiao-Fan Xu:** Conceptualization, Visualization. **Jia-Wei Xu:** Formal analysis, Data curation, Writing – original draft. **Tian-Yu Di:** Formal analysis, Data curation, Writing – original draft. **Xu-Lin Wang:** Conceptualization, Formal analysis, Data curation, Writing – original draft. **Li-Qun Huo:** Formal analysis, Data curation, Writing – original draft. **Lu Wang:** Writing – review & editing. **Jun Gu:** Writing – review & editing. **Guo-hua Zhou:** Writing – review & editing.

Declaration of Competing Interest

None.

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Availability of data and materials

Please contact the author for data requests.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2022.101467.

References

[1] D.B. Xiang, B. Wei, S.C. Abraham, et al., Molecular cytogenetic characterization of mammary neuroendocrine carcinoma, Hum. Pathol. 45 (9) (2014) 1951–1956.
[2] WHO Classification of Tumors Editorial Board, Breast Tumours, 5th ed., WHO Classification of Tumors, 2019 [M/OL].
[3] E. Lopez-Bonet, M. Alonso-Ruano, G. Barraza, et al., Solid neuroendocrine breast carcinomas: incidence, clinico-pathological features and immunohistochemical profiling, Oncol. Rep. 20 (6) (2008) 1369–1374.
[4] L. Righi, A. Sapino, C. Marchio, et al., Neuroendocrine differentiation in breast cancer: established facts and unresolved problems, Semin. Diagn. Pathol. 27 (1) (2010) 69–76.
[5] F. Rovera, M. Lavazza, S. La Rosa, et al., Neuroendocrine breast cancer: retrospective analysis of 96 patients and review of literature, Int. J. Surg. 11 (2013) S79–S83. Suppl 1.
[6] G. Bogina, E. Munari, M. Brunelli, et al., Neuroendocrine differentiation in breast carcinoma: clinicopathological features and outcome, Histopathology 68 (3) (2016) 422–432.
[7] N. Roininen, S. Takala, K.M. Haapasaari, et al., Primary neuroendocrine breast carcinomas are associated with poor local control despite favourable biological profile: a retrospective clinical study, BMC Cancer 17 (1) (2017) 72.
[8] Y. Zhang, Z. Chen, Y. Bao, et al., Invasive neuroendocrine carcinoma of the breast: a prognostic research of 107 Chinese patients, Neoplasma 60 (2) (2013) 215–222.
[9] B. Wei, T. Ding, Y. Xing, et al., Invasive neuroendocrine carcinoma of the breast: a distinctive subtype of aggressive mammary carcinoma, Cancer 116 (19) (2010) 4463–4473.
[10] J. Wang, B. Wei, C.T. Albarracin, et al., Invasive neuroendocrine carcinoma of the breast: a population-based study from the surveillance, epidemiology and end results (SEER) database, BMC Cancer 14 (2014) 147.
[11] S.Y. Kwon, Y.K. Bae, M.J. Gu, et al., Neuroendocrine differentiation correlates with hormone receptor expression and decreased survival in patients with invasive breast carcinoma, Histopathology 64 (5) (2014) 647–659.
[12] Z. Tian, B. Wei, F. Tang, et al., Prognostic significance of tumor grading and staging in mammary carcinomas with neuroendocrine differentiation, Hum. Pathol. 42 (8) (2011) 1169–1177.
[13] F. Pareja, T.M. D'alfonso, Neuroendocrine neoplasms of the breast: a review focused on the updated World Health Organization (WHO) 5th edition morphologic classification, Breast J. 26 (6) (2020) 1160–1167.
[14] L. Yang, M. Roy, H. Lin, et al., Validation of prognostic significance of the proposed uniform classification framework in neuroendocrine neoplasms of the breast, Breast Cancer Res. Treat. 186 (2) (2021) 403–415.
[15] F. Safini, Z. Bouchbika, Z. Bennani, et al., Primary large cell neuroendocrine carcinoma of the breast: a rare tumor in humans, Pan Afr. Med. J. 25 (2016) 205.
[16] N. Yoshimura, T. Sasada, S. Yonehara, Primary large-cell neuroendocrine carcinoma of the breast occurring in a pre-menopausal woman, Breast Care 10 (4) (2015) 281–283 (Basel).
[17] M. Janosky, J. Bian, S. Dhage, et al., Primary large cell neuroendocrine carcinoma of the breast, a case report with an unusual clinical course, Breast J. 21 (3) (2015) 303–307.
[18] N. Omachi, S. Shimizu, T. Kawaguchi, et al., A case of large-cell neuroendocrine carcinoma harboring an EML4-ALK rearrangement with resistance to the ALK inhibitor crizotinib, J. Thorac. Oncol. 9 (6) (2014) e40–e42.
[19] E. Psoma, O. Nikolaidou, T. Stavrogianni, et al., A rare case report of a primary large-cell neuroendocrine carcinoma of the breast with coexisting Paget disease, Clin. Imaging 36 (5) (2012) 599–601.
[20] K. Okoshi, T. Saiga, S. Hisamori, et al., A case of cytokeratin 20-positive large-cell neuroendocrine carcinoma of the breast, Breast Cancer 19 (4) (2012) 360–364.
[21] J.W. Kim, O.H. Woo, K.R. Cho, et al., Primary large cell neuroendocrine carcinoma of the breast: radiologic and pathologic findings, J. Korean Med. Sci. 23 (6) (2008) 1118–1120.
[22] Y.M. Park, Y. Wu, W. Wei, et al., Primary neuroendocrine carcinoma of the breast: clinical, imaging, and histologic features, AJR Am. J. Roentgenol. 203 (2) (2014) W221–W230.
[23] J.M. Cloyd, R.L. Yang, K.H. Allison, et al., Impact of histological subtype on long-term outcomes of neuroendocrine carcinoma of the breast, Breast Cancer Res. Treat. 148 (3) (2014) 637–644.
[24] C. Kelten Talu, C. Leblebici, T. Kilicaslan Ozturk, et al., Primary breast carcinomas with neuroendocrine features: Clinicopathological features and analysis of tumor growth patterns in 36 cases, Ann. Diagn. Pathol. 34 (2018) 122–130.
[25] M. Lavigne, E. Menet, J.C. Tille, et al., Comprehensive clinical and molecular analyses of neuroendocrine carcinomas of the breast, Mod. Pathol. 31 (1) (2018) 68–82.
[26] A. Abdelwahed, M. Ahmed, Rare epithelial breast cancer: surgery and adjuvant therapy, Transl. Cancer Res. 8 (2019) S479–S492. Suppl 5.
[27] T. Kawasaki, K. Mochizuki, H. Yamauchi, et al., High prevalence of neuroendocrine carcinoma in breast lesions detected by the clinical symptom of bloody nipple discharge, Breast 21 (5) (2012) 652–656.
[28] C. Richter-Ehrenstein, J. Arndt, A.C. Buckendahl, et al., Solid neuroendocrine carcinomas of the breast: metastases or primary tumors? Breast Cancer Res. Treat. 124 (2) (2010) 413–417.