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Outperforming Traditional Staging: A Novel Nomogram for HR-Positive Breast Cancer

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Background: Hormone receptor-positive breast cancer (HR-positive BC), the most prevalent subtype, typically has a favorable prognosis. However, treatment decision-making and survival prediction remain challenging due to the limitations of traditional staging systems like AJCC. Improved prognostic tools are needed to enhance individualized risk stratification.

Materials and Methods: Clinical information from the Surveillance, Epidemiology, and End Results (SEER) database and the First Affiliated Hospital of Nanchang University were analyzed to evaluate outcomes across HR-positive BC subtypes. Patients were divided into training and validation cohorts. A prognostic nomogram was developed using factors identified by univariate and multivariate Cox regression analyses and evaluated through C-index, Receiver Operating Characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

Results: The study included 156,378 patients (training) and 67,016 (validation) for breast cancer-specific survival (BCSS) and 165,047 (training) and 70,732 (validation) for overall survival (OS), along with 232 external validation cases. Multivariate Cox regression analysis revealed that the ER-positive/PR-negative (HR=2.317 (2.219–2.419)) and ER-negative/PR-positive (HR=3.498 (3.143–3.894)) subtypes had worse prognosis than ER-positive/PR-positive patients. The prognosis of ER-negative/PR-positive subtype (HR=1.511 (1.686–1.351)) was also worse than that of ER-positive/PR-negative subtype. A nomogram integrating age, race, tumor size, grade, histology, bone, brain, lung, and liver metastases, tumor stage, HER2, marital status, positive lymph node numbers, and radiation therapy. The nomogram had a good C-index values and area under curve values for predicting OS and BCSS in both the training and validation set. Moreover, the DCA revealed that the nomogram performed better than the AJCC (TNM) staging system in predicting the three- and five-year OS and BCSS in both the groups.

Conclusion: This study introduces and validates a novel prognostic nomogram for HR-positive BC, providing enhanced risk stratification, particularly in regions with limited access to comprehensive genetic testing. Further validation through multicenter clinical studies is recommended to confirm its clinical utility.

Keywords: breast cancer, hormone receptor, nomogram and prognosis

Introduction

In the recent years, the molecular subtyping of breast cancer (BC) has received extensive attention due to its close correlation with patient survival and therapy efficacy.[1] Estrogen receptor (ER), progesterone receptor (PR), Ki-67, and the human epidermal growth factor receptor 2 (HER2) have been recognized as effective prognostic biomarkers in BC tissues.[2] In clinical practice, BC patients are commonly classified into four subtypes: HR-positive/HER2-positive, HR-positive/HER2-negative, HR-negative/HER2-positive (HER2 overexpression), and HR-negative/HER2-negative (triple-negative BC).[3] Both ER and PR are the targets of endocrine therapy and therefore serve as predictors of its efficacy.[4] The HER2 gene is overexpressed in rapidly metastasizing tumors and associated with unfavorable prognosis.[5,6] It is well

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established that the status of ER, PR and HER2 genes determines the selection of endocrine therapy, trastuzumab/pertuzumab and systemic chemotherapy. Despite improved drug therapy, many BC patients had poor prognosis, largely due to distant metastasis.[7,8] About one-third of BC patients are estimated to have distant metastases. Bone (38.9%), lung (17.7%), liver (11.9%), and brain (2.5%) are the most common organs for BC colonization.[9] The 5-year survival rate was approximately 23% in patients with metastatic BC.[10] In newly diagnosed BC patients, ER and PR detection are clinically advised.[11] HR-positive BC has a lower aggressiveness and a better prognosis than HR-negative BC, which could be attributed to the benefits of endocrine therapy.[12]

The identification of molecular subtypes and recent advances in genomic research of BC have significantly enhanced our understanding of its biological behavior. The 8th edition of the AJCC Cancer Staging Manual has updated the prognostic staging for BC, incorporating biological factors such as ER, PR, HER2 status, tumor grade, and recurrence scores (Oncotype Dx) alongside traditional TNM anatomical staging to assess BC prognosis. These factors have strong predictive and prognostic value.[13–15] However, the AJCC staging system is complex, and in low- and middle-income regions, the lack of comprehensive genetic and biological testing has led most clinicians to favor the traditional AJCC(TNM) anatomical staging. Consequently, a simpler, more accessible staging system is urgently needed to assist clinicians in assessing treatment and prognosis. Despite substantial research efforts in this area,[15–18] large-scale simplified nomogram prognostic models for HR-positive BC patients across different stages remain rarely reported. Furthermore, although population-based screening has been emphasized during the past decade, individualized therapy remains the key approach for improving the overall prognosis of BC patients. This leaves a significant gap in clinical applicability, particularly for risk stratification and treatment decision-making in HR-positive patients. To this end, in this study, a novel prognostic nomogram was established for patients with HR-positive BC using the data from the Surveillance, Epidemiology, and End Results (SEER) database. It was further independently verified through the HR-positive BC cohort of the First Affiliated Hospital of Nanchang University.

Meanwhile, the performance of the nomogram in predicting the overall survival (OS) and specific survival of HR-positive breast cancer patients (BCSS) was compared with the existing AJCC (TNM) anatomical staging system. This study will not only provide clinicians with a novel approach to identify high-risk patients with HR-positive BC based on available clinical information but also further highlight the crucial role of precise prognostic prediction in the management of cancer patients.

Materials and Methods

Patients Data

The patient data including demographics, clinical pathology, therapy, and outcome were obtained from the SEER database (https://seer.cancer.gov/). The BC cases were extracted from SEER Research Plus Data, Nov 2019 Sub (2000–2017) data using SEER*Stat 8.3.9 (15318-Nov 2020). Since the SEER database began to incorporate HER2 status in newly diagnosed BC patients in 2010, therefore the BC patients from January 2010 to December 2015 were enrolled into the primary cohort of our investigation. The cohort consisted of 380,682 BC patients from the database. The exclusion criteria were defined as follows: 1. non-pathologically confirmed; 2. unknown or borderline ER and PR status; 3. unknown or borderline HER2 status; 4. HR-negative patients; 5. unavailable clinicopathological factors including tumor grade/size, positive lymph node numbers, and duration of follow-up. According to the SEER database's Collaborative Stage Data Collection System v02.05 manual, ER and PR positive cells exceeding 1% are considered positive. Additionally, data was further collected on HR-positive BC patients treated and pathologically diagnosed at the First Affiliated Hospital of Nanchang University between March 2016 and August 2018. The screening process is illustrated in Supplementary Figure S1.

Clinical Variables and Study Endpoints

The following demographic information was extracted: age at diagnosis, sex, marital status at diagnosis, and race. Clinical parameters included grade, primary site, laterality, positive nodes, histological type, radiotherapy, ER, PR, HER2 status, tumor stage, metastasis (bone, liver, lung, or brain), tumor size and TNM staging. The molecular subtypes were

ER-positive/PR-positive (n=191,777), ER-positive/PR-negative (n=29,086), and ER-negative/PR-positive (n=2531) in BCSS cohort. In the external validation cohort: ER-positive/PR-positive (n=191), ER-positive/PR-negative (n=37), and ER-negative/PR-positive (n=4). The patients were classified into age groups of under 30, 30–39, 40–49, 50–59, 60–69, 70–79, and over 80 years. The Grade subgroup was as follows: well-differentiated (level I), moderately differentiated (level II), poorly differentiated (level III), and undifferentiated (level IV).[13] Races were classified as Black, White, Chinese, and Others. Tumor size was classified as ≤1 cm, 1–2 cm, 2–3 cm, 3–4 cm, 4–5 cm, and >5 cm. Invasive ductal carcinoma (IDC), lobular carcinoma (LC), and other histological subtypes were included. HER2 status was classified as either negative or positive. The tumor stages were Distant, Localized, and Regional. Positive nodes were categorized as 0, 1–3, 4–9, or ≥10. The primary endpoints were the OS and the BCSS. The OS time is defined as the time from the date of diagnosis to the time of death attributed to any cause. BCSS is defined as the time from the date of diagnosis to the date of death from BC. The follow-up time for the cut-off date was December 1st 2023. The median follow-up time in the external independent validation cohort was 76.2 months. The most common adjuvant treatments in the external validation cohort were radiotherapy, chemotherapy and endocrine therapy.

Statistical Analysis

The demographic and clinical features of the patients among subgroups were analyzed by chi-square or Fisher's exact tests, as appropriate. BCSS was investigated using the Kaplan-Meier survival model, and intergroup differences were determined by Log rank tests. The hazard ratio (HR) and 95% confidence interval (CI) of OS and BCSS were calculated using univariate Cox proportional hazards regression analysis. If a factor was significant in the univariate analysis, it was then included in the multivariate analysis. The final prognostic model was constructed using the significant factors in the multivariate analysis. Time-dependent receiver operating characteristic (ROC) curves were utilized to assess the predictive accuracy of the model, with the areas under the curves (AUCs) serving as the criteria.[19] The discriminative ability was assessed using the consistency index (C-index) and its 95% confidence interval (95% CI). The calibration plots were created by comparison between the observed and predicted survival probabilities. Decision curve analysis (DCA), based on the difference between the expected benefits and expected losses associated with each treatment strategy and the proposed trial, was used to assess the quantitative net benefits under various threshold probabilities[20] and thus the model's clinical applicability.[21] All the statistical analyses were performed using SPSS 21 (IBM Corp., Armonk, NY, USA) and R 4.1.1 software. The "SURVIVAL" and "RMS" packages in R were used to create a nomogram for outcome prediction based on the multivariate model.

Results

Demographic and Pathological Characteristics

The data of 223,394 hR-positive BC patients were obtained from the SEER database in BCSS cohorts. The flow chart of patient enrollment was detailed in Figure 1. The external validation cohort included a total of 232 hR-positive breast cancer patients (Supplementary Figure S1). As shown in Table 1, the ER-positive/PR-positive, ER-positive/PR-negative and ER-negative/PR-positive subtype accounted for 85.85%, 13.02% and 1.13% of the whole cohort, respectively. In the external validation cohort, the three subtypes—ER-positive/PR-positive, ER-positive/PR-negative, and ER-negative/PR-positive—accounted for 82.32%, 15.95%, and 1.72%, respectively, as detailed in Supplementary Table S1. In terms of race, white patients accounted for 81.45%, 77.22% and 72.26% of the ER-positive/PR-positive, ER-positive/PR-negative and ER-negative/PR-positive patients, compared with black patients accounting for 8.45%, 12.66% and 17.82%, respectively. The most common subtype for male patients was the ER-positive/PR-positive subtype (0.84%). Majority of the tumors were histological confirmed at Grade I–II (76.67%) and aged over 40 (89.56%). Radiotherapy was commonly applied in the patients (55.35%). In the external independent validation cohort, 47.4% (n=110) of patients received radiotherapy. Furthermore, 83.19% of patients underwent adjuvant chemotherapy, with AC-T being the most commonly used regimen (n=79), endocrine therapy accounted for 58.62% (n=136) (Supplementary Table S2). We also found that when Ki-67 was divided into two groups based on a 20% cutoff, tumor grade and distant metastasis were significantly associated with Ki-67 expression (Supplementary Table S3). Additionally, Ki-67 >20% significantly

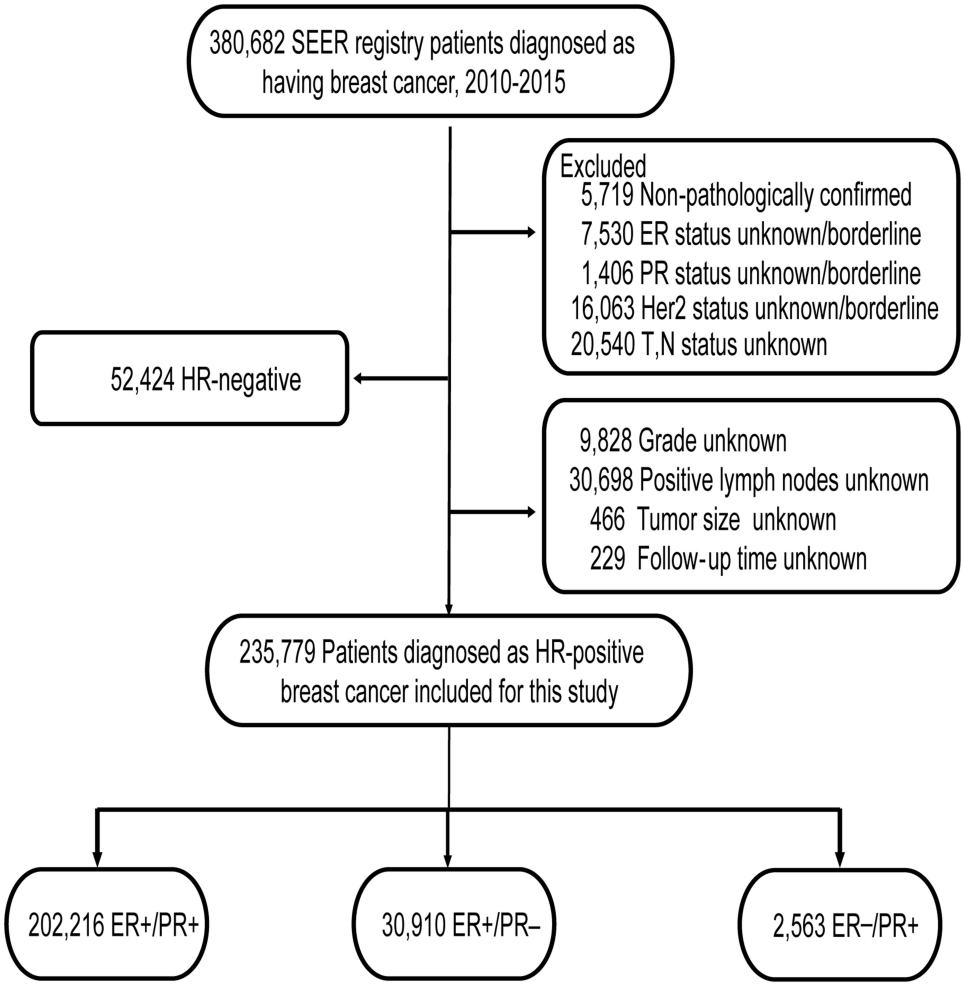

Figure 1 SEER cohort patient registration flow chart.

reduced survival in HR-positive patients ($P = 0.0164$) (Supplementary Figure S2). Patients with ER-negative/PR-positive subtype appeared to be younger, with the proportion of patients under 60 years old approaching 64.04%. Tumor sizes below 2 cm, N0, lymph node metastasis less than 3, M0, and localized stage were more common in the ER-positive/PR-positive subtype, while higher proportion of HER2-positive patients was observed in ER-negative/PR-positive subtype. IDC was more frequently found in the ER-negative/PR-positive patients, while lobular carcinoma was in the ER-positive

Table 1 Baseline demographic and clinical characteristics of HR-positive BCSS patients.

Characteristics (CSS)	All Patients (n%)	ER(+)/PR(+) (N=191,777)	ER(+)/PR(-) (N=29,086)	ER(-)/PR(+) (N=2531)	P-value
Race:					<0.001
Black	20,353(9.11)	16,210 (8.45%)	3692 (12.66%)	451 (17.82%)	
Chinese	3532(1.58)	2987 (1.56%)	505 (1.74%)	40 (1.58%)	
Other	19,031(8.52)	16,383 (8.54%)	2437 (8.38%)	211 (8.34%)	
White	18,0478(80.79)	156,197 (81.45%)	22,452 (77.22%)	1829 (72.26%)	
Sex:					<0.001
Female	221,667(99.23)	190,167 (99.16%)	28,972 (99.61%)	2528 (99.89%)	
Male	1727(0.77)	1610 (0.84%)	114 (0.39%)	3 (0.12%)	

(*Continued*)

Table 1 (Continued).

Characteristics (CSS)	All Patients (n%)	ER(+)/PR(+) (N=191,777)	ER(+)/PR(-) (N=29,086)	ER(-)/PR(+) (N=2531)	P-value
Grade:					<0.001
I	61,553(27.55)	56,461 (29.44%)	5043 (17.34%)	49 (1.94%)	
II	109,737(49.12)	97,320 (50.75%)	11,955 (41.10%)	462 (18.25%)	
III	51,738(23.16)	37,741 (19.70%)	11,990 (41.22%)	2007 (79.30%)	
IV	366(0.16)	255 (0.13%)	98 (0.34%)	13 (0.51%)	
RT:					<0.001
No	99,755(44.65)	84,567 (44.10%)	13,969 (48.03%)	1219 (48.16%)	
Yes	123,639(55.35)	107,210 (55.90%)	15,117 (51.97%)	1312 (51.84%)	
Age:					<0.001
<30	979(0.44)	784 (0.41%)	163 (0.56%)	32 (1.26%)	
≥79	13,814(6.18)	1,1647 (6.07%)	2051 (7.05%)	116 (4.58%)	
30–39	8534(3.82)	7114 (3.71%)	1215 (4.18%)	205 (8.10%)	
40–49	36,750(16.45)	32,956 (17.18%)	3236 (11.13%)	558 (22.05%)	
50–59	56,407(25.25)	47,623 (24.83%)	8074 (27.76%)	710 (28.05%)	
60–69	65,678(29.40)	56,166 (29.29%)	8934 (30.72%)	578 (22.84%)	
70–79	41,232(18.46)	35,487 (18.50%)	5413 (18.61%)	332 (13.12%)	
T:					<0.001
T1	145,531(65.15)	127,675 (66.57%)	16,671 (57.32%)	1185 (46.82%)	
T2	627,64(28.10)	52,048 (27.14%)	9655 (33.20%)	1061 (41.92%)	
T3	11,364(5.09)	9205 (4.80%)	1975 (6.79%)	184 (7.27%)	
T4	3735(1.66)	2849 (1.49%)	785 (2.70%)	101 (3.99%)	
N:					<0.001
N0	156,021(69.84)	134,692 (70.23%)	19,642 (67.53%)	1687 (66.65%)	
N1	49,857(22.32)	42,701 (22.27%)	6543 (22.50%)	613 (24.22%)	
N2	11,391(5.10)	9509 (4.96%)	1756 (6.04%)	126 (4.98%)	
N3	6125(2.74)	4875 (2.54%)	1145 (3.94%)	105 (4.15%)	
M:					<0.001
M0	220,452(98.68)	189,477 (98.80%)	28,497 (97.97%)	2478 (97.91%)	
M1	2942(1.32)	2300 (1.20%)	589 (2.03%)	53 (2.09%)	
Laterality:					0.0
Bilateral	15(0.01)	12 (0.01%)	3 (0.01%)	0 (0.00%)	
One side	223,379(99.99)	191,765 (99.99%)	29,083 (99.99%)	2531 (100%)	
Primary Site:					<0.001
Central	11,201(5.01)	9645 (5.03%)	1465 (5.04%)	91 (3.60%)	
Li	12,676(5.67)	10,864 (5.66%)	1664 (5.72%)	148 (5.85%)	
Lo	17,415(7.80)	14,899 (7.77%)	2326 (8.00%)	190 (7.51%)	
Other	77,160(34.54)	66,448 (34.65%)	9884 (33.98%)	828 (32.71%)	
Ui	28,718(12.86)	24,775 (12.92%)	3605 (12.39%)	338 (13.35%)	
Uo	76,224(34.12)	65,146 (33.97%)	10,142 (34.90%)	936 (36.98%)	
HER2:					<0.001
Negative	196,717(88.06)	172,627 (90.01%)	22,259 (76.53%)	1831 (72.34%)	
Positive	26,677(11.94)	19,150 (9.99%)	6827 (23.47%)	700 (27.64%)	
Nodes positive:					<0.001
0	157,472(70.49)	135,543 (70.68%)	20,161 (69.32%)	1768 (69.85%)	
≥10	5606(2.51)	4539 (2.37%)	978 (3.36%)	89 (3.52%)	
1–3	48,209(21.58)	41,515 (21.65%)	6153 (21.15%)	541 (21.37%)	
4–9	12,107(5.42)	10,180 (5.31%)	1794 (6.17%)	133 (5.25%)	

(*Continued*)

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Table 1 (Continued).

Characteristics (CSS)	All Patients (n%)	ER(+)/PR(+) (N=191,777)	ER(+)/PR(-) (N=29,086)	ER(-)/PR(+) (N=2531)	P-value
Tumor stage:					<0.001
Distant	3131(1.40)	2426 (1.27%)	645 (2.22%)	60 (2.37%)	
Localized	153,237(68.59)	132,438 (69.06%)	19,164 (65.89%)	1635 (64.60%)	
Regional	67,026(30.00)	56,913 (29.68%)	9277 (31.90%)	836 (33.03%)	
His:					<0.001
IDC	164,334(73.56)	140,273 (73.14%)	21,850 (75.12%)	2211 (87.36%)	
LC	23,801(10.65)	20,437 (10.66%)	3333 (11.46%)	31 (1.22%)	
Other	35,259(15.78)	31,067 (16.20%)	3903 (13.42%)	289 (11.42%)	
Tumor size cm:					<0.001
>5	12,888(5.77)	10,304 (5.37%)	2345 (8.06%)	239 (9.44%)	
<=1	62,588(28.02)	54,846 (28.60%)	7336 (25.22%)	406 (16.04%)	
1–2	83,417(37.34)	73,207 (38.17%)	9421 (32.39%)	789 (31.17%)	
2–3	41,363(18.52)	34,784 (18.14%)	5950 (20.46%)	629 (24.85%)	
3–4	15,549(6.96)	12,549 (6.54%)	2668 (9.17%)	332 (13.12%)	
4–5	7589(3.40)	6087 (3.17%)	1366 (4.70%)	136 (5.37%)	
Marital status:					<0.001
Married	129,191(57.83)	111,524 (58.15%)	16,222 (55.80%)	1445 (57.09%)	
Unmarried	94,203(42.17)	80,253 (41.85%)	12,864 (44.20%)	1086 (42.01%)	
Lung metastasis:					<0.001
No	222,839(99.75)	191,356 (99.78%)	28,972 (99.61%)	2511 (99.21%)	
Yes	555(0.25)	421 (0.22%)	114 (0.39%)	20 (0.79%)	
Liver metastasis:					<0.001
No	222,877(99.77)	191,403 (99.80%)	28,957 (99.56%)	2517 (99.45%)	
Yes	517(0.23)	374 (0.20%)	129 (0.44%)	14 (0.55%)	
Brain metastasis:					<0.001
No	223,315(99.96)	191,723 (99.97%)	29,062 (99.92%)	2530 (99.96%)	
Yes	79(0.04)	54 (0.03%)	24 (0.08%)	1 (0.04%)	
Bone metastasis:					<0.001
No	221,477(99.14)	190,228 (99.19%)	28,739 (98.81%)	2510 (99.17%)	
Yes	1917(0.86)	1549 (0.81%)	347 (1.19%)	21 (0.83%)	

/PR-positive and ER-negative/PR-positive patients. All the three subtypes are more common in married patients than unmarried patients. The overall comparison between the SEER cohort and the external independent validation cohort is presented in Supplementary Table S4. Survival analysis was then performed to compare the different subtypes in the entire BSCC cohort (Figure 2). The BCSS of ER-positive/PR-negative (HR=2.317, 95% CI: 2.219–2.419) and ER-negative/PR-positive (HR=3.498, 95% CI: 3.143–3.894) patients were significantly worse than that of ER-positive/PR-positive BC patients. Furthermore, we discovered that patients with ER-positive/PR-negative BC had a better BCSS than those with ER-negative/PR-positive BC (HR=1.511, 95% CI: 1.686–1.351). In the external independent validation cohort, it was also observed that ER-positive/PR-positive patients have a longer prognosis compared to ER-positive/PR-negative patients (Figure 3). In addition, the subgroup analysis showed the significant survival difference among the three subtypes in age (≤50 years, >50 years), tumor size (≤3cm, >3cm) (Supplementary Figure S3), grade (I–II, III–IV), number of positive lymph nodes (≤3, >3) (Supplementary Figure S4), race (Black, White, Chinese and Other) (Supplementary Figure S5), HER2 status (positive, negative) (Supplementary Figure S6), metastasis organ (liver, lung, bone and brain) (Supplementary Figure S7-8), radiotherapy (yes, no), marriage status (married, unmarried) (Supplementary Figure S9), pathological type (IDC, LC and Other), tumor stage (localized, regional and distant) (Supplementary Figure S10).

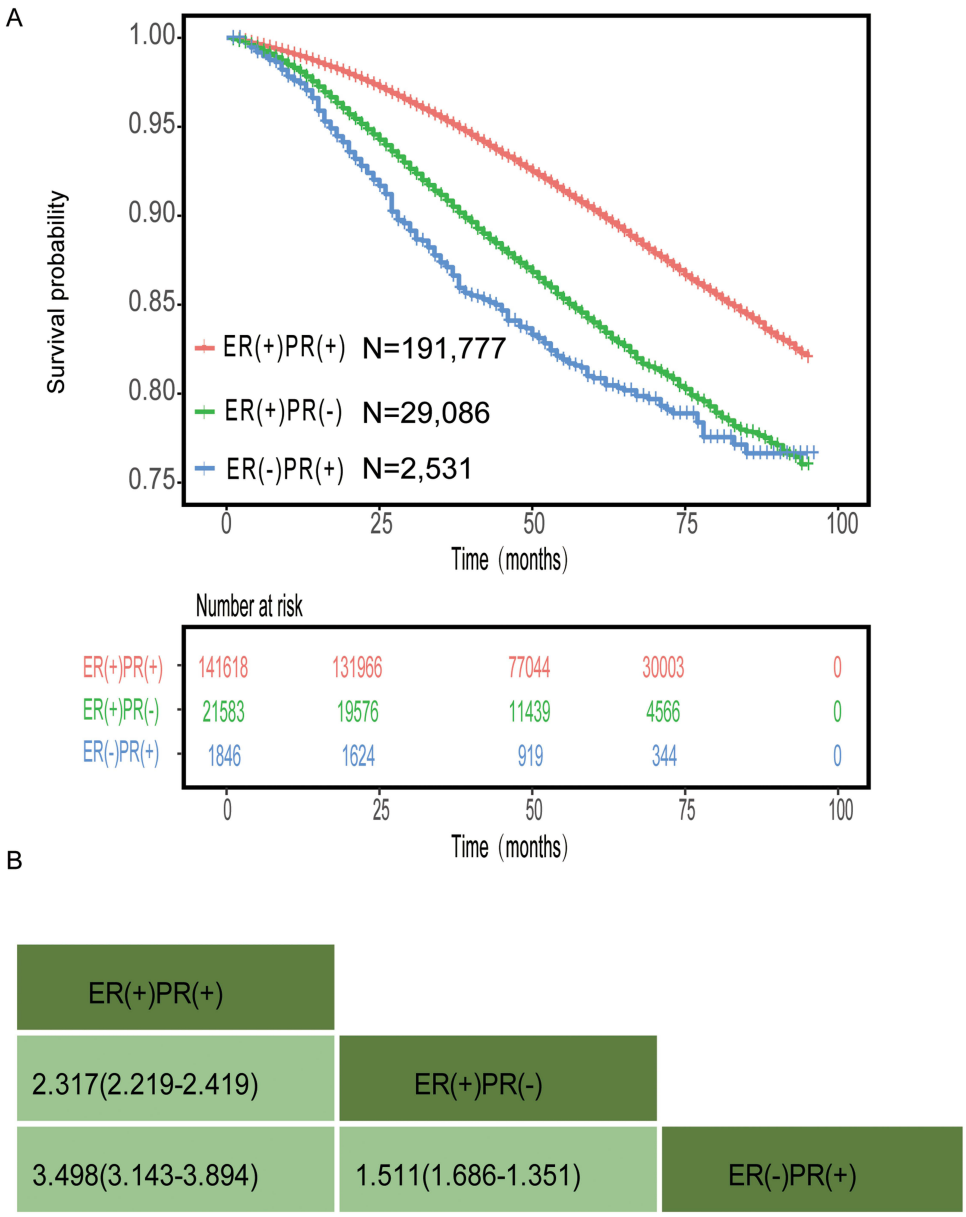

Figure 2 BCSS classified by hormone receptor status in patients with HR-positive breast cancer. (**A**) BCSS curves of patients with three HR-positive subtypes. (**B**) The information is given as hazard ratios (95% confidence intervals).
Abbreviations: HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor.

Construction and Validation of the Prognostic Nomogram

The patients were randomly allocated to the training and validation cohorts in a ratio of 7 to 3. During the follow-up period, 11,212 patients died from BC compared with 12,385 from other causes. The BCSS cohort included 223,394 patients (training set: n=156, 378, validation set: n=67,016) (Details in Table 1), while the OS cohort included 235,779 patients (training set: n=165,047, validation set: n=70,732) ((Supplementary Table S5)). Supplementary Table S6 shows the distribution of each subgroup of the HR-positive BC cohorts.

As shown in Table 2, both the univariate and multivariate analyses showed that the tumor laterality and position were unrelated to either OS or BCSS (all P >0.05). No significant difference was observed between gender and BCSS. The multivariate analysis suggested age, race, sex, marital status, grade, tumor size, lymph nodes, and metastases (bone, liver, lung, and brain, assessed individually) as independent prognostic factors affecting OS. BCSS was found to be independently affected by age, race, marital status, grade, tumor size, lymph nodes, metastases, histological type,

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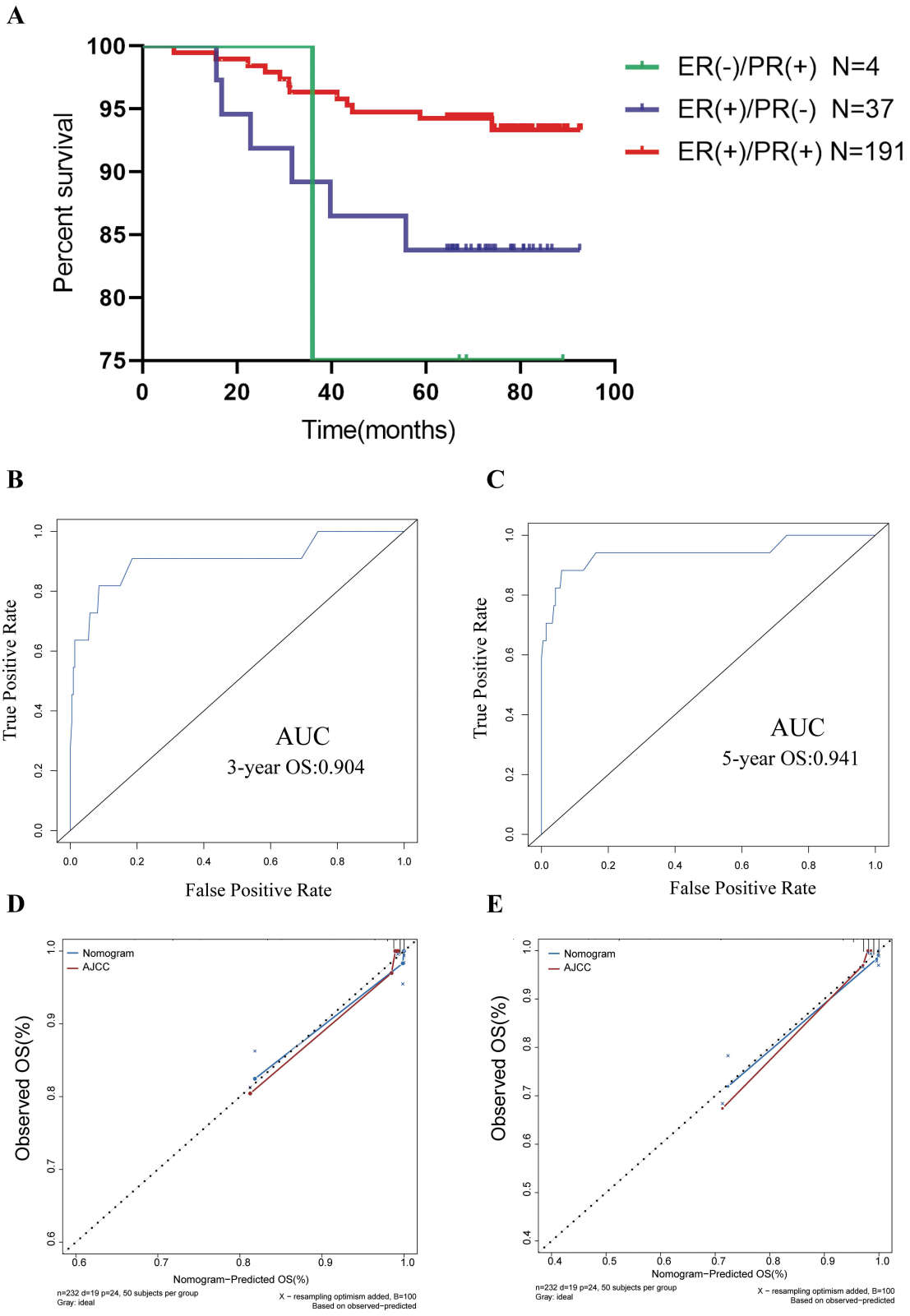

Figure 3 External independent cohort (The First Affiliated Hospital of Nanchang University) was used to validate the model. (**A**) Survival curves of three categories of HR-positive BC patients; (**B**) 3-year ROC curve for external validation cohort; (**C**) 5-year ROC curve for external validation cohort; Calibration plot of the 3- (**D**) and 5-year (**E**) HR-positive BC OS comparing the nomogram with AJCC(TNM) anatomical stage.

Table 2 Univariate and multivariate analysis of overall survival and cancer-specific survival in the training cohort.

Characteristic	OS				CSS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Grade:								
I	Reference		Reference		Reference		Reference	
II	1.37 (1.32–1.43)	<0.001	1.11 (1.07–1.16)	<0.001	2.36 (2.19–2.56)	<0.001	1.53 (1.41–1.66)	<0.001
III	2.24 (1.68–2.98)	<0.001	1.62 (1.22–2.16)	<0.001	5.05 (3.41–7.46)	<0.001	2.49 (1.68–3.68)	<0.001
IV	2.27 (2.17–2.37)	<0.001	1.66 (1.58–1.74)	<0.001	6.30 (5.83–6.80)	<0.001	3.14 (2.89–3.41)	<0.001
Marital status:								
Married	Reference		Reference		Reference		Reference	
Unmarried	1.95 (1.89–2.01)	<0.001	1.39 (1.34–1.43)	<0.001	1.68 (1.6–1.75)	<0.001	1.29 (1.23–1.35)	<0.001
Sex:								
Female	Reference		Reference		Reference		Reference	
Male	2.56 (2.3–2.86)	<0.001	1.52 (1.35–1.70)	<0.001	2.13 (1.79–2.54)	<0.001	1.18 (0.99–1.41)	0.072
Primary Site:								
central	Reference		Reference		Reference		Reference	
Li	0.66 (0.6–0.71)	<0.001	1.04 (0.95–1.14)	0.359	0.67 (0.59–0.75)	<0.001	1.23 (1.08–1.40)	0.001
Lo	0.66 (0.61–0.71)	<0.001	0.96 (0.89–1.05)	0.378	0.63 (0.56–0.71)	<0.001	0.99 (0.88–1.11)	0.826
Other	0.73 (0.69–0.78)	<0.001	0.99 (0.93–1.05)	0.652	0.79 (0.72–0.86)	<0.001	1.05 (0.96–1.15)	0.319
Ui	0.58 (0.54–0.62)	<0.001	0.99 (0.92–1.07)	0.872	0.54 (0.49–0.6)	<0.001	1.10 (0.98–1.22)	0.098
Uo	0.63 (0.59–0.67)	<0.001	0.98 (0.92–1.04	0.488	0.60 (0.55–0.66)	<0.001	0.98 (0.89–1.07)	0.609
Laterality:								
Bilateral	Reference		Reference		Reference		Reference	
One side	0.23 (0.09–0.60)	0.003	1.57 (0.59–4.22)	0.3664	0.16 (0.05–0.5)	0.001	1.85 (0.59–5.77)	0.292
Node positive:								
0	Reference		Reference		Reference		Reference	
≥10	0.18 (0.17–0.19)	<0.001	0.50 (0.45–0.55)	<0.001	0.07 (0.06–0.07)	<0.001	0.37 (0.33–0.42)	<0.001
1–3	0.30 (0.29–0.32)	<0.001	0.45 (0.42–0.48)	<0.001	0.21 (0.2–0.23)	<0.001	0.37 (0.34–0.40)	<0.001
4–9	0.57 (0.53–0.61)	<0.001	0.72 (0.67–0.77)	<0.001	0.54 (0.5–0.58)	<0.001	0.69 (0.64–0.75)	<0.001
His:								
IDC	Reference		Reference		Reference		Reference	
LC	1.15 (1.10–1.21)	<0.001	0.88 (0.84–0.92)	<0.001	1.15 (1.08–1.24)	<0.001	0.94 (0.88–1.01)	0.112
Other	1.00 (0.96–1.04)	0.967	0.93 (0.89–0.97)	<0.001	0.89 (0.83–0.95)	<0.001	0.89 (0.83–0.95)	<0.001
Race:								
Black	Reference		Reference		Reference		Reference	
Chinese	0.37 (0.32–0.45)	<0.001	0.50 (0.42–0.59)	<0.001	0.42 (0.34–0.52)	<0.001	0.61 (0.49–0.75)	<0.001
Other	0.44 (0.41–0.48)	<0.001	0.56 (0.52–0.61)	<0.001	0.43 (0.39–0.48)	<0.001	0.57 (0.51–0.63)	<0.001
White	0.69 (0.66–0.72)	<0.001	0.76 (0.72–0.80)	<0.001	0.55 (0.52–0.59)	<0.001	0.72 (0.68–0.77)	<0.001
RT:								
No	Reference		Reference		Reference		Reference	
Yes	0.59 (0.57–0.61)	<0.001	0.67 (0.65–0.69)	<0.001	0.67 (0.64–0.7)	<0.001	0.68 (0.65–0.71)	<0.001
Age:								
<30	Reference		Reference		Reference		Reference	
≥79	3.3 (2.63–4.13)	<0.001	5.18 (4.13–6.51)	<0.001	1.37 (1.07–1.74)	0.012	3.15 (2.46–4.03)	<0.001
30–39	0.73 (0.57–0.92)	0.009	0.87 (0.69–1.11)	0.276	0.77 (0.60–1.00)	0.046	0.97 (0.75–1.26)	0.832
40–49	0.42 (0.33–0.53)	<0.001	0.65 (0.51–0.82)	<0.001	0.40 (0.31–0.51)	<0.001	0.76 (0.60–0.98)	0.031
50–59	0.53 (0.42–0.67)	<0.001	0.88 (0.70–1.11)	0.279	0.43 (0.34–0.55)	<0.001	0.92 (0.72–1.17)	0.487
60–69	0.69 (0.55–0.87)	0.001	1.27 (1.01–1.60)	0.037	0.40 (0.31–0.50)	<0.001	1.00 (0.78–1.28)	0.987
70–79	1.3 (1.03–1.63)	0.025	2.39 (1.90–3.00)	<0.001	0.58 (0.46–0.75)	<0.001	1.60 (1.25–2.04)	<0.001
HER2:								
Negative	Reference		Reference		Reference		Reference	
Positive	1.07 (1.02–1.12)	0.004	1.07 (1.02–1.12)	<0.001	1.32 (1.24–1.41)	<0.001	0.77 (0.72–0.82)	<0.001

(*Continued*)

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Table 2 (Continued).

Characteristic	OS				CSS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Tumor stage:								
Distant	Reference		Reference		Reference		Reference	
Localized	0.1 (0.09–0.10)	<0.001	0.25 (0.22–0.29)	<0.001	0.03 (0.03–0.03)	<0.001	0.16 (0.14–0.19)	<0.001
Regional	0.21 (0.2–0.22)	<0.001	0.41 (0.37–0.46)	<0.001	0.15 (0.14–0.16)	<0.001	0.37 (0.33–0.42)	<0.001
Bone metastasis:								
No	Reference		Reference		Reference		Reference	
Yes	8.23 (7.65–8.85)	<0.001	1.31 (1.16–1.48)	<0.001	15.89 (14.7–17.18)	<0.001	1.45 (1.28–1.65)	<0.001
Brain metastasis:								
No	Reference		Reference		Reference		Reference	
Yes	19.07 (14.37–25.32)	<0.001	4.21 (3.15–5.62)	<0.001	43.45 (32.41–58.25)	<0.001	4.04 (2.99–5.46)	<0.001
Liver metastasis:								
No	Reference		Reference		Reference		Reference	
Yes	10.2 (8.95–11.62)	<0.001	1.79 (1.55–2.07)	<0.001	20.01 (17.5–22.88)	<0.001	1.65 (1.42–1.91)	<0.001
Lung metastasis:								
No	Reference		Reference		Reference		Reference	
Yes	9.38 (8.27–10.64)	<0.001	1.18 (1.02–1.36)	0.022	18.63 (16.32–21.26)	<0.001	1.28 (1.1–1.49)	<0.001
Tumor size cm:								
>5	Reference		Reference		Reference		Reference	
<=1	0.21 (0.19–0.22)	<0.001	0.42 (0.39–0.45)	<0.001	0.07 (0.06–0.07)	<0.001	0.27 (0.24–0.30)	<0.001
1–2	0.29 (0.28–0.31)	<0.001	0.51 (0.48–0.54)	<0.001	0.13 (0.12–0.14)	<0.001	0.37 (0.34–0.40)	<0.001
2–3	0.45 (0.43–0.47)	<0.001	0.62 (0.59–0.66)	<0.001	0.30 (0.28–0.32)	<0.001	0.54 (0.50–0.58)	<0.001
3–4	0.67 (0.63–0.71)	<0.001	0.81 (0.76–0.86)	<0.001	0.54 (0.50–0.58)	<0.001	0.74 (0.69–0.80)	<0.001
4–5	0.79 (0.74–0.85)	<0.001	0.91 (0.85–0.98)	0.016	0.68 (0.63–0.75)	<0.001	0.86 (0.79–0.94)	<0.001

radiation, and HER2 status. These independent factors were then selected to generate nomograms for predicting the three-year and five-year BCSS (Figure 4) and OS (Supplementary Figure S11).

In the training cohort, the C-index of the nomogram for predicting OS and BCSS was 0.780 (95% CI=0.784–0.776) and 0.836 (95% CI=0.832–0.840). In the validation cohort, the C-index for OS and BCSS was 0.779 (95% CI=0.773–0.785) and 0.830 (95% CI=0.822–0.837). As shown in Table 3, the C-index of the nomogram for OS and BCSS was significantly better than that of AJCC (TNM) anatomical staging in both the training and validation cohort. The ROC analysis was then performed to assess the predictive ability of the nomogram. The AUC values of ROC curves for 3- and 5-year BCSS in the training cohort were 0.798 and 0.780, compared with 0.792 and 0.765 in the validation cohort (Figure 5). With regard to OS, the AUC values of ROC curves for 3- and 5-year OS were 0.710 and 0.695 in the training cohort, compared with 0.708 and 0.691 in the validation cohort (Supplementary Figure S12). In the external independent validation cohort, the 3-year and 5-year ROC curves achieved AUC values of 0.904 and 0.941, respectively (Figure 3). The DCA of the three- and five-year BCSS (Figure 6) and OS (Supplementary Figure S13) showed that the nomogram performed better than AJCC(TNM) anatomical staging in both the cohorts. Moreover, the curves for predicting three- and five-year BCSS (Supplementary Figure S14) and OS (Supplementary Figure S15) in both the two cohorts are close to the standard curves, indicating the reliability of the nomogram. Furthermore, to investigate the applicability of the model in ER-positive and IDC patients, we validated it using 2531 ER-positive patients from the SEER database. The AUC values of ROC curves for 3- and 5-year OS were 0.810 and 0.798, respectively (Supplementary Figure S16). The C-index of the OS nomogram was significantly higher than that of the AJCC(TNM) anatomical staging system (0.792 (95% CI = 0.768–0.816) vs 0.742 (95% CI = 0.715–0.769)). In the external independent validation cohort of IDC patients, the AUC values of ROC curves for 3- and 5-year OS were 0.893 and

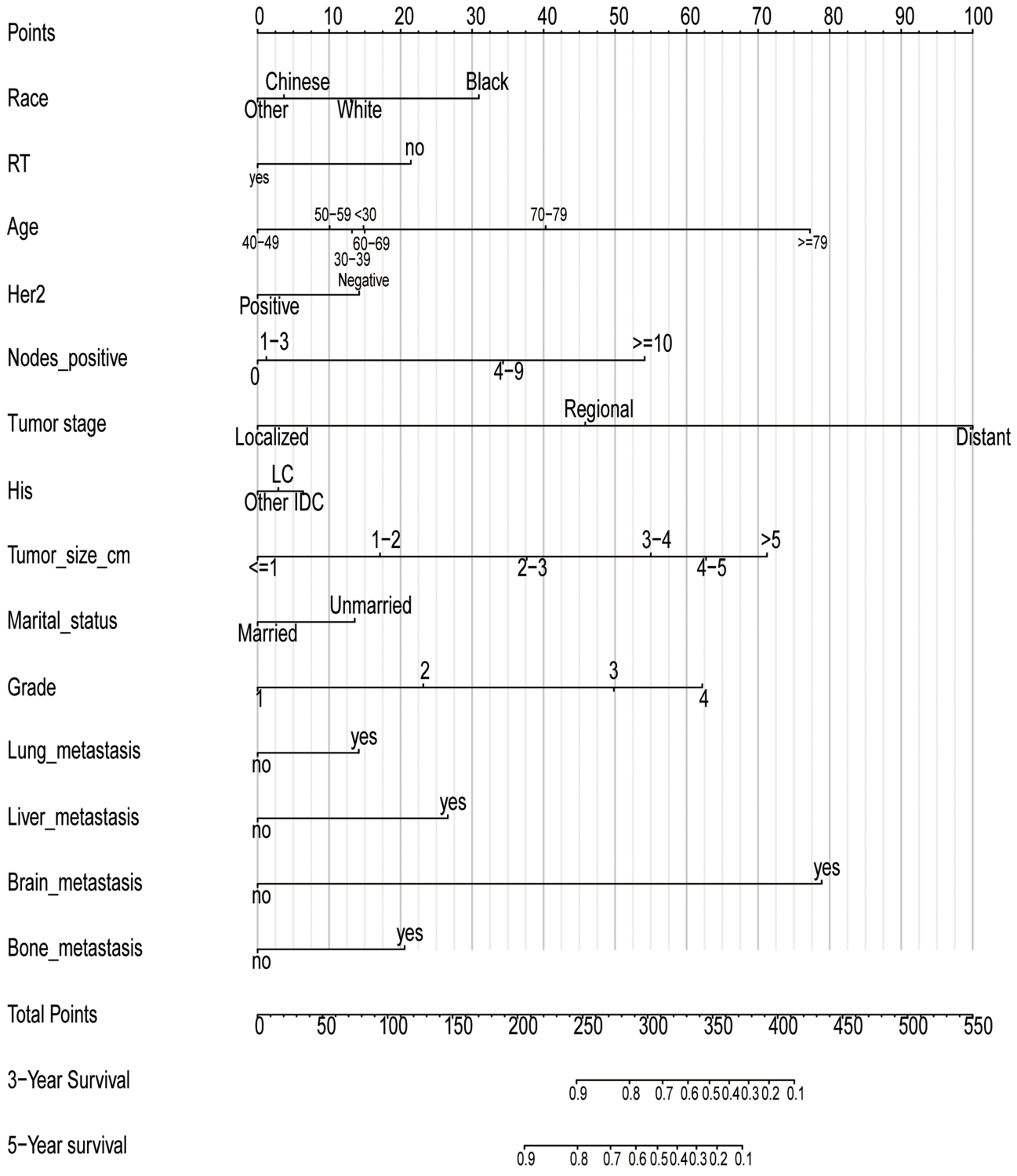

Figure 4 The nomogram containing various factors for the 3-, 5-year BCSS.
Abbreviations: RT, radiation therapy; HER2, human epidermal growth factor receptor 2; His, histology; IDC, invasive ductal carcinoma; LC, lobular carcinoma.

0.936, respectively (Supplementary Figure S17). The C-index of the OS nomogram demonstrated a significant improvement over the AJCC(TNM) anatomical staging system (0.956 (95% CI = 0.913–0.999) vs 0.887 (95% CI = 0.799–0.975)).

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Table 3 Comparison of the C-indexes between the nomogram and AJCC (TNM) anatomical staging in HR-positive patients.

Characteristics	Training Set			Validation Set		
	C-index	95% CI	P-value	C-index	95% CI	P-value
OS						
Nomogram	0.780	(0.784–0.776)	<0.001	0.779	(0.773–0.785)	<0.001
AJCC(TNM) stage	0.661	(0.665–0.657)	<0.001	0.657	(0.649–0.665)	<0.001
BCSS						
Nomogram	0.836	(0.832–0.840)	<0.001	0.830	(0.822–0.837)	<0.001
AJCC(TNM) stage	0.791	(0.791–0.779)	<0.001	0.776	(0.768–0.784)	<0.001

Discussion

Both ER and PR have been shown to be critical in evaluating heterogeneity and treatment efficacy in BC patients.[22] Inhibiting ER signaling is a cornerstone of ER-positive BC treatment, significantly improving patient survival.[23] PR, as a target gene of ER, also promotes tumor cell growth and metastasis, serving as an independent prognostic factor.[24,25] Studies have shown that ER-positive BC exhibits patient-specific hormone sensitivity and is dependent on PR expression.[25] Furthermore, race, ethnicity, and reproductive factors significantly influence the risk of different BC subtypes.[26] In addition, HER2 plays a crucial prognostic role in BC. In this study, we found that in HER2-negative patients, ER-positive PR-positive (partially Luminal A and partially Luminal B) patients had significantly better prognosis than ER-positive PR-negative (Luminal B) patients and better than patients with PR-positive alone, underscoring the relatively favorable prognosis of ER-positive patients. Simultaneously, the study by Li et al[27] found that compared with PR negativity, ER negativity raised the risk of BC-specific death by 18%, and of all-cause death by 7%. In HER2-positive patients, studies suggest that the prognosis of single ER-positive patients is similar to that of single PR-positive patients,[13,28] which is consistent with our findings. Therefore, we speculated that HER2 status can significantly influence the survival prognosis of HR single-positive patients.

Previous evidence has found that 90% of BC patients are newly diagnosed in the early stages, with more than 70% of them being HR-positive,[29,30] which is consistent with our findings. Although HR-positive BC patients have better OS, they often suffer from a range of physiological complications, psychological stress, and social functional impairments, significantly affecting their quality of life. Approximately 30% to 40% of early-stage breast cancer cases eventually progress to advanced stages, with a small subset developing distant metastases. Endocrine therapy is the cornerstone of treatment for HR-positive BC patients. However, genetic mutations in cancer cells can lead to endocrine resistance,[31] with about 20% of patients experiencing recurrence and/or distant metastasis within 10 years. Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), in combination with endocrine therapy, inhibit malignant proliferation of tumor cells and modulate the microenvironment to induce cell cycle arrest, thus transforming the clinical treatment paradigm for HR-positive/HER2-negative advanced BC.[32,33] Furthermore, the PARP inhibitors Olaparib[34] and Talazoparib[35] are recommended as alternative treatment strategies for metastatic BC with BRCA1/2 mutations. With the rapid advancement of immunotherapy, atezolizumab, a monoclonal antibody targeting programmed death-ligand 1 (PD-L1), is used in combination with albumin-bound paclitaxel to treat unresectable or metastatic triple-negative BC that expresses PD-L1.[36] The survival and therapy response of BC patients is influenced by multiple simultaneous factors. In order to predict clinical outcome precisely and therefore make individualized treatment, it is critical to integrate available clinical and pathological information to form novel evaluation systems for prognostic prediction. In this study, a novel prognostic was established and proved to be superior to traditional AJCC(TNM) anatomical staging in predicting BCSS and OS. Furthermore, we have noted that several nomograms have been utilized for outcome prediction in patients with HER2-positive,[13] different molecular types,[3,37] and male BC.[38] The latest 8th edition of the AJCC staging system incorporates a range of molecular and genetic information. However, to our knowledge, the AJCC staging system has certain

limitations in predicting the prognosis of specific patient subtypes.[15,39] Furthermore, few effective nomograms are

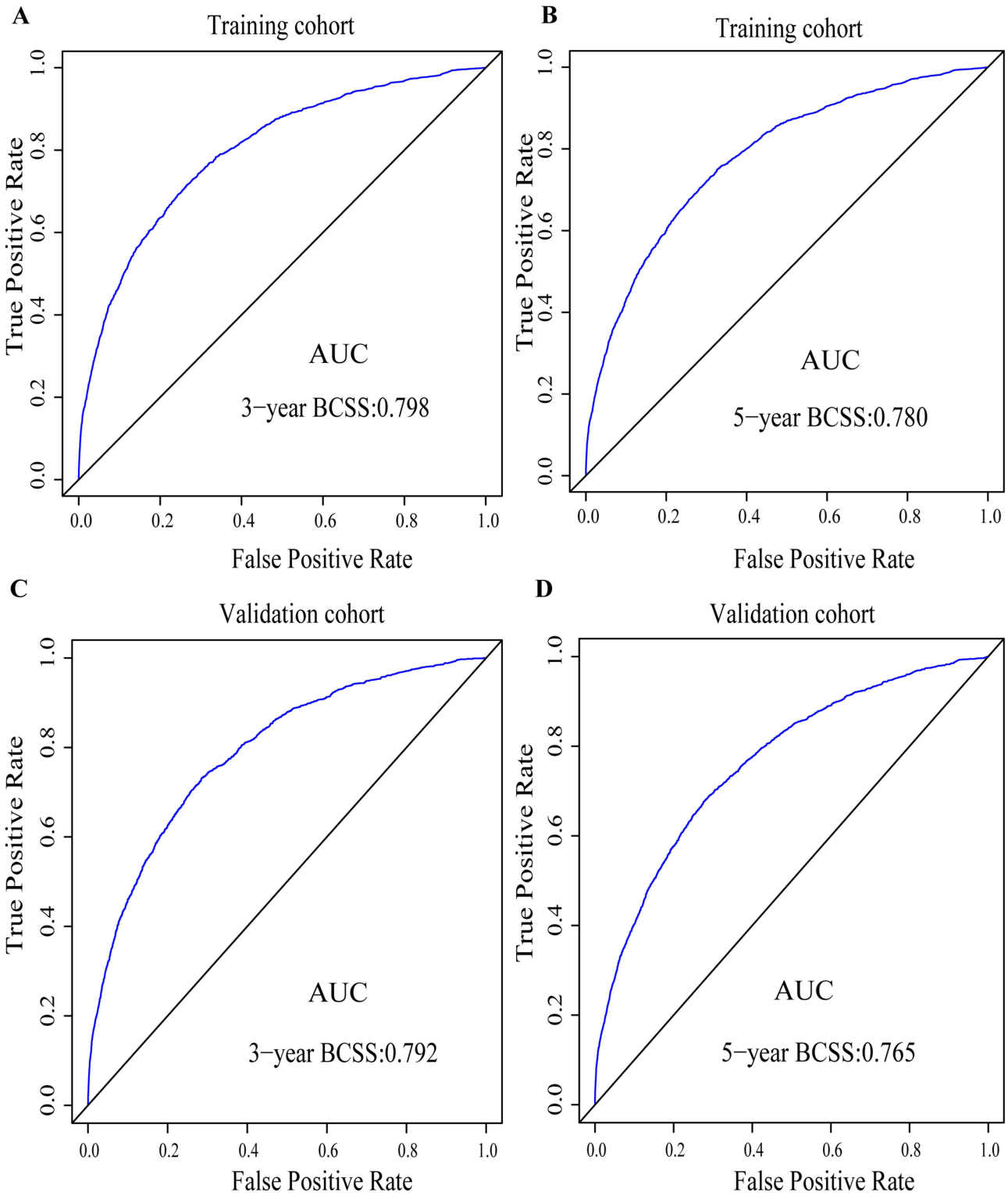

Figure 5 ROC curves to predict 3- and 5-year BCSS. (**A**) 3-year BCSS in the training cohort. (**B**) 5-year BCSS in the training cohort. (**C**) 3-year BCSS in the validation cohort. (**D**) 5-year BCSS in the validation cohort.
Abbreviations: AUC, area under the curve; BCSS, breast cancer-specific survival.

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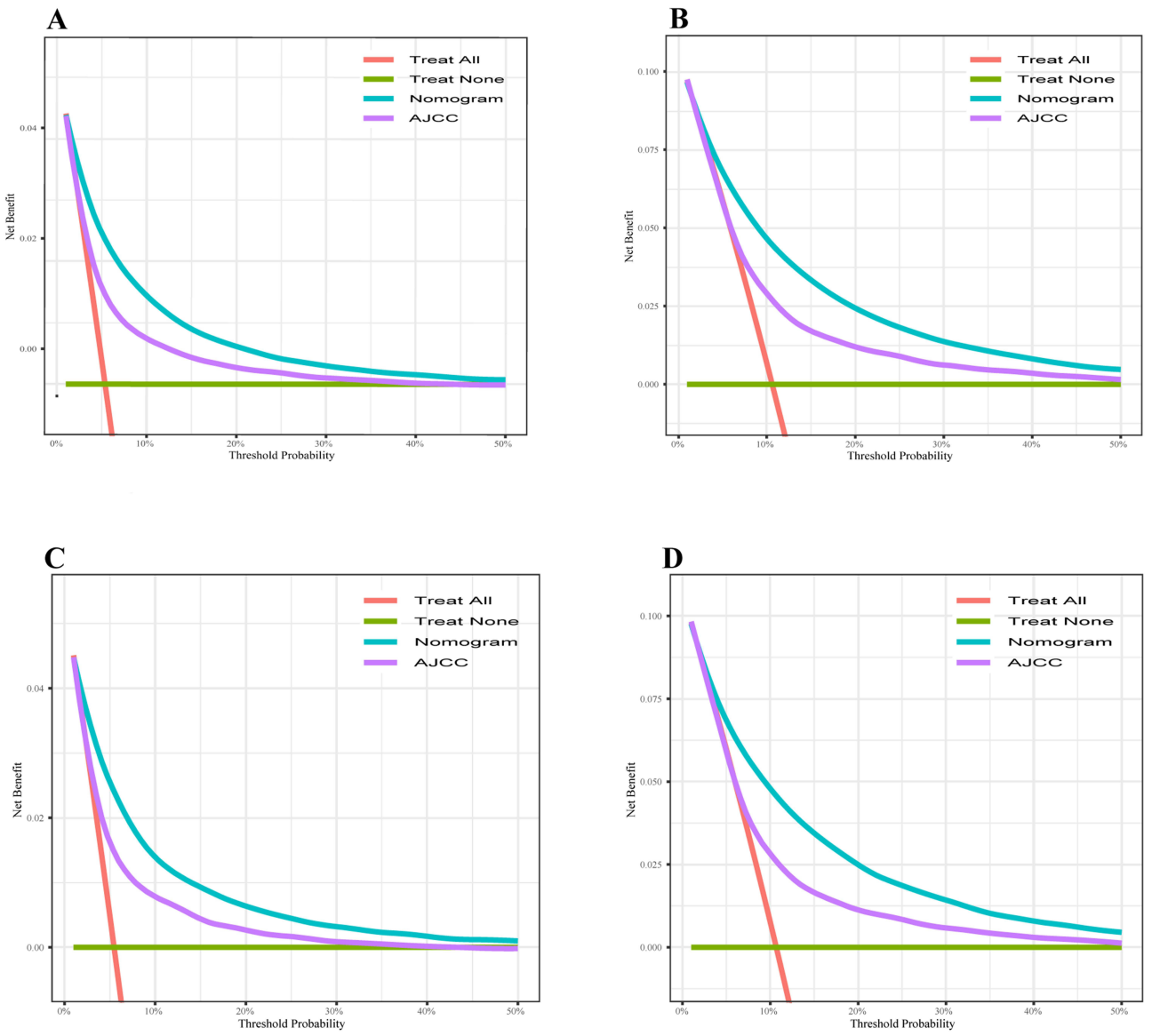

Figure 6 DCA of the 3- and 5-year BCSS comparing the nomogram with AJCC(TNM) anatomical staging in the training and validation cohort. (**A**) 3-year BCSS in the training cohort; (**B**) 5-year BCSS in the training cohort; (**C**) 3-year BCSS in the validation cohort; (**D**) 5-year BCSS in the validation cohort.

available to predict the prognosis for HR-positive BC patients. Based on sufficiently clinical resources from the SEER database, our study not only provides a novel nomogram for precise management of HR-positive BC patients but also further highlights the crucial role of integrating clinical information before decision-making.

In this study, since numerous clinical factors were related to patient prognosis in addition to TNM staging, we therefore integrated them into a prognostic nomogram. The result demonstrated our nomogram performed better than TNM staging in predicting OS as well as BCSS, suggesting its potential to help clinicians to identify high- or low-risk subpopulation from HR-positive patients. For patients with early HR-positive BC, endocrine therapy could be performed with or without chemotherapy. For those receiving no chemotherapy, a recent study has found delayed endocrine therapy was associated with adverse prognosis.[40] A similar investigation also demonstrated that HR-positive BC patients who did not receive adjuvant chemotherapy and began endocrine therapy more than 6 months postoperatively had worse survival than those who began endocrine therapy within 6 months postoperatively.[41] In this regard, our nomogram may be utilized to identify high-risk patients who need aggressive combined therapy or early intervention. On the other hand, a meta-analysis has suggested the omission of adjuvant radiotherapy or endocrine therapy in elderly low-risk HR-positive BC

patients, suggesting the importance of avoiding overtreatment.[42] However, a considerable proportion of low-risk patients are currently receiving combined radiation and endocrine therapy.[43,44] Our nomogram may provide novel evidence for reducing needless therapies in low-risk patients, which may minimize therapy-related adverse events and economic concerns to improve the overall life quality. Importantly, the nomogram can also serve as a valuable decision-support tool in regions with limited access to genetic or molecular testing. Furthermore, the model's high clinical applicability and robust reliability were validated in an external independent validation cohort of single ER-positive, IDC-type BC patients.

Previous studies have shown that the ER-positive/PR-negative subtype is more prevalent among elderly and postmenopausal women.[45,46] This was confirmed in our study, showing that it was most common in patients aged over 60 years. We also observed that ER-negative/PR-positive is most common in patients aged between 30 and 49 years. The ER-positive/PR-positive subtype accounts for a minor proportion of patients younger than 40 years old. In terms of pathological type, a higher proportion of IDC was found in ER-negative/PR-positive subtype, while that of other type was in ER-positive/PR-positive subtype. According to our study, unmarried BC patients are more likely to be initially diagnosed at advanced stage with higher incidence of metastasis and therefore shorter survival. This result may be partly attributed to the important impact of being married on the earlier cancer detection.[47] In addition, married patients had a higher proportion of ER-positive/PR-positive subtype, and the majority of which are found to have better clinical outcome than other subtypes. Previous evidence has found male BC patients had a higher mortality risk than female BC patients, although the lifetime risk of suffering BC is about 1/1000 compared with 1/8 in females.[48] Here, we found that most male patients were ER-positive/PR-positive subtype that was related better prognosis, but the multivariate analysis failed to identify gender as an independent prognostic factor. A previous report had demonstrated more male BC patients were diagnosed at advanced stage but only 65% of them were receiving surgery combined with radiation therapy.[49] Therefore, our result may be partly explained by delayed early diagnosis and insufficient adjuvant radiotherapy in male patients. Finally, our study found that the proportion of ER-negative/PR-positive subtype was highest in blacks, which was speculated as a potential reason for the unfavorable outcome as compared with whites. This speculation was also supported by a recent retrospective report showing a worse OS and higher recurrence rate of blacks compared with whites under the same medical conditions.[50]

Despite its strengths, this study has several limitations that warrant further exploration. The external validation cohort, although valuable, was limited to a single-center Chinese population and included only four ER-negative/PR-positive cases, restricting its generalizability. Moreover, the SEER database lacks detailed information on specific treatment regimens, such as endocrine therapy protocols or Ki67 expression, which are known to influence patient prognosis. Additionally, potential selection bias may have occurred during patient inclusion, as cases with incomplete data were excluded. For example, approximately 144,903 BC patients were excluded from the SEER cohort due to missing data, which may have introduced bias in the cohort's composition. Future studies should address these limitations by incorporating multicenter, multiethnic cohorts and expanding the dataset to include molecular and genomic variables. Building on this foundation, future research should focus on validating the nomogram across diverse populations and healthcare settings. Furthermore, integrating real-world treatment data, including response to endocrine and chemotherapy regimens, will provide a more comprehensive understanding of its clinical applicability. As precision medicine advances, this nomogram represents a step toward more individualized and effective management strategies for HR-positive BC patients. Finally, since HER2 status was included in the SEER database just after 2010, the survival analysis may be partly affected by the follow-up time. Therefore, continuous investigations based on updated follow-up data are necessary. Simultaneously, this study focuses more on HR-positive patients and does not fully address the impact of HER2 status on HR-positive patients. The mechanisms by which HER2 status affects single HR-positive BC patients remain an area for future exploration.

Conclusion

In conclusion, this study developed a validated nomogram that significantly enhances risk prediction for HR-positive BC patients, offering a practical tool for individualized clinical decision-making, particularly in regions with limited access

to comprehensive genetic testing. More importantly, the nomogram performed better than the traditional AJCC anatomical staging system in predicting OS and BCSS in both the training and validating cohort, suggesting its great potential in clinical practice. However, due to study limitations, more clinical validations based on sufficiently samples are needed to examine the actual performance of our nomogram in HR-positive BC patients.

Abbreviations

HR, hormone receptor-positive; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BC, breast cancer; SEER, surveillance, epidemiology, and end results; HR, hazard ratio; CI, confidence interval; C-index, consistency index; ROC, Receiver Operating Characteristic Curve; DCA, decision curve analysis; BCSS, breast cancer-specific survival; OS, overall survival; IDC, Invasive ductal carcinoma.

Data Sharing Statement

The datasets for this study can be found in the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/) of the National Cancer Institute using SEER*Stat software (version 8.3.9; SEER Research Plus Data, 18 Registries, November 2019 Sub [2000–2017 varying] database). The login account is 15318-Nov 2020. Other data can be reasonably obtained by contacting the corresponding author.

Ethics Approval and Consent to Participate

This study utilized deidentified data from the SEER database that is a publicly available. Additionally, this study is a retrospective study and has been reviewed by the Ethics Committee of the First Affiliated Hospital of Jiangxi Medical College of Nanchang University. The ethics committee approved the study with the ethics number IIT [2024] Lin Lun Shen No. 223. The ethics of this study also comply with the Declaration of Helsinki, and all patient data are kept confidential.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7–30. doi:10.3322/caac.21442

2. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International expert consensus on the primary therapy of early breast cancer 2013. *Ann Oncol*. 2013;24(9):2206–2223. doi:10.1093/annonc/mdt303
3. Chu J, Yang D, Wang L, Xia J. Nomograms predicting survival for all four subtypes of breast cancer: a SEER-based population study. *Ann Transl Med*. 2020;8(8):544. doi:10.21037/atm-20-2808
4. Lim E, Metzger-Filho O, Winer EP. The natural history of hormone receptor-positive breast cancer. *Oncology*. 2012;26(8):688–694,696.
5. Loibl S, Gianni L. HER2-positive breast cancer. *Lancet*. 2017;389(10087):2415–2429. doi:10.1016/S0140-6736(16)32417-5
6. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997–4013. doi:10.1200/JCO.2013.50.9984
7. Genre L, Roche H, Varela L, et al. External validation of a published nomogram for prediction of brain metastasis in patients with extra-cerebral metastatic breast cancer and risk regression analysis. *Eur J Cancer*. 2017;72:200–209. doi:10.1016/j.ejca.2016.10.019
8. Jhaveri K, Eli LD, Wildiers H, et al. Neratinib + fulvestrant + trastuzumab for HR-positive, HER2-negative, HER2-mutant metastatic breast cancer: outcomes and biomarker analysis from the SUMMIT trial. *Ann Oncol*. 2023;34(10):885–898. doi:10.1016/j.annonc.2023.08.003
9. Largillier R, Ferrero JM, Doyen J, et al. Prognostic factors in 1038 women with metastatic breast cancer. *Ann Oncol*. 2008;19(12):2012–2019. doi:10.1093/annonc/mdn424
10. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590
11. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784–2795. doi:10.1200/JCO.2009.25.6529
12. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet*. 1998;351(9114):1451–1467. doi:10.1016/S0140-6736(97)11423-4
13. Fan Y, Wang Y, He L, Imani S, Wen Q. Clinical features of patients with HER2-positive breast cancer and development of a nomogram for predicting survival. *ESMO Open*. 2021;6(4):100232. doi:10.1016/j.esmoop.2021.100232
14. Tolaney SM, Punie K, Carey LA, et al. Real-world treatment patterns and outcomes in patients with HR+/HER2- metastatic breast cancer treated with chemotherapy in the United States. *ESMO Open*. 2024;9(9):103691. doi:10.1016/j.esmoop.2024.103691
15. Fei F, Zhang K, Siegal GP, Wei S. A simplified breast cancer prognostic score: comparison with the AJCC clinical prognostic staging system. *Mod Pathol*. 2021;34(12):2141–2147. doi:10.1038/s41379-021-00890-y
16. Li Z, Kang D, Xu S, et al. Collagen signature adds prognostically significant information to staging for breast cancer. *ESMO Open*. 2024;9(12):103990. doi:10.1016/j.esmoop.2024.103990
17. Lammers SWM, Meegdes M, Vriens IJH, et al. Treatment and survival of patients diagnosed with high-risk HR+/HER2- breast cancer in the Netherlands: a population-based retrospective cohort study. *ESMO Open*. 2024;9(5):103008. doi:10.1016/j.esmoop.2024.103008
18. Nelson DR, Brown J, Morikawa A, Method M. Breast cancer-specific mortality in early breast cancer as defined by high-risk clinical and pathologic characteristics. *PLoS One*. 2022;17(2):e0264637. doi:10.1371/journal.pone.0264637
19. Cui X, Song D, Li X. Construction and validation of nomograms predicting survival in triple-negative breast cancer patients of childbearing age. *Front Oncol*. 2020;10:636549. doi:10.3389/fonc.2020.636549
20. Capogrosso P, Vickers AJ. a systematic review of the literature demonstrates some errors in the use of decision curve analysis but generally correct interpretation of findings. *Med Decis Making*. 2019;39(5):493–498. doi:10.1177/0272989X19832881
21. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. *JAMA*. 2015;313(4):409–410. doi:10.1001/jama.2015.37
22. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: st Gallen International Expert Consensus on the primary therapy of early breast cancer 2015. *Ann Oncol*. 2015;26(8):1533–1546. doi:10.1093/annonc/mdv221
23. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*. 2002;359(9324):2131–2139.
24. Van Asten K, Slembrouck L, Olbrecht S, et al. Prognostic value of the progesterone receptor by subtype in patients with estrogen receptor-positive, HER-2 negative breast cancer. *Oncologist*. 2019;24(2):165–171. doi:10.1634/theoncologist.2018-0176
25. Scabia V, Ayyanan A, De Martino F, et al. Estrogen receptor positive breast cancers have patient specific hormone sensitivities and rely on progesterone receptor. *Nat Commun*. 2022;13(1):3127. doi:10.1038/s41467-022-30898-0
26. John EM, Koo J, Phipps AI, et al. Reproductive characteristics, menopausal status, race and ethnicity, and risk of breast cancer subtypes defined by ER, PR and HER2 status: the breast cancer etiology in minorities study. *Breast Cancer Res*. 2024;26(1):88. doi:10.1186/s13058-024-01834-5
27. Li Y, Yang D, Yin X, et al. Clinicopathological characteristics and breast cancer-specific survival of patients with single hormone receptor-positive breast cancer. *JAMA Network Open*. 2020;3(1):e1918160. doi:10.1001/jamanetworkopen.2019.18160
28. Zhao H, Gong Y. The prognosis of single hormone receptor-positive breast cancer stratified by HER2 status. *Front Oncol*. 2021;11:643956. doi:10.3389/fonc.2021.643956
29. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *JNCI J National Cancer Inst*. 2014;106(5). doi:10.1093/jnci/dju055.
30. Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: decade report (2005–2015). *Breast*. 2018;39:131–138. doi:10.1016/j.breast.2018.03.002
31. Huppert LA, Gumusay O, Idossa D, Rugo HS. Systemic therapy for hormone receptor-positive/human epidermal growth factor receptor 2-negative early stage and metastatic breast cancer. *CA Cancer J Clin*. 2023;73(5):480–515. doi:10.3322/caac.21777
32. Kay C, Martinez-Perez C, Meehan J, et al. Current trends in the treatment of HR+/HER2+ breast cancer. *Future Oncol*. 2021;17(13):1665–1681. doi:10.2217/fon-2020-0504
33. watt AC, Goel S. Cellular mechanisms underlying response and resistance to CDK4/6 inhibitors in the treatment of hormone receptor-positive breast cancer. *Breast Cancer Res*. 2022;24(1):17. doi:10.1186/s13058-022-01510-6
34. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *New Engl J Med*. 2017;377(17):1700. doi:10.1056/NEJMx170012
35. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *New Engl J Med*. 2018;379(8):753–763. doi:10.1056/NEJMoa1802905

36. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, Phase 3 trial. *Lancet*. 2020;396(10257):1090–1100. doi:10.1016/S0140-6736(20)31953-X
37. Tu Q, Hu C, Zhang H, et al. Establishment and validation of novel clinical prognosis nomograms for luminal a breast cancer patients with bone metastasis. *Biomed Res Int*. 2020;2020:1972064. doi:10.1155/2020/1972064
38. Chen S, Liu Y, Yang J, et al. Development and validation of a nomogram for predicting survival in male patients with breast cancer. *Front Oncol*. 2019;9:361. doi:10.3389/fonc.2019.00361
39. Li GQ, Yu Y, Zhang WW, et al. Impact of AJCC prognostic staging on prognosis and postmastectomy radiotherapy decision-making in hormone receptor-positive and HER2-positive breast cancer. *BJS Open*. 2022;6(2). doi:10.1093/bjsopen/zrac025.
40. Fu F, Yu L, Zeng B, et al. Association of adjuvant hormone therapy timing with overall survival among patients with hormone receptor-positive human epidermal growth factor receptor-2-negative early breast cancer without chemotherapy. *JAMA Network Open*. 2022;5(2):e2145934. doi:10.1001/jamanetworkopen.2021.45934
41. Li S, Alapati A, Riba L, Fleishman A, James TA, Sharma R. Delayed adjuvant hormonal therapy and its impact on mortality in women with breast cancer. *Breast J*. 2020;26(5):952–959. doi:10.1111/tbj.13652
42. Savard MF, Clemons M, Hutton B, et al. De-escalating adjuvant therapies in older patients with lower risk estrogen receptor-positive breast cancer treated with breast-conserving surgery: a systematic review and meta-analysis. *Cancer Treat Rev*. 2021;99:102254. doi:10.1016/j.ctrv.2021.102254
43. Goldberg M, Sutradhar R, Paszat L, et al. Patterns of adjuvant care and outcomes of elderly women with stage I breast cancer after breast-conserving surgery: a population-based analysis. *Breast Cancer Res Treat*. 2019;176(3):657–667. doi:10.1007/s10549-019-05266-0
44. Nichol AM, Chan EK, Lucas S, et al. The use of hormone therapy alone versus hormone therapy and radiation therapy for breast cancer in elderly women: a population-based study. *Int J Radiat Oncol Biol Phys*. 2017;98(4):829–839. doi:10.1016/j.ijrobp.2017.02.094
45. Bae SY, Kim S, Lee JH, et al. Poor prognosis of single hormone receptor- positive breast cancer: similar outcome as triple-negative breast cancer. *BMC Cancer*. 2015;15:138. doi:10.1186/s12885-015-1121-4
46. Purdie CA, Quinlan P, Jordan LB, et al. Progesterone receptor expression is an independent prognostic variable in early breast cancer: a population-based study. *Br J Cancer*. 2014;110(3):565–572. doi:10.1038/bjc.2013.756
47. Buja A, Lago L, Lago S, Vinelli A, Zanardo C, Baldo V. Marital status and stage of cancer at diagnosis: a systematic review. *Eur J Cancer Care*. 2018;27(1):e12755. doi:10.1111/ecc.12755
48. Liu N, Johnson KJ, Ma CX. Male breast cancer: an updated surveillance, epidemiology, and end results data analysis. *Clin Breast Cancer*. 2018;18(5):e997–e1002. doi:10.1016/j.clbc.2018.06.013
49. Eskander MF, Li Y, Bhattacharyya O, et al. Hormone receptor-positive breast cancer and black race: does sex matter? *Breast Cancer Res Treat*. 2021;190:111–119. doi:10.1007/s10549-021-06359-5
50. Albain KS, Gray RJ, Makower DF, et al. Race, ethnicity, and clinical outcomes in hormone receptor-positive, HER2-negative, node-negative breast cancer in the randomized TAILORx trial. *J Natl Cancer Inst*. 2021;113(4):390–399. doi:10.1093/jnci/djaa148