Original Article

Development and validation of a prognostic nomogram for early HER2-positive and lymph node-negative breast cancer

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Background: Dual-targeted therapy is currently the standard adjuvant treatment for human epidermal growth factor receptor 2-positive (HER2+) and lymph node-positive (LN+) breast cancer. However, the optimal therapeutic strategy for patients with HER2+ and lymph node-negative (LN–) breast cancer remains unclear. This population-based study aimed to explore the factors associated with survival in patients with HER2+ and LN– breast cancer, and develop a survival-predicting nomogram in the era of trastuzumab-based single-targeted therapy.

Methods: We collected the clinicopathological information of HER2+ and LN– breast cancer patients who underwent chemotherapy and surgery from The Surveillance, Epidemiology, and End Results (SEER) database (2010–2016, the Trastuzumab-based single-targeted therapy era). We subsequently explored the risk factors for breast cancer-specific survival (BCSS) and overall survival (OS) using a Cox proportional hazards regression model, aiming to identify subgroups with worse prognosis, which would indicate potential demand for dual-targeted therapy. Three- and 5-year survival probability-predictive nomograms were established and subjected to bootstrap internal validation. The concordance index (C-index) and calibration curve were applied to evaluate the performance of the model.

Results: After data cleansing, a total of 13,755 patients were included in the current analysis. Using univariate and multivariate Cox proportional hazards regression, higher clinical T stage, hormone receptors-negative (HR-), and partial mastectomy without radiotherapy were identified as independent risk factors for BCSS and OS in patients with HER2+ and LN– breast cancer. Nomograms for 3- and 5-year BCSS and OS incorporating the selected prognostic factors were established. Calibration curves verified good consistency between the actual and nomogram-predicted survival probability. The C-index values of the BCSS and OS predictions and 95% confidence interval (CI) were 0.773 (0.740–0.806) and 0.764 (0.737–0.791), respectively.

Conclusions: Higher clinical T stage, HR-, and partial mastectomy without radiotherapy predicted worse prognosis in patients with HER2+ and LN– breast cancer. In clinical practice, patients can be recommended for single-targeted or dual-targeted therapy according to the individualized factors.

Keywords: Breast cancer; HER2-positive; lymph node-negative; nomogram; survival analysis

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Introduction

Approximately 15–20% of all patients with breast cancer overexpress human epidermal growth factor receptor 2 (HER2), which was considered a risk factor associated with disease aggression and reduced response to traditional chemotherapy before the advent of HER2-directed therapies (1). In the era of anti-HER2 targeted therapy, the prognosis of HER2+ breast cancers has markedly improved (2-8). Trastuzumab, an anti-HER2 humanized monoclonal antibody, was approved by the U.S. Food and Drug Administration (FDA) in 1998. Ever since, it has become an anti-HER2 treatment choice, regardless of early-stage or metastatic breast cancer (4,9-12). However, despite the significant improvements realized by single-targeted therapy, a considerable number of HER2+ patients with inherent and acquired resistance to trastuzumab will still suffer relapse and disease progression (3,5,11,13-15). Numerous attempts with novel approaches to target therapy have been performed to improve outcomes for patients with early HER2+ breast cancer (16).

The phase III APHINITY trial (NCT01358877) proved that pertuzumab significantly improved the rates of invasive-disease-free survival among patients with HER2+ operable breast cancer when added to trastuzumab and chemotherapy. Hence, the combination of pertuzumab plus trastuzumab and chemotherapy was approved in 2017 by the U.S. FDA for the adjuvant treatment of patients with early HER2+ breast cancer with high risk of recurrence (17,18). However, in the APHINITY trial, in the cohort of patients with node-negative breast cancer, the 3-year rate of invasive-disease-free survival (iDFS) of patients in the pertuzumab group did not show significant improvement compared to those in the placebo group (hazard ratio, 1.13; 95% CI, 0.68–1.86; P=0.64) (17), which was confirmed by a long-term follow-up in 2019 (19).

Also, the phase III ExteNET trial (NCT00878709) confirmed the efficacy of neratinib, a tyrosine kinase inhibitor (TKI) of HER1, HER2, and HER4, after trastuzumab-based adjuvant therapy in patients with early-stage HER2+ breast cancer (20-22). The concurrent or sequential treatment of neratinib within 1 year after trastuzumab adjuvant therapy significantly improved the 5-year iDFS and 8-year overall survival (OS) of HER2+ breast cancer patients. However, in the subgroup analysis of the ExteNET trial, the LN– cohort (n=255) did not show significant improvement in the 5-year iDFS (hazard ratio, 0.37; 95% CI, 0.08–1.24) (22), which was similar to the APHINITY trial. Neither APHINITY trial and ExteNET trial support of the routine use of dual-targeted treatment over HER2+ and LN– breast cancer, hence it remains controversial whether dual-targeted therapy is suitable for HER2+ and LN– breast cancer patients.

Therefore, we used the data of HER2+ and LN– breast cancer patients who were diagnosed between 2010 and 2016 (before dual-targeted therapy was approved), and designed a protocol to screen out risk factors associated with survival outcomes in this population. Furthermore, we established and validated prognostic nomograms, in an attempt to identify subgroups with poorer survival outcomes, indicating the potential demand of dual-targeted therapy (trastuzumab plus pertuzumab or TKIs, or sequential TKIs after trastuzumab therapy). We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/gs-21-392).

Methods

Data source and patient selection

All procedures performed in the study involving human participants were in accordance with Helsinki declaration (as revised in 2013). Data for this study were selected from 18 registries of the Surveillance, Epidemiology, and End Results (SEER) program, and obtained using SEER*Stat software version 8.3.6 (23). The target population was extracted based on the following criteria in the SEER database: (I) patients diagnosed between January 1, 2010 and December 31, 2016; (II) female patients; (III) histologically confirmed malignant breast cancer; (IV) known primary tumor status and not carcinoma *in situ*; (V) first and primary tumor without distant metastasis; (VI) HER2+ and LN– subtype; (VII) patients who underwent chemotherapy and cancer-directed surgery; (VIII) survival data with complete and available dates, and more than 0 days of survival; (IX) patients with medical insurance; (X) clear demographics and clinicopathological information available for all variables of interest including age at diagnosis, race, laterality, grade, clinical T stage, hormone receptor (HR) status, radiotherapy status, and surgery type. Since chemotherapy plus surgery is the standard treatment for patients with non-metastatic operable breast cancer (24,25), only those that underwent both chemotherapy and surgery were included.

Variables

The primary endpoints were breast cancer-specific survival (BCSS) and OS. BCSS was defined as the time from the date of diagnosis until death due to breast cancer. OS was defined as the time from the date of diagnosis until death due to any cause. The cut-off date was December 31, 2016, which was the last update on follow-up time.

The following variables were selected as potential prognostic factors: age at diagnosis; ethnicity [White, Black, and other (American Indian/Alaska Native, Asian/Pacific Islander)]; laterality (left or right); pathological grade (well-differentiated, moderately differentiated, poorly differentiated); clinical T stage (T1, T2, T3, and T4); HR status (ER+/PR+, ER+/PR–, ER–/PR+, ER–/PR–); radiotherapy status (yes or none/unknown); and surgery type (mastectomy or partial mastectomy). Clinical Tumor, lymph node and metastasis (TNM) stage was not included because of its collinearity with T stage under circumstances of N0 and M0.

Statistical analysis

Descriptive results were reported as counts and percentages for categorical variables, and as means ± standard deviations for continuous variables. Kruskal-Wallis and Chi-squared tests were used to examine differences between the patient groups. A univariate Cox proportional hazards regression model was employed to analyze the independent variables associated with BCSS and OS. Variables with statistical significance (P<0.05) in the univariate analysis were included in the multivariate Cox proportional hazards regression model to estimate the adjusted hazard ratios (HRs) with 95% confidence interval (CI) of risk factors and to construct the nomograms. Survival results were generated using the Kaplan-Meier method and were compared using log-rank tests. A nomogram was built to predict the 3- and 5-year prognoses of BCSS and OS (26).

To validate the model, Harrell's concordance index (C-index) was introduced to calculate the discrimination between the actual result and the predicted result of the Cox survival analysis (27). The nomogram was validated internally by 1000 bootstrap resamples and by plotting calibration curves that compared the actual survival probability with predicted survival probability generated by the bootstrapping. 1000 bootstrap repetitions were chosen since higher repetition times can hardly improve the estimates.

P<0.05 was considered to indicate statistical significance, and all P values were two-sided. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) and R 4.0.2 (R Foundation, https://www.r-project.org/).

Results

Patients' characteristics

The patients' demographics and clinicopathologic features are summarized in *Table 1*. In total, 13,755 patients with early HER2+ and LN– breast cancer were enrolled in this study. Among these, 209 patients had breast cancer-specific deaths, and 325 patients died due to all causes. The average age of patients was 55.82 years [interquartile range (IQR), 48–64 years].

Only a minority of patients had pathological grade I tumors (4.6%), while grade II (37.0%) and grade III (58.4%) tumors accounted for the majority of cases. Most patients had a stage T1 primary tumor (60.2%), and the proportion decreased progressively with higher T stages. In terms of hormone receptors, estrogen receptor-positive (ER+)/progesterone receptor-positive (PR+) accounted for approximately half of the total (51.7%), whereas the proportions were 20.2% for ER+/PR– or ER–/PR+ and 28.1% for ER–/PR–. With regards to the choice of surgery type and radiotherapy, the majority of patients received mastectomy without radiotherapy (36.7%) or partial mastectomy with radiotherapy (45.2%), which was consistent with the clinical consensus (28).

Survival outcomes

The 3-year survival rate of all patients was 97.9% (95% CI, 97.6–98.2%), and the 5-year survival rate was 95.7% (95% CI, 95.2–96.3%). After an unadjusted survival analysis, age group, ethnicity, grade, T stage, HR, and therapy exhibited a significant association with either BCSS or OS (*Table 2*), and were included in the multivariate Cox proportional hazards regression model. Forest plots of HR in the multivariate Cox analysis are shown in *Figure 1A*,*B*.

Among the different age groups, the >80 years old group had a significantly higher risk than the younger reference group both in terms of BCSS (HR =5.22, 95% CI: 1.19–22.83, P=0.028) and OS (HR =6.20, 95% CI: 1.87–20.58, P=0.003). As for ethnicity, American Indian/Alaska Native/Asian/Pacific Islander patients had a significantly better

Table 1 Demographics and clinicopathologic characteristics of the entire cohort

Variable	N=13,755
Age, mean (SD), years	55.82 (11.65)
Ethnicity, n (%)	
White	10,576 (76.9)
Black	1,506 (10.9)
Other*	1,673 (12.2)
Laterality, n (%)	
Left	6,975 (50.7)
Right	6,780 (49.3)
Grade, n (%)	
I	639 (4.6)
II	5,087 (37.0)
III	8,029 (58.4)
T stage, n (%)	
1	8,274 (60.2)
2	4,819 (35.0)
3 or 4	662 (4.8)
Hormone receptors, n (%)	
ER+/PR+	7,105 (51.7)
ER+/PR– or ER–/PR+	2,779 (20.2)
ER–/PR–	3,871 (28.1)
Therapy, n (%)	
Only mastectomy	5,054 (36.7)
Only partial mastectomy	1,808 (13.1)
Mastectomy + radiotherapy	678 (4.9)
Partial mastectomy + radiotherapy	6,215 (45.2)

*, American Indian/Alaska Native, Asian/Pacific Islander. SD, standard deviation; ER, estrogen receptor; PR, progesterone receptor.

survival in terms of BCSS (HR =0.48, 95% CI: 0.26–0.90, P=0.021) and OS (HR =0.60, 95% CI: 0.39–0.93, P=0.022) compared to White patients. T2 patients (HR =1.85, 95% CI: 1.46–2.34, P<0.001) and T3 or T4 patients (HR =2.38, 95% CI: 1.55–3.66, P<0.001) had a significantly higher risk of total cause of death than T1 patients. The ER+/PR+ HR status exhibited the lowest risk among the four types, while the ER–/PR– patients had a significantly poorer BCSS (HR =2.23, 95% CI: 1.58–3.15, P<0.001) and OS (HR =1.46, 95% CI: 1.13–1.90, P=0.004). Patients that underwent partial mastectomy without radiotherapy (HR =1.95, 95% CI: 1.45–2.61, P<0.001) and mastectomy with radiotherapy (HR =1.70, 95% CI: 1.12–2.59, P=0.013) showed significantly higher risk, while patients that underwent partial mastectomy with radiotherapy had a lower risk (HR =0.69, 95% CI: 0.52–0.91, P=0.008) of all cause death than those that underwent mastectomy without radiotherapy. By comparing the clinicopathological parameters of patients that underwent different therapies, we found that those who underwent mastectomy with radiotherapy had a significantly higher proportion of clinical T3 or T4 stages (Table S1), which may explain their higher risk of death. Significance associations were not observed in the other variables.

Figure 2 displays the OS curves of the total population and subgroups divided by clinicopathological parameters.

Construction and validation of prognostic nomograms

The nomograms of 3- and 5-year BCSS and OS incorporating the selected prognostic factors were established (*Figure 3A*,*B*). The calibration plots verified good consistency between the actual and nomogram-predicted survival probability in terms of both BCSS and OS (*Figure 4*). The C-index of BCSS and OS predictions were 0.773 (95% CI, 0.740–0.806) and 0.764 (95% CI, 0.737–0.791), respectively.

Discussion

In this population-based study, we identified several independent risk factors associated with the survival of HER2+ and LN– breast cancer patients, and developed and validated prognostic nomograms for predicting survival. To the best of our knowledge, this is first observational research exploring the prognostic factors of HER2+ and LN– populations in the H-based single-targeted therapy era, which can, to some extent, provide a reference for precision treatment in the era of dual-targeted therapy.

Although H-based, single-targeted therapy has considerably improved the prognosis of HER2+ breast cancer patients, inevitable recurrence and metastasis in some populations several years after treatment of early-stage disease necessitates intensive treatment (3,5,11,13-15). The APHINITY and KAITLIN trials established dual-targeted therapy as adjuvant treatment in HER2+ and LN+ breast cancer; however, the optimal choice for patients with

Table 2 Univariate Cox analysis of BCSS and OS

Variables	BCSS			OS		
	Log-rank test	Univariate analysis	P value	Log-rank test	Univariate analysis	P value
	P value	HR (95% CI)		P value	HR (95% CI)	
Age group (years)	<0.001			<0.001		
18–30		Reference			Reference	
30–40		0.82 (0.18, 3.65)	0.790		0.68 (0.20, 2.36)	0.546
40–50		0.54 (0.13, 2.27)	0.397		0.48 (0.15, 1.56)	0.221
50–60		0.81 (0.20, 3.34)	0.775		0.76 (0.24, 2.41)	0.642
60–70		0.92 (0.22, 3.80)	0.912		1.26 (0.40, 3.98)	0.69
70–80		1.62 (0.39, 6.77)	0.508		2.52 (0.79, 7.99)	0.117
>80		6.41 (1.48, 27.73)	0.013		7.11 (2.16, 23.38)	0.001
Ethnicity	0.014			0.007		
White		Reference			Reference	
Black		1.22 (0.81, 1.86)	0.342		1.18 (0.85, 1.63)	0.319
Other*		0.48 (0.26, 0.88)	0.018		0.56 (0.36, 0.86)	0.009
Laterality	0.970			0.349		
Left		Reference			Reference	
Right		0.99 (0.75, 1.33)	0.97		0.90 (0.72, 1.12)	0.349
Grade	0.013			0.024		
I		Reference			Reference	
II		3.85 (0.94, 15.73)	0.061		1.88 (0.87, 4.03)	0.107
III		4.64 (1.15, 18.75)	0.031		2.26 (1.07, 4.80)	0.034
T Stage	<0.001			<0.001		
1		Reference			Reference	
2		2.27 (1.67, 3.10)	<0.001		2.00 (1.59, 2.53)	<0.001
3 or 4		4.69 (2.96, 7.44)	<0.001		3.50 (2.40, 5.09)	<0.001
Hormone receptors	<0.001			<0.001		
ER+/PR+		Reference			Reference	
ER+/PR– or ER–/PR+		1.68 (1.12, 2.51)	0.012		1.52 (1.14, 2.02)	0.005
ER–/PR–		2.67 (1.92, 3.73)	<0.001		1.82 (1.41, 2.33)	<0.001
Therapy	<0.001			<0.001		
Only mastectomy		Reference			Reference	
Only partial mastectomy		1.80 (1.22, 2.66)	0.003		2.04 (1.53, 2.72)	<0.001
Mastectomy + radiotherapy		2.86 (1.83, 4.48)	<0.001		2.19 (1.50, 3.20)	<0.001
Partial mastectomy + radiotherapy		0.64 (0.45, 0.93)	0.018		0.69 (0.52, 0.91)	0.008

*, American Indian/Alaska Native, Asian/Pacific Islander. BCSS, breast cancer-specific survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor.

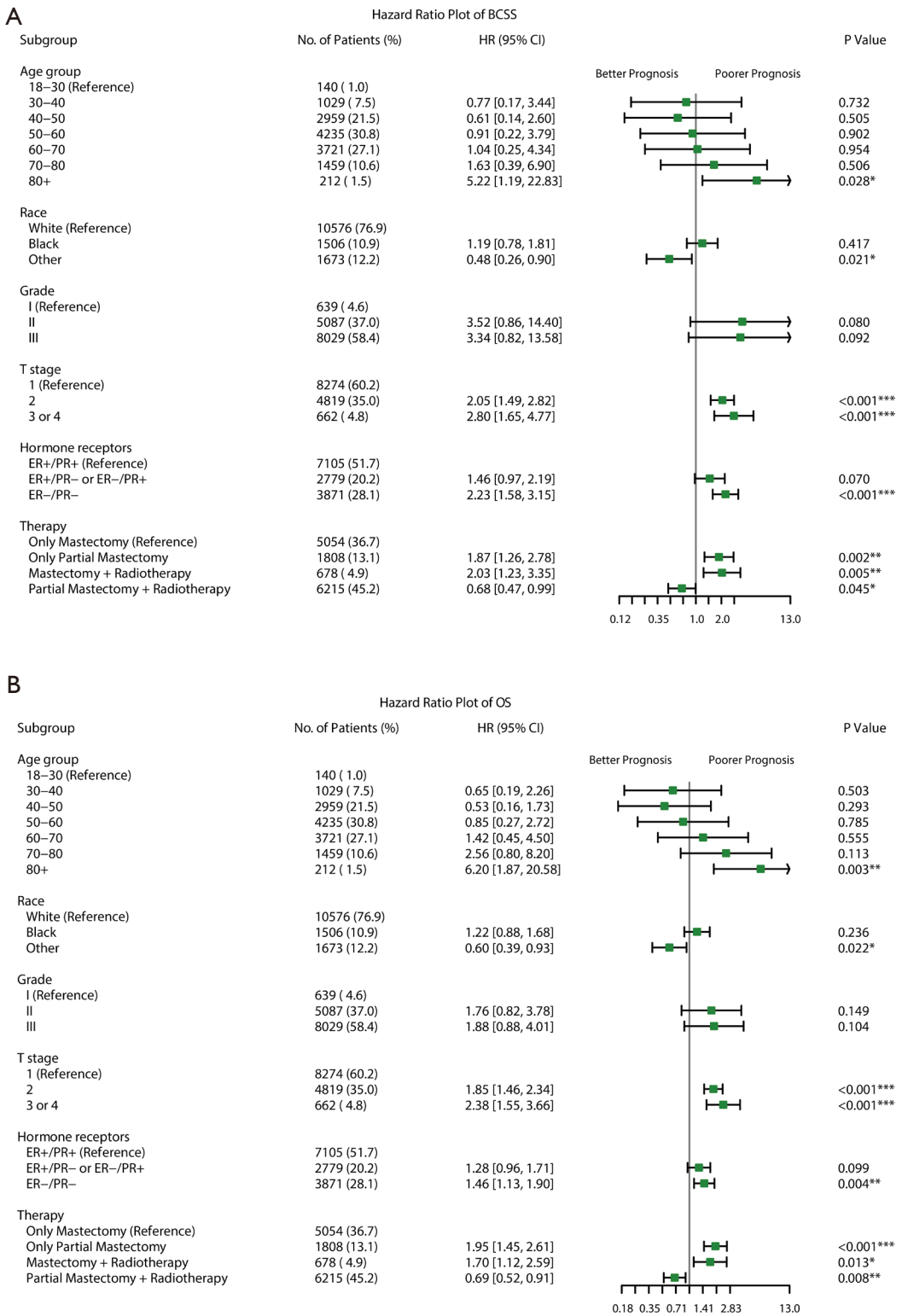

Figure 1 Forest plots of multivariate Cox analysis. (A) Breast cancer-specific survival; (B) overall survival. *, P<0.05; **, P<0.01; ***, P<0.001.

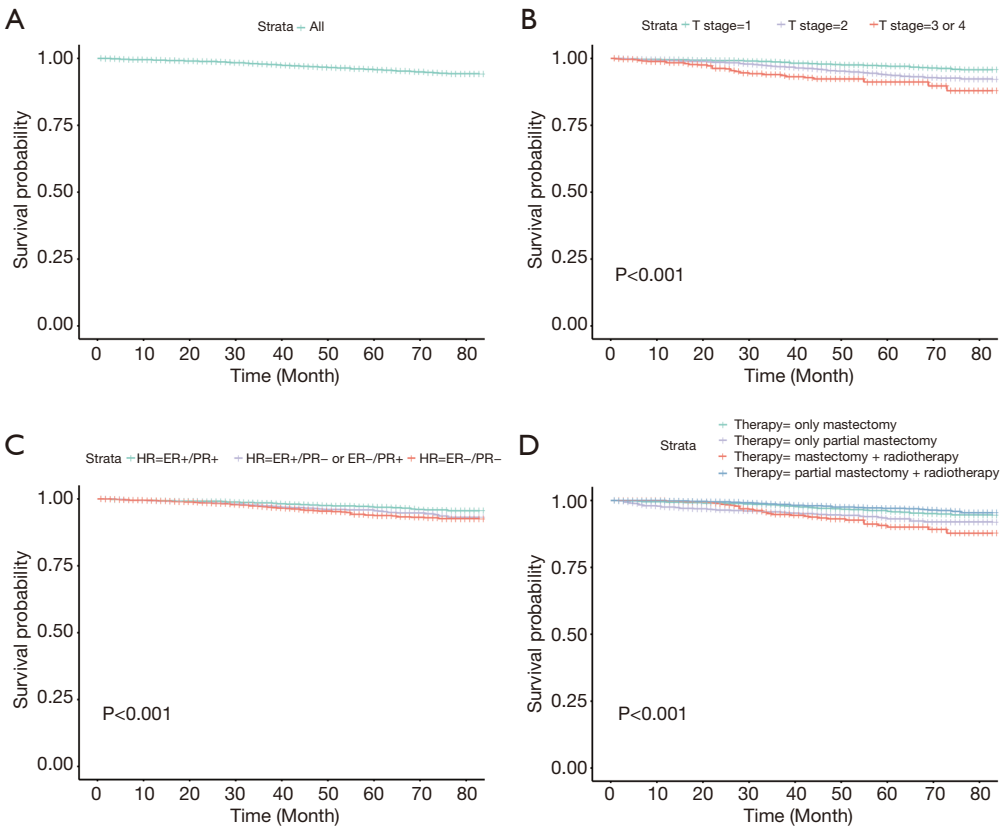

Figure 2 Kaplan-Meier overall survival curves. (A) Overall cohort; and for each prognostic factor: (B) T stage; (C) hormone receptors (HR); (D) therapy.

LN− cancer is still a blind spot for clinicians and remains to be determined (17,19,22,29). Therefore, we designed this observational study to explore the high-risk factors of the LN− population in the single-targeted era of treatment. A total of 13,755 patients were screened from the SEER database according to our inclusion and exclusion criteria. According to the univariate and multivariate Cox analyses, some variables were significantly associated with both BCSS or OS, including age group, ethnicity, clinical T stage, HR status, and surgical type. Generally, age ≥80 years was an independent risk factor associated with poor prognosis, but no differences were found among other age groups. Owing to the intrinsic high mortality rate of patients aged ≥80 years, it is reasonable to believe that age is not directly related to prognosis. Differences identified between ethnicities may be related to a variety of complex social and economic factors, and were therefore not considered. T stage and prognosis were negatively correlated, as higher T stage was indicative of poorer BCSS and OS than lower T stage. Furthermore, HR status was also found to be associated with survival, wherein ER+/PR+ exhibited the lowest risk among the four types, which may be due to benefits from a variety of endocrine therapies. ER+/PR− or ER−/PR+ and ER−/PR− populations separately were associated with increased risks owing to the lack of endocrine therapy, highlighting the need for more effective anti-HER2 treatments. In terms of therapy, partial mastectomy without radiotherapy and mastectomy with radiotherapy exhibited a higher risk, while the latter may be related to higher clinical T stage.

To individually predict the survival of the HER2+ and LN− populations, a Cox proportional hazards regression model was applied to construct the nomogram, and the performance of the nomogram was evaluated by internal bootstrap validation and displayed using calibration curves. In our model, the calibration curves demonstrated good consistency between the estimated and actual probabilities for both BCSS and OS. On the other hand, the C-index values were >0.75 in both BCSS and OS, which also confirmed the high credibility of the model.

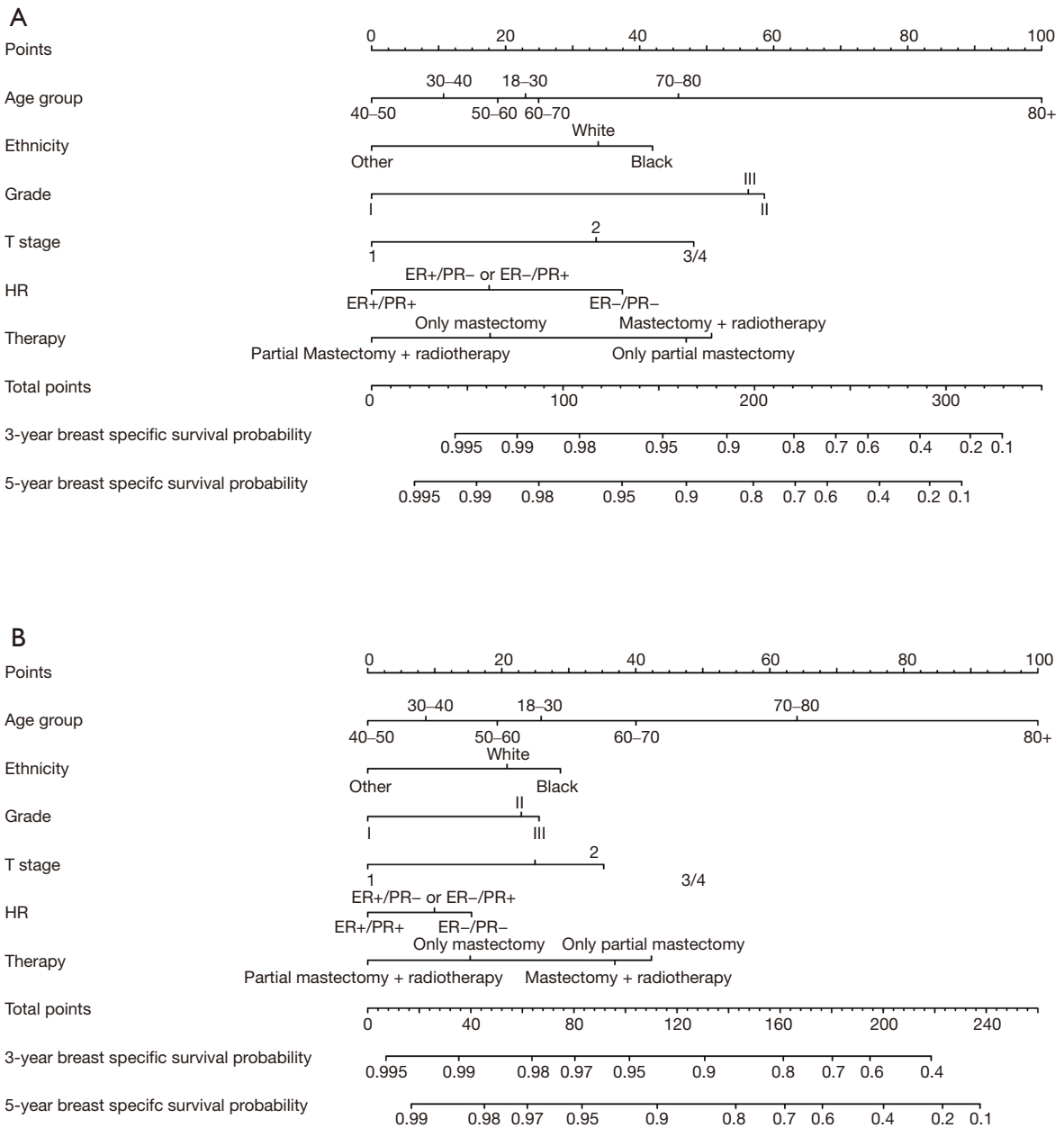

Figure 3 Nomograms for predicting the 3- and 5-year survival. (A) Breast cancer-specific survival; (B) overall survival. Each variable corresponds to a score on the points scale. After adding up the total points, the predicted survival possibility could be obtained by projecting the total points to the survival axis.

This nomogram can be used in clinical practice to evaluate the individual survival risk of HER2+ LN– breast cancer according to clinicopathological variables, and patients with high total scores in the nomogram (T3 or T4 stage, ER–/PR–, partial mastectomy without radiotherapy) can be recommended for dual-targeted therapy, including trastuzumab combined with pertuzumab or TKIs, or sequential TKIs after trastuzumab therapy.

Despite its novelty, our study still has some limitations that should be noted. Firstly, given the nature of retrospective research, a high potential for selection bias and a lack of standardized specimen handling were inevitable.

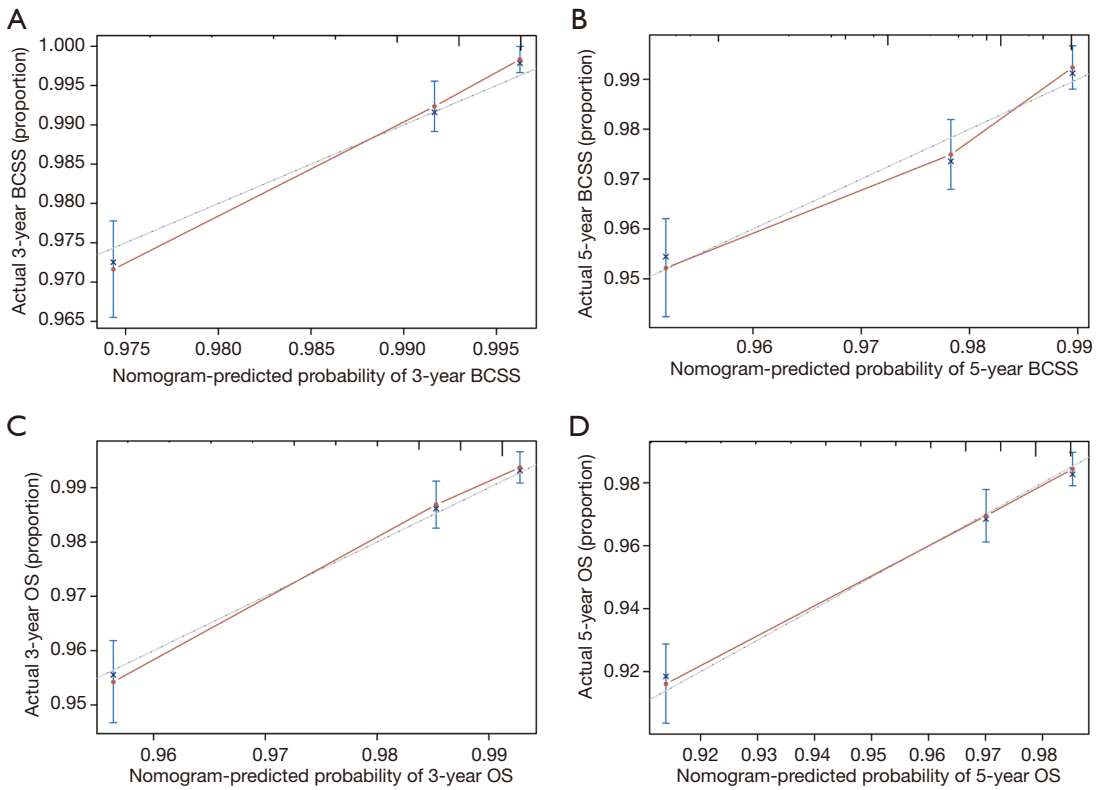

Figure 4 Calibration curves for the nomogram-predicted probability of 3- and 5-year survival. (A,B) BCSS; (C,D) OS. Nomogram-predicted survival probability is plotted on the X-axis and actual probability is plotted on the Y-axis. The dotted red line (plotted by function y=x) indicates the perfect match of actual and predicted results. BCSS, breast cancer-specific survival; OS, overall survival.

Secondly, only internal bootstrap validation was applied due to the lack of databases with sufficient information. The model would be more robust and persuasive with external validation. Further prospective studies are encouraged to improve and verify our models.

Conclusions

Higher clinical T stage, HR– status, and partial mastectomy without radiotherapy are independent risk factors for BCSS and OS in patients with HER2+ and LN– breast cancer. In this study, prognostic nomograms targeting this population were established and validated, which could be useful in clinical counseling. In clinical practice, patients can be recommended for single-targeted (H) or dual-targeted (trastuzumab plus pertuzumab or TKIs, or sequential TKIs after trastuzumab) therapy according to individualized factors.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://dx.doi.org/10.21037/gs-21-392

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/gs-21-392). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Clinicopathologic characteristics' distribution of different therapy groups

Variables	P value	Therapy			
		Only mastectomy	Only partial mastectomy	Mastectomy + radiotherapy	Partial mastectomy + radiotherapy
n		5,054	1,808	678	6,215
Age group (years)	<0.001				
18–30		85 (1.7)	5 (0.3)	18 (2.7)	32 (0.5)
30–40		575 (11.4)	70 (3.9)	118 (17.4)	266 (4.3)
40–50		1,318 (26.1)	331 (18.3)	170 (25.1)	1,140 (18.3)
50–60		1,478 (29.2)	570 (31.5)	185 (27.3)	2,002 (32.2)
60–70		1,120 (22.2)	514 (28.4)	125 (18.4)	1,962 (31.6)
70–80		407 (8.1)	278 (15.4)	54 (8.0)	720 (11.6)
>80		71 (1.4)	40 (2.2)	8 (1.2)	93 (1.5)
Ethnicity	<0.001				
White		3,841 (76.0)	1,407 (77.8)	518 (76.4)	4,810 (77.4)
Black		462 (9.1)	183 (10.1)	96 (14.2)	765 (12.3)
Other*		751 (14.9)	218 (12.1)	64 (9.4)	640 (10.3)
Grade	0.147				
I		212 (4.2)	94 (5.2)	34 (5.0)	299 (4.8)
II		1,851 (36.6)	683 (37.8)	233 (34.4)	2,320 (37.3)
III		2,991 (59.2)	1,031 (57.0)	411 (60.6)	3,596 (57.9)
T Stage	<0.001				
1		2,811 (55.6)	1,174 (64.9)	202 (29.8)	4,087 (65.8)
2		2,002 (39.6)	598 (33.1)	235 (34.7)	1,984 (31.9)
3 or 4		241 (4.8)	36 (2.0)	241 (35.5)	144 (2.3)
HR	<0.001				
ER+/PR+		2,489 (49.2)	913 (50.5)	303 (44.7)	3,400 (54.7)
ER+/PR– or ER–/PR+		1,064 (21.1)	380 (21.0)	136 (20.1)	1,199 (19.3)
ER–/PR–		1,501 (29.7)	515 (28.5)	239 (35.3)	1,616 (26.0)

*, American Indian/Alaska Native, Asian/Pacific Islander. HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor.

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