Adjuvant chemotherapy guidance for pT1–3N0–1 breast cancer patients with HR$^+$, HER2$^-$ subtype: a cohort study based on the SEER database

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Background: Although the results of gene testing can guide early breast cancer patients with hormone receptor (HR)$^+$, human epidermal growth factor receptor 2 (HER2)$^-$ to decide whether they need chemotherapy (CHT), there are still many patients worldwide whose problems cannot be resolved by genetic testing.

Methods: A total of 144,735 patients with HR$^+$, HER2$^-$, pT1–3N0–1 breast cancer from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015 were included. They were divided into CHT and no CHT groups, and after propensity score matching (PSM), overall survival (OS) and breast cancer-specific survival (BCSS) were tested using the Kaplan-Meier plot. The Cox proportional hazards regression model was used to identify independent prognostic factors. A nomogram was constructed to score each patient. Patients were divided into high- or low-risk groups according to their nomogram score using X-tile.

Results: Patients receiving CHT had better OS before and after matching ($P<0.05$), but BCSS was not significantly different between patients with and without CHT after matching. Independent prognostic factors were included to construct the nomogram, which could calculate the risk score for each patient, and then all patients were divided into two groups using X-tile: a risk score ≤238 was classified as the low-risk group and >238 was classified as the high-risk group. Patients in the high-risk group (score >238) could achieve better OS and from CHT; however, the low-risk group (score ≤238) could not.

Conclusions: In this study, a well-validated nomogram and a risk stratification model was built. Patients in the high-risk group should receive CHT, while patients in low-risk group may be exempt from CHT.

Keywords: Breast cancer; Surveillance, Epidemiology, and End Results program (SEER program); nomograms; hormone receptor (HR); chemotherapy (CHT)

Submitted Oct 28, 2021. Accepted for publication Dec 06, 2021.
doi: 10.21037/atm-21-5937
View this article at: https://dx.doi.org/10.21037/atm-21-5937

Introduction

Breast cancer is the second leading cause of death among women worldwide (1), and the prognosis of patients with different molecular subtypes varies (2-4). Chemotherapy (CHT) is an important and effective treatment for breast cancer. For high-risk breast cancer with poor prognosis, such as triple negative, human epidermal growth factor receptor 2 (HER2) overexpression, larger tumor, and more positive lymph nodes, CHT can significantly improve overall survival (OS) and breast cancer-specific survival (BCSS). However, for patients with hormone receptor

(HR)+, HER2− early breast cancer, the effect of CHT remains controversial. Some people hold that CHT is effective (5), while others believe that endocrine therapy is a more effective treatment, and CHT is both ineffective and may also result in side effects.

At present, most guidelines recommend that patients with HR+, HER2− early breast cancer should be tested for Oncotype DX or MammaPrint to determine whether CHT is necessary (6,7). However, gene testing has its disadvantages. Firstly, the high cost limits the degree of popularization in both developing and developed countries (8), and there are also copyright problems. Secondly, neither Oncotype DX nor MammaPrint can solve the problem of all patients receiving the test. The results of oncotype DX are divided into three groups: high-, intermediate-, and low-risk. For high- and low-risk patients, endocrine therapy followed by CHT or endocrine therapy alone can be selected according to the guideline, but the systematic treatment for the intermediate-risk population (26–30 points), which accounts for about 22–36% (9,10), is still unclear (6). Notably, in the TAILORx study, due to the redefinition of the criteria for risk grouping (intermediate risk: 11–25 points), the intermediate-risk cohorts accounted for 67.3% (11). For intermediate-risk patients, even after 21-gene testing, it is still unclear whether they could benefit from CHT. However, the results of the TAILORx study on 21-gene detection in these patients showed that endocrine therapy was not inferior to CHT; meanwhile, some patients ≤50 years in this cohort could still benefit from CHT (11). The clinical utility of the 70-gene signature (MammaPrint®) to guide CHT use in T1–3N0–1 breast cancer was demonstrated in the Microarray in Node-Negative and one to three Positive Lymph Node Disease May Avoid CHT (MINDACT) study, and its clinical risk stratification was based on the modified adjuvant! Online. The evaluation index did not include factors such as age or tumor thrombus (12,13), so the so-called "low risk" and "high risk" need to be considered individually. Based on the above reasons, constructing a simple clinical prediction model independent of gene testing for patients without clear stratification of gene testing is crucial.

In this study, we conducted a retrospective analysis of the HR+, HER2−, T1–3N0–1 breast cancer population in the Surveillance, Epidemiology, and End Results (SEER) database. Patients were matched using propensity score matching (PSM), and a nomogram was then built to predict BCSS among patients without CHT, and each patient was scored using the nomogram. Finally, the risk degree was stratified using X-tile, which could help clinicians to classify patients more reasonably, target CHT to those patients who will benefit most, and avoid CHT in patients who are at low risk of recurrence and would therefore obtain limited absolute benefit. Compared to existing articles focused on gene testing, we believe that this study can provide a cheaper, and more convenient and practical tool to individually estimate the survival risk of HR+, HER2−, T1–3N0–1 breast cancer patients and help make decisions on CHT.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5937).

Methods

Cohort selection

Data from the SEER database were required to identify female patients aged between 18 and 85 years old who were diagnosed with HR+, HER2−, T1–3N0–1 [American Joint Committee on Cancer seventh edition (AJCC T, 7th ed.)] invasive breast cancer as their only and primary cancer from January 1, 2010 to December 31, 2015. The detailed exclusion criteria are illustrated in *Figure 1*. Briefly, patients with <3 months' survival or unknown follow-up, and with unknown or unspecified variable's information were excluded. After exclusion, 144,735 patients were included in this study. Patients included in this study were divided into a CHT group (n=38,392) and a no CHT group (n=106,343). The number of cases in the area during the study period determined the sample size. Follow-up information came from the SEER database. Patients who were lost to follow-up were excluded from this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables involved in this study were as follows: demographic characteristics (age at diagnosis, race, marital status), disease characteristics (tumor location, grade, T stage, and number of positive nodes), treatment characteristics (breast surgery type, CHT, and radiotherapy), survival status (survival time and cause of death) and follow-up months. Based on the code information in SEER, we divided tumor location into three groups (outer quadrant, inner quadrant, and others).

Statistical analysis

The clinicopathological characteristics between the CHT

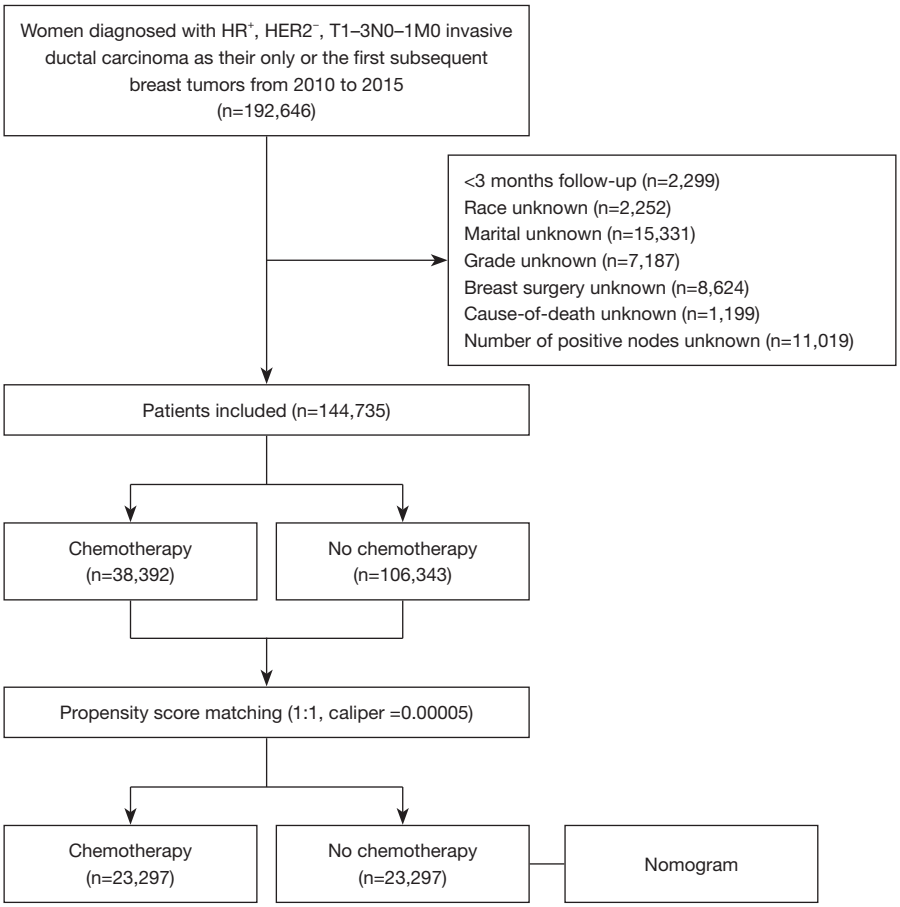

Figure 1 Patient selection flowchart. HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

and no CHT groups were compared using the Pearson's χ^2 test or Student's *t*-test. To eliminate the obvious differences between the baseline of variables and inherent selection bias, we conducted a PSM analysis between patients who underwent CHT and those who did not (using 1:1 nearest neighbor matching with a caliper of 0.00005). PSM is a tool for narrowing the selection bias in non-randomized studies and achieving balanced variables across treatment groups (14-16). We used the Cox regression hazard model to predict the impact of variables on survival outcomes.

The primary endpoint of this study was BCSS and the secondary endpoint was OS. BCSS was defined as the time from the date of diagnosis to the date of death attributed to breast cancer and was calculated using the cause-specific death classification in the SEER database. OS was defined as the time from the date of diagnosis to death due to any cause. The Kaplan-Meier plot and log-rank test were utilized to compare OS and BCSS between the different groups. Subsequently, a nomogram was developed to predict 3- and 5-year BCSS for the no CHT group by incorporating independent prognostic factors identified by the multivariate Cox analysis. Internal validation in the no CHT group and external validation in the CHT group were performed to evaluate the accuracy of the nomogram using the bootstrap validation method with 1,000 resamples. The concordance index (C-index) was applied to measure the discrimination of the model. The consistency between the actual observed outcomes and the nomogram predicted survival probability was estimated by calibration curves. Patients were divided into high- or low-risk groups according to their nomogram score using X-tile (version 3.4.7, Yale University).

Analyses were conducted by STATAMP, version 16.0 (StataCorp LP, College Station, TX, USA) and the packages (rms, hmisc, survival, etc.) in R software version 3.6.1 (https://www.r-project.org). Statistical significance was determined with a two-tailed $P<0.05$.

Results

Characteristics of eligible patients and analysis of survival benefits from CHT before PSM

A cohort of 144,735 female patients (including 38,392 in the CHT group and 106,343 in the no CHT group) were involved in this analysis. Before PSM, there were statistically significant differences in demographic and disease characteristics between the CHT and no CHT groups, including age, race, marital status, tumor location, nuclear grade, T stage, tumor size, N stage, number of positive nodes, and breast surgery (all P<0.001) (*Table 1*). Patients in the CHT group were younger, had higher nuclear grade, larger tumor size, more lymph node metastasis, etc.

As shown in the Kaplan-Meier plot, among the unmatched patients, those in CHT group had a better OS [hazard ratio =0.908; 95% confidence interval (CI): 0.861 to 0.958; P=0.00041], but had worse BCSS (hazard ratio =2.529; 95% CI: 2.342 to 2.731; P<0.0001) (*Figure 2A,2B*).

Analysis of survival benefits from CHT after PSM

After PSM, there were no significant differences in the demographic and disease characteristics between the CHT and no CHT groups. In total, 23,297 pairs of patients were included in the next analysis step (after PSM). The baseline characteristics (after PSM) (caliper =0.00005) are shown in *Table 1*.

After PSM, the CHT group still had a better OS, and the difference was more obvious than before (hazard ratio =0.663; 95% CI: 0.611 to 0.719; P<0.0001). However, there was no significant difference in BCSS between the CHT and no CHT groups in the matched cohort (hazard ratio =1.005; 95% CI: 0.897 to 1.126; P=0.93) (*Figure 2C,2D*).

Survival-related risk factors in patients without CHT

Genetic testing suggests that there must be patients who could benefit from CHT; however, the total population has not benefited from CHT significantly, so we can conclude that there must be some patients who cannot benefit from CHT. In order to classify accurately, univariate and multivariate Cox proportional hazards regression associated with BCSS was performed in the no CHT patients. In the univariate cox model, 11 variables were identified as significant risk factors for BCSS (P<0.05): age, race, marital, tumor location, T stage, tumor size, N stage, number of positive nodes, nuclear grade, breast surgery type, and radiation. In the multivariate cox model, eight variables were identified as significant risk factors for BCSS (P<0.05): age, race, marital, tumor size, number of positive nodes, nuclear grade, breast surgery type, and radiation (*Table 2*).

Table 1 Demographic and disease characteristics between the CHT and no CHT cohorts before and after PSM

Variables	Overall	Before PSM			After PSM		
		No CHT	CHT	P value	No CHT	CHT	P value
N	144,735	106,343	38,392		23,297	23,297	
Age, n (%)				<0.001			0.926
<35	1,888 (1.3)	519 (0.5)	1,369 (3.6)		253 (1.1)	261 (1.1)	
30–59	63,580 (43.9)	38,954 (36.6)	24,626 (64.1)		12,937 (55.5)	12,950 (55.6)	
>60	79,267 (54.8)	66,870 (62.9)	12,397 (32.3)		10,107 (43.4)	10,086 (43.3)	
Race, n (%)				<0.001			0.511
White	118,159 (81.6)	88,103 (82.8)	30,056 (78.3)		19,075 (81.9)	19,034 (81.7)	
Black	12,622 (8.7)	8,297 (7.8)	4,325 (11.3)		2,106 (9.0)	2,175 (9.3)	
AIA/API	13,954 (9.6)	9,943 (9.3)	4,011 (10.4)		2,116 (9.1)	2,088 (9.0)	
Marital, n (%)				<0.001			0.795
Unmarried	55,884 (38.6)	42,458 (39.9)	13,426 (35.0)		8,401 (36.1)	8,429 (36.2)	
Married	88,851 (61.4)	63,885 (60.1)	24,966 (65.0)		14,896 (63.9)	14,868 (63.8)	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Overall	Before PSM			After PSM		
		No CHT	CHT	P value	No CHT	CHT	P value
Tumor location, n (%)				<0.001			0.958
Outer	62,693 (43.3)	46,010 (43.3)	16,683 (43.5)		10,189 (43.7)	10,205 (43.8)	
Inner	28,480 (19.7)	21,610 (20.3)	6,870 (17.9)		4,159 (17.9)	4,173 (17.9)	
Others[a]	53,562 (37.0)	38,723 (36.4)	14,839 (38.7)		8,949 (38.4)	8,919 (38.3)	
Grade, n (%)				<0.001			0.823
I	47,013 (32.5)	41,814 (39.3)	5,199 (13.5)		3,852 (16.5)	3,897 (16.7)	
II	71,743 (49.6)	53,374 (50.2)	18,369 (47.8)		12,442 (53.4)	12,387 (53.2)	
III/IV[b]	25,979 (17.9)	11,155 (10.5)	14,824 (38.6)		7,003 (30.1)	7,013 (30.1)	
T, n (%)				<0.001			0.972
T1	102,808 (71.0)	84,932 (79.9)	17,876 (46.6)		13,287 (57.0)	13,287 (57.0)	
T2	37,111 (25.6)	19,746 (18.6)	17,365 (45.2)		9,019 (38.7)	9,029 (38.8)	
T3	4,816 (3.3)	1,665 (1.6)	3,151 (8.2)		991 (4.3)	981 (4.2)	
Tumor size (cm), n (%)				<0.001			0.999
0–1	44,665 (30.9)	40,793 (38.4)	3,872 (10.1)		3,168 (13.6)	3,162 (13.6)	
1–2	58,143 (40.2)	44,139 (41.5)	14,004 (36.5)		10,119 (43.4)	10,125 (43.5)	
2–3	25,398 (17.5)	14,424 (13.6)	10,974 (28.6)		6,298 (27.0)	6,327 (27.2)	
3–4	8,265 (5.7)	3,864 (3.6)	4,401 (11.5)		2,005 (8.6)	1,997 (8.6)	
4–5	3,448 (2.4)	1,458 (1.4)	1,990 (5.2)		716 (3.1)	705 (3.0)	
>5	4,816 (3.3)	1,665 (1.6)	3,151 (8.2)		991 (4.3)	981 (4.2)	
N, n (%)				<0.001			0.134
N0	112,335 (77.6)	93,734 (88.1)	18,601 (48.5)		15,069 (64.7)	14,913 (64.0)	
N1	32,400 (22.4)	12,609 (11.9)	19,791 (51.5)		8,228 (35.3)	8,384 (36.0)	
Number of positive node, n (%)				<0.001			0.998
0	112,723 (77.9)	93,757 (88.2)	18,966 (49.4)		15,075 (64.7)	15,065 (64.7)	
1	20,500 (14.2)	9,377 (8.8)	11,123 (29.0)		5,896 (25.3)	5,910 (25.4)	
2	7,745 (5.4)	2,357 (2.2)	5,388 (14.0)		1,725 (7.4)	1,718 (7.4)	
3	3,767 (2.6)	852 (0.8)	2,915 (7.6)		601 (2.6)	604 (2.6)	
Breast surgery, n (%)				<0.001			0.903
Lumpectomy	94,731 (65.5)	74,948 (70.5)	19,783 (51.5)		13,509 (58.0)	13,495 (57.9)	
Mastectomy	50,004 (34.5)	31,395 (29.5)	18,609 (48.5)		9,788 (42.0)	9,802 (42.1)	
Radiation, n (%)				0.218			0.717
No/unknown	60,046 (41.5)	44,016 (41.4)	16,030 (41.8)		11,064 (47.5)	11,024 (47.3)	
Yes	84,689 (58.5)	62,327 (58.6)	22,362 (58.2)		12,233 (52.5)	12,273 (52.7)	
Survival months, mean (SD)	43.45 (21.17)	43.00 (21.12)	44.71 (21.25)	<0.001	42.54 (21.05)	45.07 (21.36)	<0.001

[a], "others" includes "central portion of breast", "breast includes nipple", and "overlapping lesion of breast such as 3, 6, 9, 12 o'clock" as recorded in the SEER database; [b], "IV" represents undifferentiated. CHT, chemotherapy; PSM, propensity score matching; AIA, American Indian/Alaska Native; API, Asian or Pacific Islander; SEER, Surveillance, Epidemiology, and End Results.

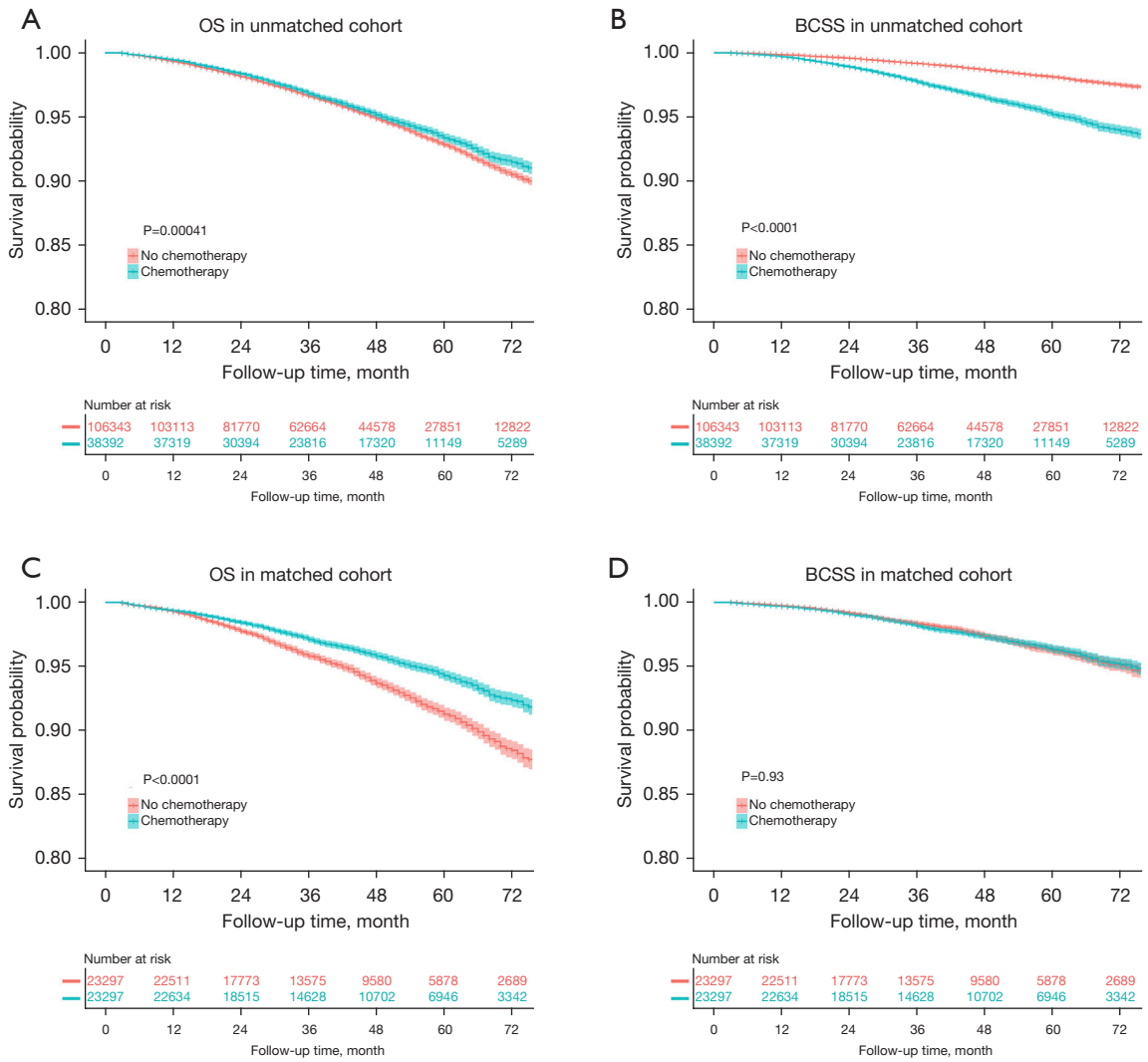

Figure 2 OS (A,C) and BCSS (B,D) of patients with and without CHT before and after PSM. OS, overall survival; BCSS, breast cancer-specific survival; CHT, chemotherapy; PSM, propensity score matching.

Construction and validation of the nomogram

In the previous survival analysis, we found patients with CHT had better OS in the matched patient cohort, but there was no significant difference in BCSS. Obviously, compared with OS, BCSS can more objectively reflect the benefits of CHT in patients. The reason why BCSS showed no differences between CHT and no CHT patients may be explained by the fact that CHT cannot improve survival for some patients. In fact, some patients may even experience increased CHT-related complications. However, there are some people who could benefit from CHT but do not receive CHT. We constructed a nomogram to predict the 3- and 5-year BCSS for patients without CHT using the independent risk factors identified in the multivariate Cox analysis (age, race, marital, grade, tumor size, number of positive nodes, breast surgery type, and radiation) in order to identify the population who can benefit from CHT and those who cannot (*Figure 3*). According to the point scale in the nomogram, a total point can be calculated by adding all points based on the patient's individual clinicopathological characteristics. A lower score was considered to have a better prognosis. By comparing the survival outcomes predicted by the nomograms, clinicians and patients can weigh the risk-benefit gained from CHT and make a tailored decision.

Table 2 Univariate and multivariate Cox models for patients without CHT (BCSS)

Variables	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age		<0.001		<0.001
<35	Ref		Ref	
35–59	2.007 (0.498, 8.078)	0.327	2.007 (0.498, 8.078)	0.399
60–85	4.595 (1.145, 18.443)	0.031	4.595 (1.145, 18.443)	0.095
Race		<0.001		0.022
White	Ref		Ref	
Black	1.402 (1.092, 1.800)	0.008	1.402 (1.092, 1.800)	0.114
AIA/API	0.606 (0.417, 0.882)	0.009	0.606 (0.417, 0.882)	0.044
Marital		<0.001		0.001
Unmarried	Ref		Ref	
Married	0.590 (0.501, 0.695)	<0.001	0.590 (0.501, 0.695)	0.001
Tumor location		0.115		–
Outer	Ref		–	
Inner	1.068 (0.843, 1.352)	0.585	–	–
Others[a]	1.209 (1.009, 1.449)	0.039	–	–
T		<0.001		–
T1	Ref		–	
T2	3.022 (2.516, 3.629)	<0.001	–	–
T3	5.012 (3.737, 6.721)	<0.001	–	–
Tumor size (cm)		<0.001		<0.001
<1	Ref		Ref	
1–2	1.763 (1.170, 2.658)	0.007	1.490 (0.988, 2.248)	0.057
2–3	3.889 (2.600, 5.816)	<0.001	2.803 (1.868, 4.205)	<0.001
3–4	6.760 (4.423, 10.333)	<0.001	4.618 (3.007, 7.094)	<0.001
4–5	7.307 (4.473, 11.937)	<0.001	5.104 (3.102, 8.399)	<0.001
>5	7.902 (5.017, 12.446)	<0.001	6.714 (4.214, 10.696)	<0.001
N		<0.001		–
N0	Ref		–	
N1	1.864 (1.581, 2.197)	<0.001	–	–
No. of positive nodes		<0.001		<0.001
0	Ref		Ref	
1	1.512 (1.247, 1.833)	<0.001	1.816 (1.491, 2.211)	<0.001
2	2.446 (1.907, 3.137)	<0.001	2.318 (1.799, 2.987)	<0.001
3	3.553 (2.552, 4.946)	<0.001	2.743 (1.967, 3.845)	<0.001

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Univariate		Multivariate	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Nuclear grade		<0.001		<0.001
Well	Ref		Ref	
Moderately	1.542 (1.093, 2.177)	0.014	1.354 (0.958, 1.914)	0.086
Poorly	4.739 (3.402, 6.601)	<0.001	4.466 (3.188, 6.256)	<0.001
Breast surgery		<0.001		0.008
Lumpectomy	Ref		Ref	
Mastectomy	1.401 (1.189,1.652)	<0.001	0.761 (0.622, 0.932)	0.008
Radiation		<0.001		<0.001
No/unknown	Ref		Ref	
Yes	0.555 (0.469, 0.658)	<0.001	0.549 (0.448, 0.671)	<0.001

[a], "others" includes "central portion of breast", "breast includes nipple", and "overlapping lesion of breast such as 3, 6, 9, 12 o'clock" as recorded in the SEER database. CHT, chemotherapy; BCSS, breast cancer-specific survival; CI, confidence interval; Ref, reference; AIA, American Indian/Alaska Native; API, Asian or Pacific Islander; SEER, Surveillance, Epidemiology, and End Results.

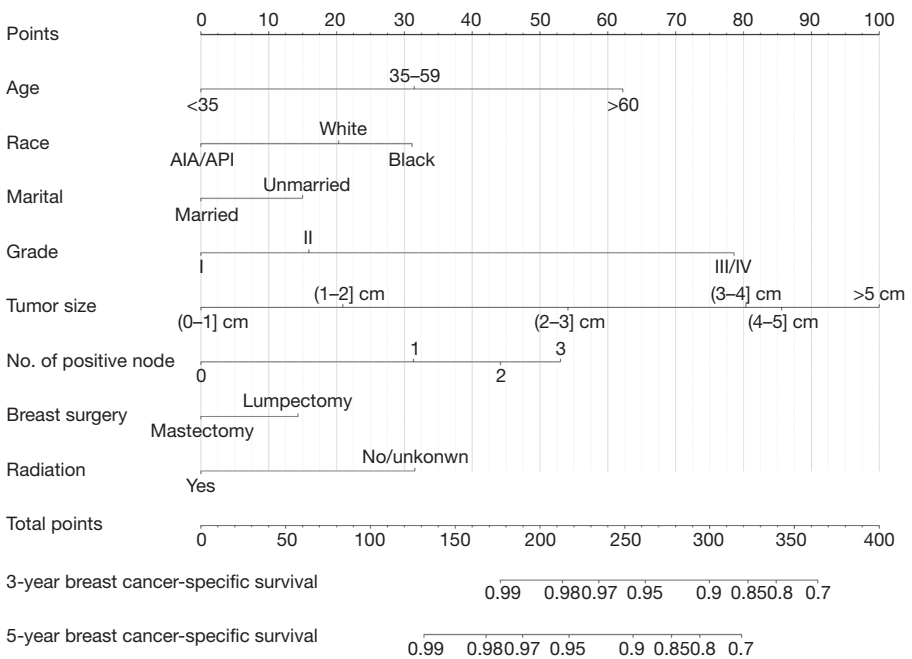

Figure 3 Nomogram for predicting the 3- and 5-year BCSS in pT1–3N0–1 breast cancer patients with HR+, HER2– subtypes who did not receive CHT. BCSS, breast cancer-specific survival; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CHT, chemotherapy; AIA, American Indian/Alaska Native; API, Asian or Pacific Islander.

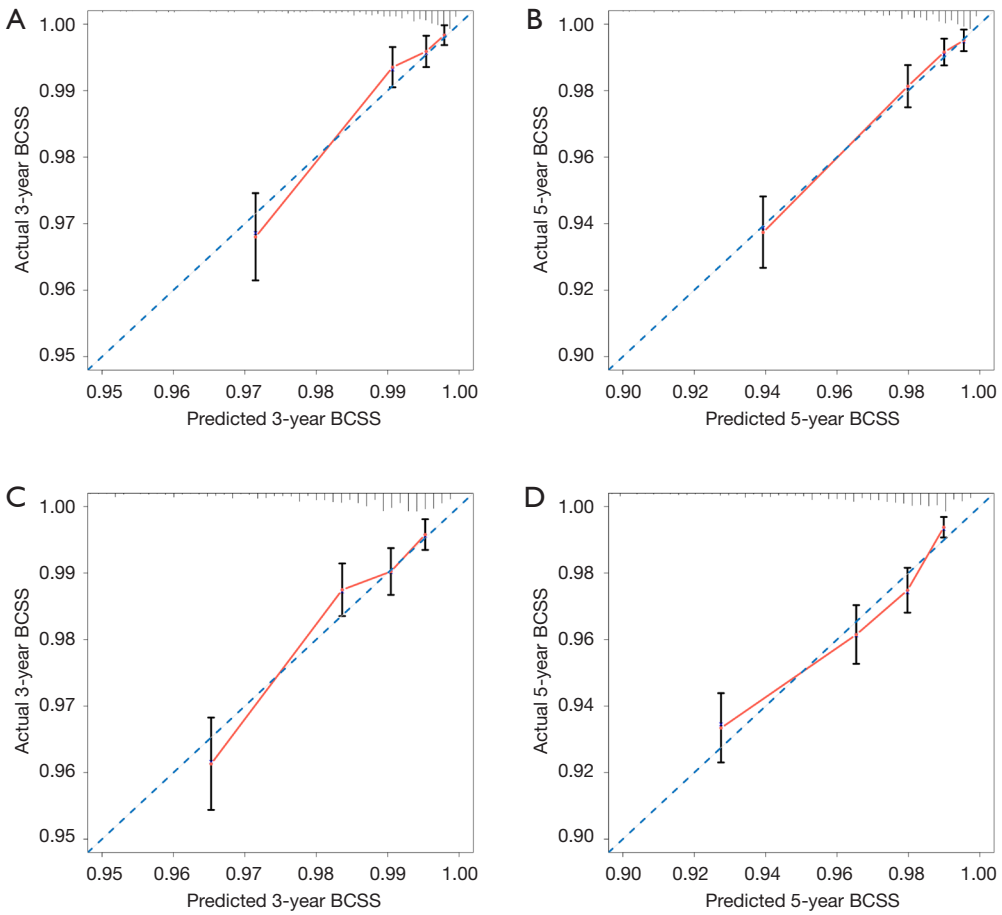

Figure 4 Calibration curves for nomograms: internal validation (A,B) and external validation (C,D) for 3-, 5-year BCSS. The blue dotted line represents the ideal reference and the red lines represent the nomogram-predicted probabilities for each group. BCSS, breast cancer-specific survival.

The baseline between patients with and without CHT was well balanced after PSM, so the two cohorts conformed to the random cohorts. Therefore, the nomogram was validated internally and externally using the no CHT cohort (training set) and the CHT cohort (validation set). The C-index was 0.794 (95% CI: 0.774 to 0.814) in the internal validation and 0.736 (95% CI: 0.716 to 0.756) in the external validation. Calibration curves showed high consistency between the observed and nomogram-predicted outcomes (*Figure 4*). Both the internal and external validation demonstrated the sufficient accuracy of the model.

Risk group stratification based on nomogram score

The nomogram could calculate the risk score for each patient, and then all patients were divided into two groups using X-tile: risk scores ≤238 were classified as the low-risk group (n=39,962, 85.77%) and >238 were classified as the high-risk group (n=6,632, 14.23%) (*Figure 5*). Interestingly, Kaplan-Meier plots showed that in the low-risk group, patients who received CHT had better OS (hazard ratio =0.718; 95% CI: 0.649 to 0.794; P<0.0001) but had worse BCSS (hazard ratio =1.216; 95% CI: 1.046 to 1.414; P=0.011). However, in the high-risk group, patients with CHT had better OS (hazard ratio =0.583; 95% CI: 0.507 to 0.671; P<0.0001) and BCSS (hazard ratio =0.791; 95% CI: 0.663 to 0.944; P=0.0091) (*Figure 6*). These results indicated that patients in the high-risk group could benefit from CHT while those in the low-risk group should eschew CHT to avoid unnecessary side effects.

Discussion

After screening and analyzing the data from the SEER

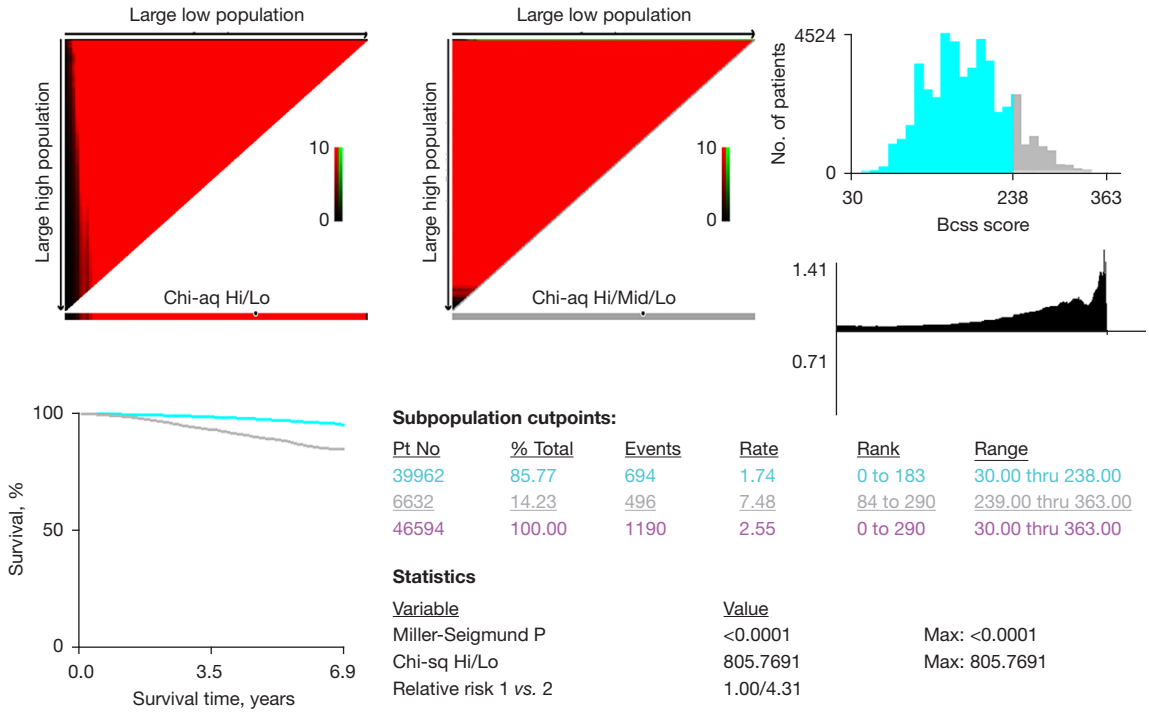

Figure 5 Risk stratification of the patients with the nomogram score cutting by X-tile.

database, eight independent prognostic factors (age, race, marital, grade, tumor size, number of positive nodes, breast surgery type, and radiation) were included to build the nomogram to predict patients' BCSS. Next, X-tile was used to find a binary critical point of the risk model, which could help T1–3N0–1 breast cancer patients with HR+, HER2− judge whether CHT is necessary. We were surprised to find that CHT should be recommended for high-risk patients, but patients in the low-risk group may receive endocrine monotherapy because no benefit was gained from CHT, which may help in clinical practice. Therefore, patients can be divided into two groups: those who require CHT and those that do not, without an intermediate-risk group. For low-risk patients, CHT may not improve survival but will increase the burden of patients, and is more likely to result in CHT-related complications and side effects. For high-risk patients, CHT can provide survival benefits. For patients who do not receive genetic testing, or whose test results are at medium risk, the model proposed in this study plays a complementary role.

In this study, before PSM, the OS of the CHT group was better than that of the no CHT group. The possible reasons for this are as follows: firstly, the underlying diseases and baseline of the two groups are inconsistent (the no CHT group had more patients >60 years old); secondly, compared with patients without CHT, CHT group patients may have fewer underlying diseases, so the better OS of CHT group may not be completely attributed to the effect of CHT. The BCSS of CHT group was worse than that of no CHT group, which may be due to the fact that patients in the CHT group had larger tumors and a higher stage.

After PSM, the CHT group had better OS benefit when the baseline (demographic and clinical characteristics) of the two groups was well balanced, but there was no difference in the BCSS between the two groups. However, the underlying diseases of patients in this study could not be obtained from the database. The results seem to suggest that CHT cannot improve the BCSS of this population; however, this does not mean that these people do not require CHT. As the results of genetic testing suggest, because high-risk groups can benefit from CHT, and our conclusion is that the overall population does not benefit, it is likely that some patients benefit, while others are damaged by CHT. This is why we hope to achieve precise treatment as much as possible through accurate classification.

Many clinical trials and retrospective analyses have confirmed that some patients with HR+, HER2− early breast cancer can benefit from CHT (17-19). For instance,

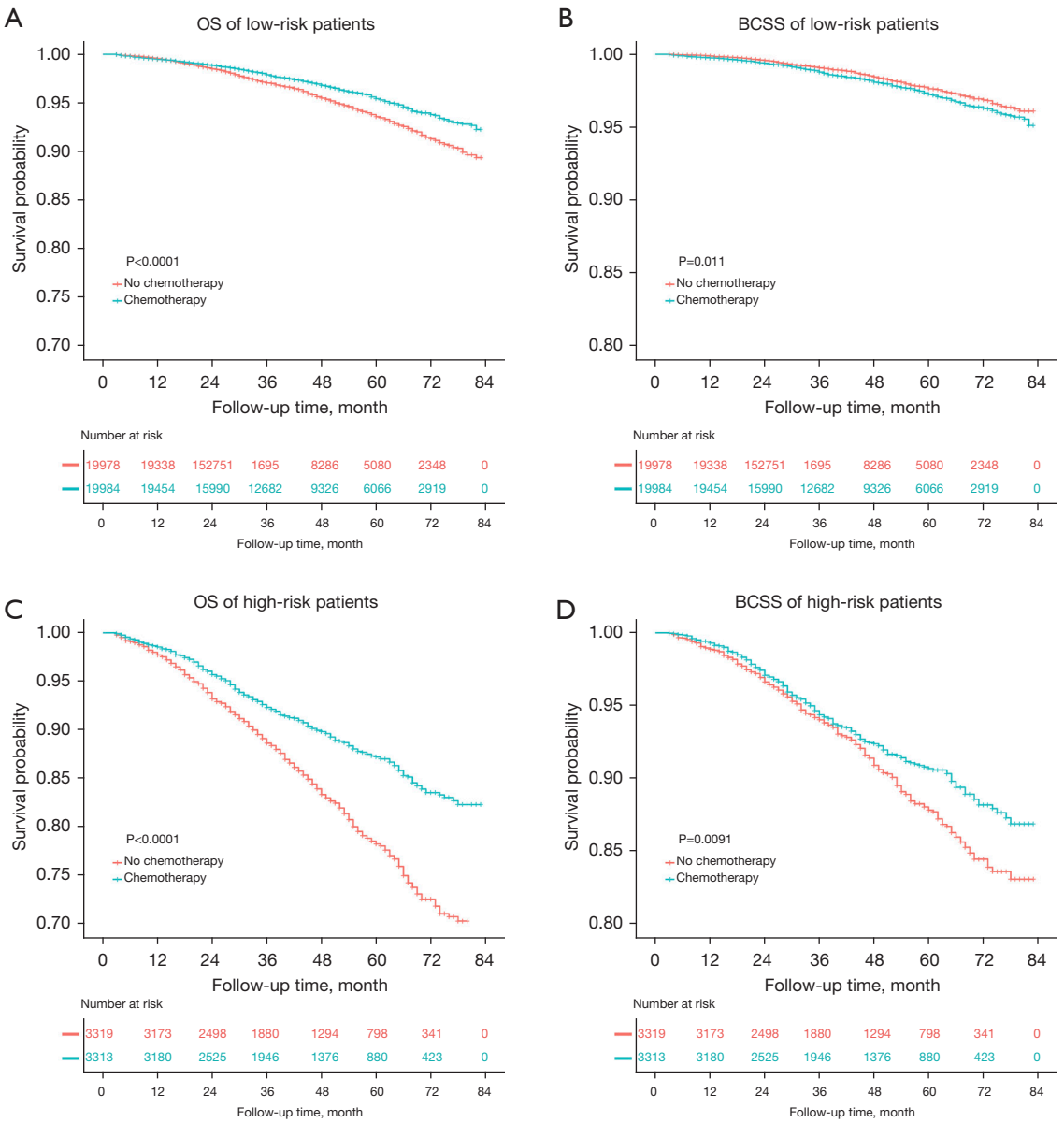

Figure 6 Survival benefit of CHT in different risk groups. (A) OS in the low-risk group; (B) BCSS in the low-risk group; (C) OS in the high-risk group; (D) BCSS in the high-risk group. CHT, chemotherapy; OS, overall survival; BCSS, breast cancer-specific survival.

the ongoing Southwest Oncology Group (SWOG) S1007 RxPONDER trial (20) assigned women with 1–3 lymph node-positive nodes, HR^+, $HER2^-$ breast cancer and a recurrence score (RS) ≤25 to standard endocrine therapy with or without adjuvant CHT. This trial expects to determine the benefit (if any) of CHT for patients in this cohort. Based on the results of our study that there is no difference in BCSS between the CHT and no CHT groups, we speculate that CHT can provide a better BCSS for some high-risk patients, but does not benefit low-risk groups.

In order to precisely identify who can benefit from CHT, we have used a nomogram and X-tile to identify the low- and high-risk groups in this study. The results showed that CHT did not improve the survival of low-risk patients, and the BCSS was slightly damaged. We speculated that breast cancer-related death may be caused by CHT-related injuries (such as CHT-related pneumonia and CHT-related myelosuppression), and thus, these patients should cease

CHT. For high-risk patients, CHT can provide obvious BCSS benefits, and the OS benefit is further increased (hazard ratio decreased from 0.663 to 0.583); therefore, so this perspective, CHT is necessary for these people.

In recent years, there have been a number of single- and multi-center retrospective analyses to discuss whether patients with HR+, HER2− early breast cancer need adjuvant CHT according to the clinicopathological factors (12,21,22). In a population-based study from British Columbia, most of the 1,187 T1–2N0 early breast cancer patients without adjuvant systemic therapies (>70%) did not have locoregional or distant recurrence within 10 years after diagnosis (22), which indicates that a considerable proportion of patients with HR+, HER2− early breast cancer can avoid CHT without sacrificing the curative effect. Another study combined clinicopathological factors with gene test results to determine whether CHT is necessary (23), which showed that the two methods had their own advantages and complemented each other. There were also some studies that aimed to replace Oncotype DX by constructing imaging or clinical indicators model equations (8,24). However, most of these were single-center studies and were limited by the sample size and follow-up time, so the results were somewhat inconsistent and unreliable. The risk model proposed in this study is a supplement to the existing methods for clinicians and patients, and is the largest retrospective analysis of early breast cancer population with T1–3N0–1, HR+, and HER2−. Besides, optimal cutoff for the dataset determined using X-Tile is more objective.

This study also had some limitations that should be noted. For example, we could not obtain information of ki-67, endocrine therapy and CHT regimen from the SEER database. The current AC (anthracycline and cyclophosphamide), T (paclitaxel) C or AC-T CHT for HR+, HER2− early breast cancer patients (6) are widely used. And the CHT regimens used for some of the patients in the cohort are no longer a preferred treatment. Therefore, our analysis may underestimate the health benefits of current CHT regimens. Besides, the missing information of basic diseases, which could affect the CHT decision-making of doctors and patients, were considered to be potential confounders. This study is a retrospective analysis. Although the baseline of the two groups was balanced by PSM, it needs to be further confirmed by multi-center clinical trials. Although the baseline of the two groups was balanced by PSM, the retrospective nature of this study could not replace a randomized controlled trial (RCT).

It is worth noting that the nomogram and risk model constructed in this study have been verified by survival analysis, which played an effective role in deciding whether to undergo CHT or not for HR+, HER2− early breast cancer patients, and we expect it could be useful for the design of future RCT experiments.

Conclusions

In conclusion, breast cancer patients with HR+, HER2− subtypes and stage pT1–3N0–1 may benefit from CHT if they are in the high-risk group, as estimated by the risk stratification model (risk score >238). However, patients in the low-risk group (risk score ≤238) may be exempt from CHT.

Acknowledgments

The authors would like to thank the SEER database for providing valuable and public datasets.
Funding: This work was supported by the Department of Science and Technology of Sichuan Province, China (No. 2020YFS0199) and the Chengdu Science and Technology Bureau (No. 2019-YF05-01082-SN).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-5937

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5937). 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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(English Language Editor: A. Kassem)

Cite this article as: Wen N, Qiu J, Xu L, Wang Y, Zhang J, Xie Y, Lv Q, Du Z. Adjuvant chemotherapy guidance for pT1–3N0–1 breast cancer patients with HR+, HER2− subtype: a cohort study based on the SEER database. Ann Transl Med 2021;9(24):1779. doi: 10.21037/atm-21-5937

