Original Article

An exploratory study of whether axillary lymph node dissection can be avoided in breast cancer patients with positive lymph nodes

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Background: Breast cancer patients with positive axillary lymph nodes usually require axillary lymph node dissection (ALND), with many postoperative complications, such as lymphedema. For these patients, whether sentinel lymph node biopsy (SLNB) can replace ALND has been a research hotspot in the field of breast cancer. This study developed two risk stratification models for predicting the clinical outcomes of breast cancer patients with positive axillary lymph nodes receiving SLNB alone or ALND to determine which patients could potentially avoid ALND.

Methods: A total of 21,942 breast cancer patients, including a training set (n=15,362) and a testing set (n=6,580), were enrolled in this study from Surveillance, Epidemiology, and End Results (SEER) between 2000 and 2017. The risk factors associated with breast cancer-specific survival (BCSS) and overall survival (OS) were evaluated using multivariate Cox regression analysis and then integrated into nomograms and risk stratification models examined by receiver operating characteristic (ROC) curves and calibration curves. The survival discrepancies were compared between the SLNB and ALND subgroups with different risk scores with Kaplan-Meier plots.

Results: In multivariate Cox regression analyses, grade, marital status, T stage, radiotherapy and lymph node metastasis (GMTRL) were independent risk factors in breast cancer patients with both OS and BCSS status in the ALND cohort from the training set. Nomograms have been developed based on these factors to predict 3- and 5-year OS and BCSS in patients with ALND. Calibration curves and ROC curves in both the training and testing sets confirmed the excellent overall predictive performance of the nomograms. Furthermore, we developed two risk stratification models based on OS and BCSS status, revealing that patients with low GMTRL scores might avoid ALND in both OS and BCSS status [OS: hazard ratio (HR) =0.929, 95% confidence interval (CI): 0.841–1.027, P=0.150; BCSS: HR =0.953, 95% CI: 0.831–1.094, P=0.495], but patients with moderate (OS: HR =0.756, 95% CI: 0.666–0.859, P<0.001; BCSS: HR =0.643, 95% CI: 0.537–0.768, P<0.001) and high GMTRL scores could not (OS: HR =0.719, 95% CI: 0.549–0.940, P=0.014; BCSS: HR =0.731, 95% CI: 0.549–0.974, P=0.031).

Conclusions: Breast cancer patients with positive nodes could be treated with SLNB alone rather than ALND without affecting prognosis based on GMTRL scores. Patients with high or moderate GMTRL scores benefited greatly from ALND, but not for patients with low GMTRL scores. This study may assist clinicians in tailoring treatments.

Keywords: Breast cancer; sentinel lymph node biopsy (SLNB); axillary lymph node dissection (ALND); nomogram; risk stratification model

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Introduction

The most common malignant tumor in women worldwide is breast cancer, which has become a major threat to women's health (1). Both sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) are widely accepted nodal staging methods (2). SLNB is required for patients with clinically negative axillary lymph nodes (3-5). Patients with positive axillary lymph nodes commonly receive ALND, which maintains local lymph node control. However, ALND is notorious for its high risk of postoperative complications, such as lymphedema and decreased upper extremity motion, which have a significant impact on quality of life in patients with breast cancer (6-8). Determining which patients with positive axillary lymph nodes can receive SLNB alone instead of ALND has always been a research hotspot in the field of breast cancer surgery.

According to several analyses, the long-term survival outcomes for patients with sentinel node macrometastases were not significantly different between those who did not undergo ALND and those who did (3,9). The Z0011 trial in the American College of Surgeons Oncology Group (ACOSOG) used to be the first randomized managed scientific trial to determine whether patients with breast cancer, whose sentinel lymph nodes were positive, could be likely to avoid ALND (8). The trial showed that patients with T_{1-2} tumors who underwent breast-conserving treatment and postoperative radiotherapy could avoid ALND when the number of positive sentinel lymph nodes was one to two (10-12). There was also evidence that SLNB can safely replace ALND under certain conditions in other clinical trials (13,14). However, a conclusion has not yet been reached regarding the necessary conditions for patients with positive lymph nodes to receive SLNB alone rather than ALND.

In this study, clinicopathological statistics of breast cancer patients with positive nodes were accrued from the Surveillance, Epidemiology, and End Results (SEER) database. The survival outcomes of patients receiving SLNB versus ALND were analyzed and compared. Furthermore, we constructed nomograms to predict survival outcomes using risk stratification models to evaluate which patients can be safely exempted from ALND. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1639/rc).

Highlight box

Key findings

- We found that patients with moderate and high grade, marital status, T stage, radiotherapy and lymph node metastasis (GMTRL) scores benefited signifi cantly from axillary lymph node dissection (ALND), nevertheless, patients with low GMTRL scores did not differ significantly in survival outcomes between sentinel lymph node biopsy (SLNB) alone and ALND.

What is known and what is new?

- ALND is commonly performed in breast cancer patients with positive axillary lymph nodes, however, it has become notorious for its numerous side effects. Breast oncologists have been studying which patients with positive nodes may safely stay away from ALND.
- The innovation of this study is not only to provide nomograms predicting over all survival and breast cancer-specific survival of 3- and 5-year in breast can cer patients, but also to set up two risk stratified models based on GMTRL scores to quickly determine which patients with positive lymph nodes can be treated with SLNB alone instead of ALND without affecting prognosis.

What is the implication, and what should change now?

- This study finds that ALND can be avoided in breast cancer patients with low GMTRL scores, which plays a guiding role in our clinical treatments. More prospective randomized controlled trials are needed to confirm our conclusions in the future.

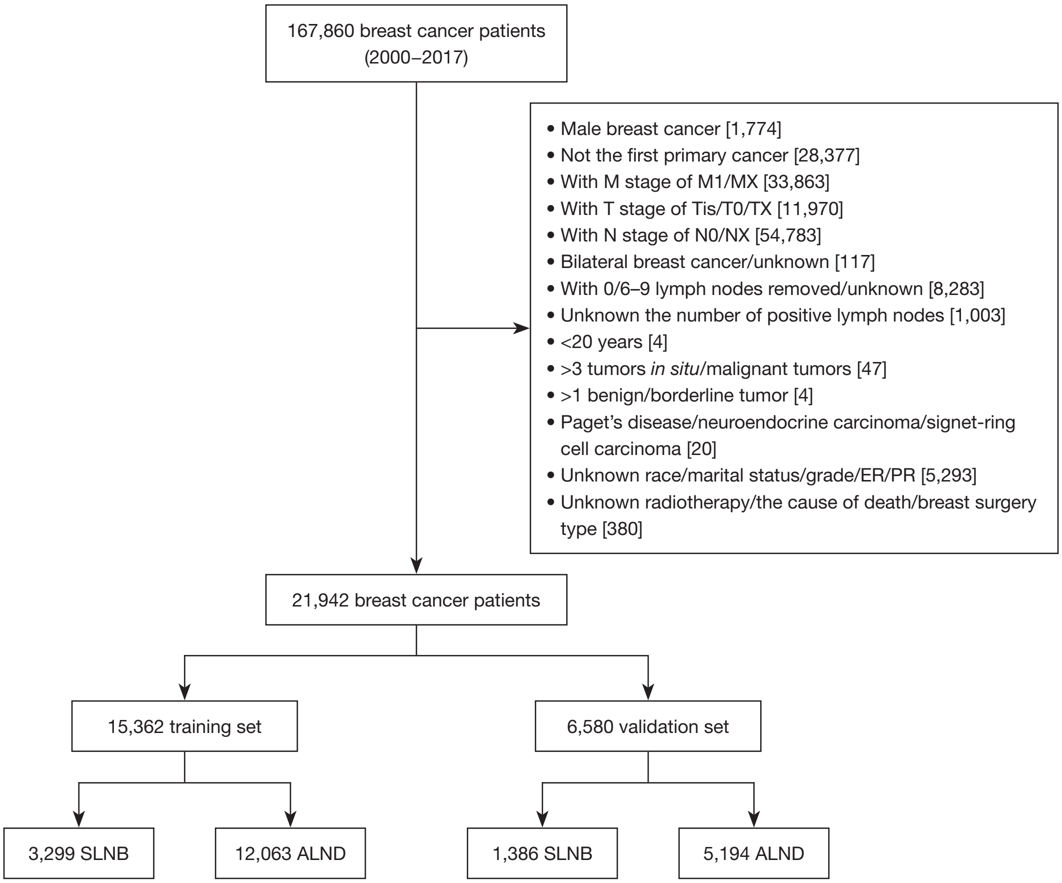

Figure 1 Flow chart for screening patients. ER, estrogen receptor; PR, progesterone receptor; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

Methods

Database and patient selection

We collected information on breast cancer patients from 17 cancer registries between 2000 and 2017 using SEER*Stat (version 8.4.0). The SEER database involved only public information, and the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The following variables were gathered from SEER*Stat: age, race, marriage, laterality, grade, histology, T stage, positive lymph nodes, breast surgery type, radiotherapy, chemotherapy and subtype, survival time and survival condition.

Age and number of positive lymph nodes were converted into categorical variables (age: <45, 45–59, ≥60 years; positive lymph nodes: 1–3, 4–6, 7–9, ≥10). Axillary surgery types were not clearly identified in the SEER database; therefore, we determined SLNB or ALND by counting the number of lymph nodes in the region. Based on previous studies (9,15), we defined SLNB as the resection of 1–5 lymph nodes and ALND as the resection of more than 10 lymph nodes. Due to unclear and controversy-ridden grades, patients with 6–9 lymph nodes removed were excluded. In addition, patients without lymph nodes examined and unknown numbers of removed nodes were excluded as well. Ultimately, a total of 21,942 breast cancer patients were blanketed for analyses, as illustrated in *Figure 1*.

Statistical analysis

Two groups of eligible patients were randomly assigned, namely, the training cohort and the validation cohort, based on a 7:3 ratio. Using the Pearson Chi-squared test, classification characteristics were compared. The results for this study included overall survival (OS) and breast cancer-specific survival (BCSS). According to SEER's cause-specific death classifications, OS refers to the time between diagnosis and death from any cause, whereas BCSS means the time from diagnosis to loss of life caused by breast cancer. Univariate and multivariate Cox regression analyses were carried out to assess independent factors influencing survival. Furthermore, Kaplan-Meier and log-rank assessments were used to evaluate the OS and BCSS of the SLNB and ALND groups. All elements with P<0.05 during univariate Cox evaluations were integrated into multivariate Cox analyses.

Survival analysis was conducted for the ALND group of the training set. Based on the results of multivariate Cox regression analyses, two nomograms were built to forecast the 3- and 5-year OS and BCSS of the ALND cohorts using risk factors. Nomograms were validated internally and externally in the training and validation cohorts, the accuracy of which was measured by 100 duplicate bootstrap validation methods. The discrimination of the models was measured through receiver operating characteristic (ROC) curves. Calibration curves were adopted to estimate the consistency between authentic outcomes and predicted survival probabilities. To predict prognosis, patients were categorized into low-, moderate-, and high-risk groups on the basis of the nomograms.

Data analyses were carried out with SPSS statistical software (version 26.0) and packages (rms, survival, etc.) in R software (version 4.2.1). To determine statistical significance, a two-tailed P<0.05 was applied.

Results

Patient characteristics

A normal variety of 21,942 patients were enrolled in this study, which had been segmented into the training cohort (n=15,362) and the validation cohort (n=6,580) at random. Baseline scientific traits no longer varied appreciably between the two corporations (*Table 1*). Among the 15,362 patients in the training set, 3,299 (21.5%) received SLNB alone, while 12,063 (78.5%) received ALND.

Construction and validation of nomograms

To detect multiple factors affecting OS and BCSS among the ALND group of the training set, univariate and multivariate Cox risk regression analyses were carried out (*Table 2*). Finally, grade, marital status, T stage, radiotherapy and lymph node metastasis (GMTRL) were integrated into nomograms to predict 3- and 5-year OS and BCSS

Table 1 Baseline characteristics of the enrolled population

Variables	All patients (n=21,942), n (%)	Training cohort (n=15,362), n (%)	Validation cohort (n=6,580), n (%)	P
Age				0.406[a]
<45 years	4,302 (19.6)	3,047 (19.8)	1,255 (19.1)	
45–59 years	9,009 (41.1)	6,373 (41.5)	2,636 (40.1)	
≥60 years	8,631 (39.3)	5,942 (38.7)	2,689 (40.9)	
Race				0.563
White	17,496 (79.7)	12,248 (79.7)	5,248 (79.8)	
Black	2,574 (11.7)	1,819 (11.8)	755 (11.5)	
Other[b]	1,872 (8.5)	1,295 (8.4)	577 (8.8)	
Laterality				0.477
Left	11,154 (50.8)	7,785 (50.7)	3,369 (51.2)	
Right	10,788 (49.2)	7,577 (49.3)	3,211 (48.8)	
Marriage				0.362
Married	13,104 (59.7)	9,144 (59.5)	3,960 (60.2)	
Not married[c]	8,838 (40.3)	6,218 (40.5)	2,620 (39.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	All patients (n=21,942), n (%)	Training cohort (n=15,362), n (%)	Validation cohort (n=6,580), n (%)	P
Grade				0.100
I	2,566 (11.7)	1,794 (11.7)	772 (11.7)	
II	9,640 (43.9)	6,682 (43.5)	2,958 (45.0)	
III & IV	9,736 (44.4)	6,886 (44.8)	2,850 (43.3)	
Histology[d]				0.902
Ductal carcinoma	15,476 (70.5)	10,835 (70.5)	4,641 (70.5)	
Lobular carcinoma	2,266 (10.3)	1,599 (10.4)	667 (10.1)	
Mixed carcinoma	3,182 (14.5)	2,215 (14.4)	967 (14.7)	
Other	1,018 (4.6)	713 (4.6)	305 (4.6)	
Stage T				0.660
T_{1-2}	16,547 (75.4)	11,572 (75.3)	4,975 (75.6)	
T_{3-4}	5,395 (24.6)	3,790 (24.7)	1,605 (24.4)	
LNM				0.574
1–3	13,462 (61.4)	9,393 (61.1)	4,069 (61.8)	
4–6	3,344 (15.2)	2,336 (15.2)	1,008 (15.3)	
7–9	1,762 (8.0)	1,255 (8.2)	507 (7.7)	
≥10	3,374 (15.4)	2,378 (15.5)	996 (15.1)	
Breast surgery type				0.705
No surgery[e]/BCS	4,396 (20.0)	3,088 (20.1)	1,308 (19.9)	
Mastectomy	17,546 (80.0)	12,274 (79.9)	5,272 (80.1)	
Radiotherapy				0.674
Yes	11,192 (51.0)	7,850 (51.1)	3,342 (50.8)	
No	10,750 (49.0)	7,512 (48.9)	3,238 (49.2)	
Chemotherapy				0.482
Yes	15,771 (71.9)	11,063 (72.0)	4,708 (71.6)	
No/unknown	6,171 (28.1)	4,299 (28.0)	1,872 (28.4)	
Subtype[f]				0.233
HR^+, $HER2^+$	1,104 (5.0)	762 (5.0)	342 (5.2)	
HR^+, $HER2^-$	6,510 (29.7)	4,529 (29.5)	1,981 (30.1)	
HR^-, $HER2^+$	445 (2.0)	294 (1.9)	151 (2.3)	
HR^-, $HER2^-$	720 (3.3)	505 (3.3)	215 (3.3)	
Unknown	13,163 (60.0)	9,272 (60.4)	3,891 (59.1)	

[a], obtained by the Cochran-Mantel-Haenszel test. [b], "other" includes American Indian, AK Native, Asian and Pacific Islander as recorded in the SEER database. [c], "Not Married" includes divorced, separated, single, unmarried or domestic partner and widowed. [d], "Mixed carcinoma" includes infiltrating duct mixed with other types of carcinoma, infiltrating lobular mixed with other types of carcinoma and infiltrating duct and lobular carcinoma; "Other" means histological types other than above three types. [e], "No surgery" means that the primary breast lesion is not operated on, and it is possible that only the axilla was operated on. [f], "HR" means the statuses of ER and PR: "HR+" means that the expression of ER or PR is positive; "HR–" means that the expressions of both ER and PR are negative; "Unknown" means unknown HER2 expression in the SEER database. LNM, lymph node metastasis; BCS, breast-conserving surgery; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.

Table 2 Univariate and multivariate Cox regression analyses of the ALND group in the training set

Characteristics	Univariate Cox regression analysis				Multivariate Cox regression analysis			
	OS		BCSS		OS		BCSS	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age								
<45 years	Reference		Reference		Reference		Reference	
45–59 years	0.970 (0.889–1.058)	0.489	0.844 (0.768–0.927)	<0.001	–		–	
≥60 years	2.092 (1.927–2.270)	<0.001	1.156 (1.052–1.271)	0.003	–		–	
Race								
White	Reference		Reference		Reference		Reference	
Black	1.443 (1.330–1.565)	<0.001	1.555 (1.411–1.715)	<0.001	–		–	
Other	0.949 (0.851–1.059)	0.353	1.074 (0.944–1.221)	0.280	–		–	
Laterality								
Left	Reference		Reference		Reference		Reference	
Right	1.002 (0.946–1.061)	0.951	1.011 (0.942–1.086)	0.759	–		–	
Marriage								
Married	Reference		Reference		Reference		Reference	
Not married	1.649 (1.556–1.746)	<0.001	1.410 (1.313–1.515)	<0.001	1.575 (1.486–1.669)	<0.001	1.342 (1.249–1.442)	<0.001
Grade								
I	Reference		Reference		Reference		Reference	
II	1.315 (1.172–1.476)	<0.001	1.775 (1.499–2.102)	<0.001	1.229 (1.095–1.380)	<0.001	1.603 (1.353–1.899)	<0.001
III & IV	1.962 (1.754–2.195)	<0.001	3.172 (2.691–3.739)	<0.001	1.733 (1.548–1.939)	<0.001	2.647 (2.245–3.122)	<0.001
Histology								
Ductal carcinoma	Reference		Reference		Reference		Reference	
Lobular carcinoma	1.090 (0.991–1.199)	0.077	1.031 (0.915–1.162)	0.612	–		–	
Mixed carcinoma	0.877 (0.805–0.956)	0.003	0.852 (0.765–0.948)	0.003	–		–	
Other	1.817 (1.623–2.034)	<0.001	1.933 (1.688–2.213)	<0.001	–		–	
Stage T								
$T_{1–2}$	Reference		Reference		Reference		Reference	
$T_{3–4}$	2.113 (1.989–2.244)	<0.001	2.523 (2.347–2.712)	<0.001	1.651 (1.547–1.762)	<0.001	1.781 (1.647–1.925)	<0.001
LNM								
1–3	Reference		Reference		Reference		Reference	
4–6	1.524 (1.404–1.654)	<0.001	1.852 (1.668–2.055)	<0.001	1.450 (1.334–1.576)	<0.001	1.677 (1.508–1.864)	<0.001
7–9	1.990 (1.812–2.184)	<0.001	2.459 (2.188–2.764)	<0.001	1.810 (1.644–1.992)	<0.001	2.097 (1.860–2.364)	<0.001
≥10	2.999 (2.796–3.216)	<0.001	4.348 (3.989–4.739)	<0.001	2.581 (2.394–2.782)	<0.001	3.465 (3.160–3.799)	<0.001
Breast surgery type								
No surgery/BCS	Reference		Reference		Reference		Reference	
Mastectomy	1.382 (1.273–1.501)	<0.001	1.549 (1.392–1.723)	<0.001	0.987 (0.906–1.076)	0.772	1.041 (0.932–1.164)	0.478

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariate Cox regression analysis				Multivariate Cox regression analysis			
	OS		BCSS		OS		BCSS	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Radiotherapy								
Yes	Reference		Reference		Reference		Reference	
No	1.064 (1.005–1.127)	0.034	0.895 (0.833–0.961)	0.002	1.326 (1.249–1.408)	<0.001	1.192 (1.107–1.283)	<0.001
Chemotherapy								
Yes	Reference		Reference		Reference		Reference	
No/Unknown	1.489 (1.398–1.585)	<0.001	0.965 (0.886–1.051)	0.417	–		–	
Subtype								
HR^+, $HER2^+$	Reference		Reference		Reference		Reference	
HR+, $HER2^-$	0.953 (0.788–1.153)	0.622	1.026 (0.811–1.298)	0.829	–		–	
HR^-, $HER2^+$	1.369 (1.018–1.840)	0.038	1.490 (1.041–2.133)	0.029	–		–	
HR^-, $HER2^-$	2.843 (2.271–3.559)	<0.001	3.474 (2.654–4.548)	<0.001	–		–	
Unknown	1.277 (1.068–1.526)	0.007	1.425 (1.142–1.778)	0.002	–		–	

HR, the statuses of ER and PR: HR^+, the expression of ER or PR is positive; HR^-, the expressions of both ER and PR are negative. ALND, axillary lymph node dissection; OS, overall survival; BCSS, breast cancer-specific survival; CI, confidence interval; LNM, lymph node metastasis; BCS, breast-conserving surgery; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor.

in patients with ALND (*Figure 2A,2B*). Each variable was scored according to the scoring scales of each nomogram (*Table 3*), and the sum of the scores could predict patients' 3- and 5-year OS and BCSS by assessing the clinical factors. The credibility of the nomograms was judged by internal and external validation of the training and validation sets. Model predictions and observations matched well on calibration curves for 3- and 5-year OS and BCSS (*Figure 3*). Figure S1 displays the ROC curves for the two nomogram prediction models verified both internally and externally. Both internal and external validation indicated that these models were sufficiently accurate.

Survival benefits in different GMTRL risk scores

To further differentiate which patients were eligible for SLNB alone rather than ALND and which patients were not, we set up two risk stratification models on the basis of the two nomograms forecasting OS and BCSS of the ALND group in the training set. According to the total scores of the nomograms, we defined low GMTRL scores (OS: total score ≤105, BCSS: total score ≤107), moderate GMTRL scores (OS: 106≤ total score ≤188, BCSS: 108≤ total score ≤160) and high GMTRL scores (OS: total score ≥189, BCSS: total score ≥161). The OS and BCSS of patients receiving ALND in the training set were significantly different among these three GMTRL score groups (*Figure 4A,4B*).

The ALND group in the training set and all the SLNB groups from both the training and validation sets constituted a new dataset, which was categorized into low GMTRL score groups (OS: 9,348/16,748; BCSS: 9,804/16,748), moderate GMTRL score groups (OS: 5,390/16,748; BCSS: 3,855/16,748) and high GMTRL score groups (OS: 2,010/16,748; BCSS: 3,089/16,748) based on the two risk stratification models. To minimize determination bias and stability of the baseline between the SLNB and ALND groups, propensity score matching (PSM) was carried out in the low, moderate, and high GMTRL score cohorts, with a caliper width of 0.02 and a ratio of 1:1 barring replacement. Figure S2 shows the propensity score distributions for paired versus unpaired patients. Kaplan-Meier plots (*Figure 5A-5F*) revealed that ALND significantly increased the survival time for patients with

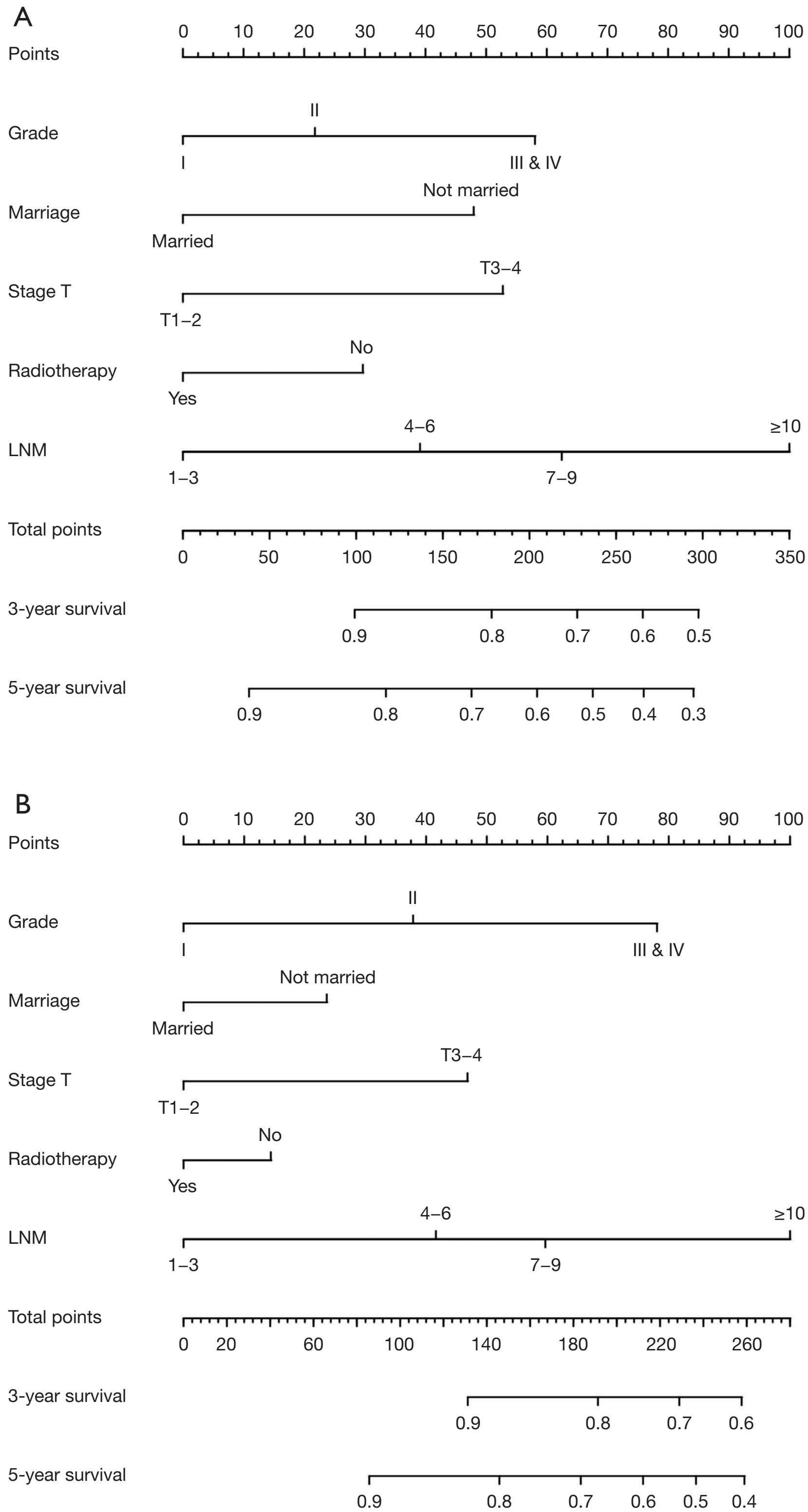

Figure 2 Nomograms for predicting 3- and 5-year OS (A) and BCSS (B) in patients with breast cancer. LNM, lymph node metastasis; OS, overall survival; BCSS, breast cancer-specific survival.

Table 3 Scores of clinical variables in each nomogram

Variables	OS	BCSS
Grade		
I	0	0
II	22	38
III & IV	58	78
Marriage		
Married	0	0
Not married	48	24
Stage T		
$T_{1–2}$	0	0
$T_{3–4}$	53	47
Radiotherapy		
Yes	0	0
No	30	14
LNM		
1–3	0	0
4–6	39	42
7–9	62	60
≥10	100	100

OS, overall survival; BCSS, breast cancer-specific survival; LNM, lymph node metastasis.

moderate [OS: hazard ratio (HR) =0.756, 95% confidence interval (CI): 0.666–0.859, P<0.001; BCSS: HR =0.643, 95% CI: 0.537–0.768, P<0.001] and high GMTRL scores (OS: HR =0.719, 95% CI: 0.549–0.940, P=0.014; BCSS: HR =0.731, 95% CI: 0.549–0.974, P=0.031) but not for patients with low GMTRL scores (OS: HR =0.929, 95% CI: 0.841–1.027, P=0.150; BCSS: HR =0.953, 95% CI: 0.831–1.094, P=0.495).

The ALND group of the validation set and all the SLNB groups constituted another dataset, which was classified into low GMTRL score groups (OS: 6,074/9,879; BCSS: 6,397/9,879), moderate GMTRL score groups (OS: 2,892/9,879; BCSS: 2,105/9,879) and high GMTRL score groups (OS: 913/9,879; BCSS: 1,377/9,879) according to the two risk stratification models. PSM was implemented between the SLNB and ALND cohorts in each GMTRL score group, demonstrating the matched results for the distribution of propensity ratings for paired and unpaired patients in Figure S3. Afterward, survival analyses were performed among the matched populations in the three GMTRL score groups (*Figure 6A-6F*). Consistent with the results obtained from the training set, SLNB and ALND did not differ significantly in OS and BCSS among patients with low GMTRL scores (OS: HR =0.891, 95% CI: 0.791–1.004, P=0.058; BCSS: HR =0.920, 95% CI: 0.784–1.079, P=0.304). Nevertheless, ALND significantly increased survival time for both the moderate (OS: HR =0.764, 95% CI: 0.662–0.883, P<0.001; BCSS: HR =0.675, 95% CI: 0.549–0.830, P<0.001) and high GMTRL score groups (OS: HR =0.750, 95% CI: 0.567–0.993, P=0.042; BCSS: HR =0.746, 95% CI: 0.558–0.999, P=0.047).

Multivariate Cox regression analyses of different GMTRL score groups

Ultimately, multivariate analyses were executed on the low, moderate and high GMTRL score cohorts to ascertain the independent prognostic element affecting the survival outcomes of patients in different GMTRL score groups. Forest plots (*Figure 7A-7F*) demonstrated that grade, marital status, T stage and lymph node metastasis were all elements determining OS and BCSS in the low GMTRL score cohort, while radiotherapy significantly affected OS but not BCSS. Furthermore, marriage, T stage, and radiotherapy were risk factors for survival in both the moderate and high GMTRL score groups. The number of metastatic lymph nodes greatly impacted the survival of patients in the moderate GMTRL score group.

Discussion

In recent years, there have been ongoing debates over which breast cancer patients with positive axillary nodes can avoid ALND without compromising their survival chances. In comparison with ALND, SLNB substantially improves the quality of life and reduces complications, making it a gold standard method for axillary surgeries of patients with early breast tumors (8,16-18). Our study analyzed data on 21,942 breast cancer patients from 2000 to 2017 in the SEER database.

This study was a retrospective analysis based on a large population, aiming to explore which breast cancer patients can be treated with SLNB alone as an alternative to ALND by establishing risk stratification models. In accordance with our risk models, ALND significantly prolonged OS and BCSS in both the moderate and high GMTRL score groups. Nevertheless, no statistically significant differences

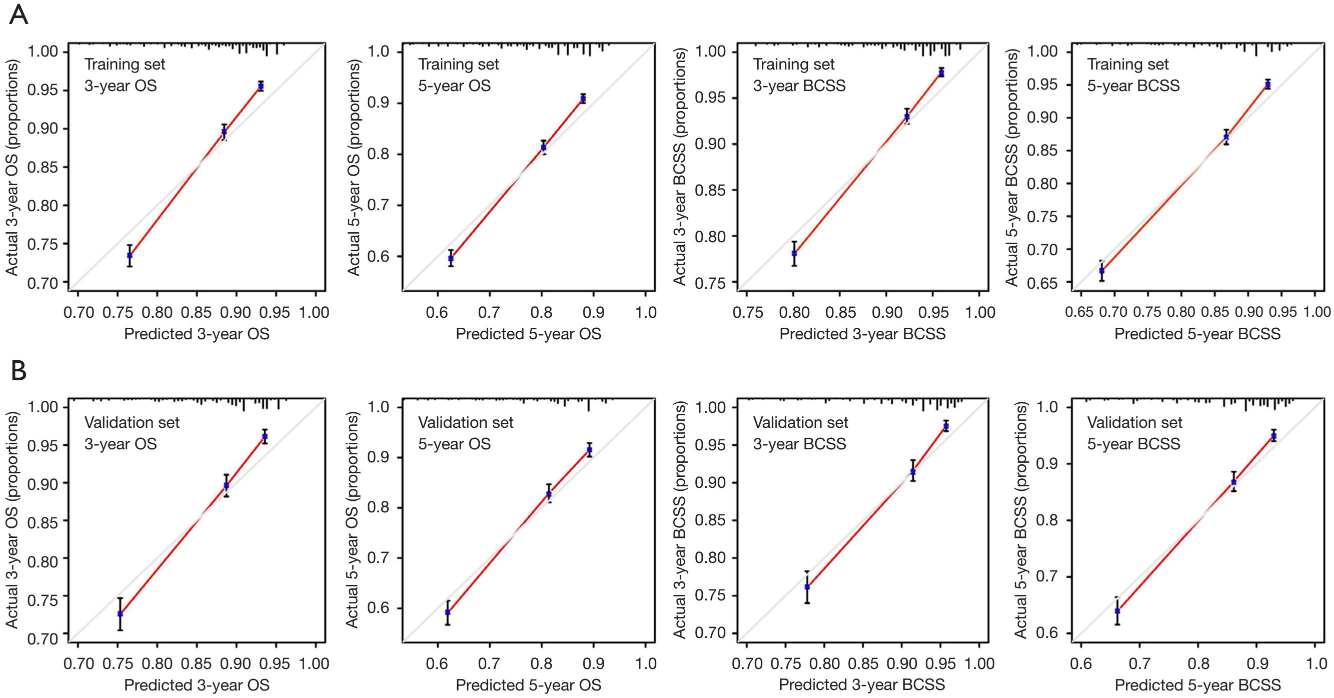

Figure 3 Calibration curves for these nomograms in training set (A) and validation set (B). The 45° dotted line represents the ideal reference, which means the nomogram-predicted survival probabilities (x-axis) exactly match the actual survival proportions (y-axis). Blue dots represent nomogram-predicted probabilities for each group, and black error bars represent the 95% CIs of these estimates. OS, overall survival; BCSS, breast cancer-specific survival; CI, confidence interval.

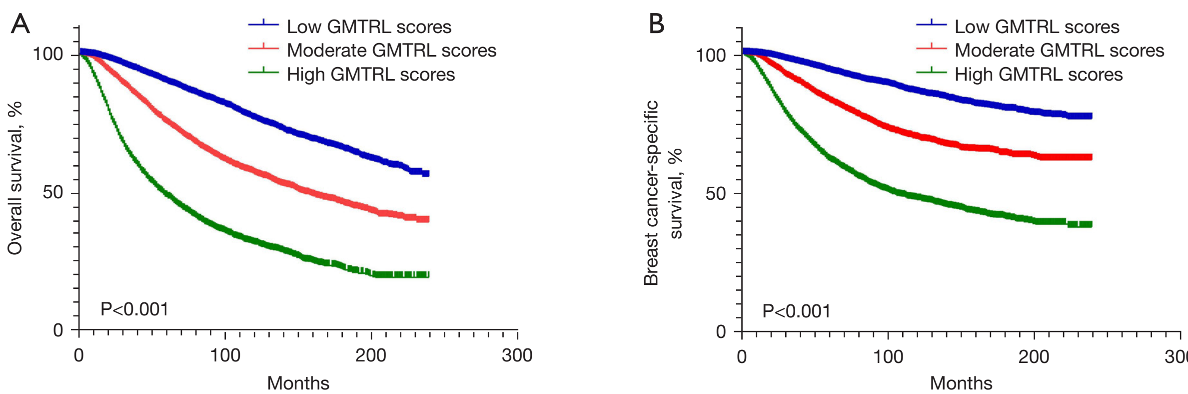

Figure 4 Comparison of survival among the three GMTRL-score groups. (A) OS of the ALND group in the training set; (B) BCSS of the ALND group in the training set. GMTRL, grade, marital status, T stage, radiotherapy and lymph node metastasis; OS, overall survival; BCSS, breast cancer-specific survival; ALND, axillary lymph node dissection.

were found in survival outcomes between SLNB alone and ALND for people with low GMTRL scores. These outcomes suggest that ALND might be prevented in patients with low GMTRL scores, without compromising survival and resulting in a more cost-effective treatment. We believe that these nomograms and GMTRL risk scores will allow clinical doctors and patients to think about the risk-benefit stability between SLNB and ALND.

Sentinel lymph node metastasis means an increased risk of non-sentinel lymph node involvement, and the quantity

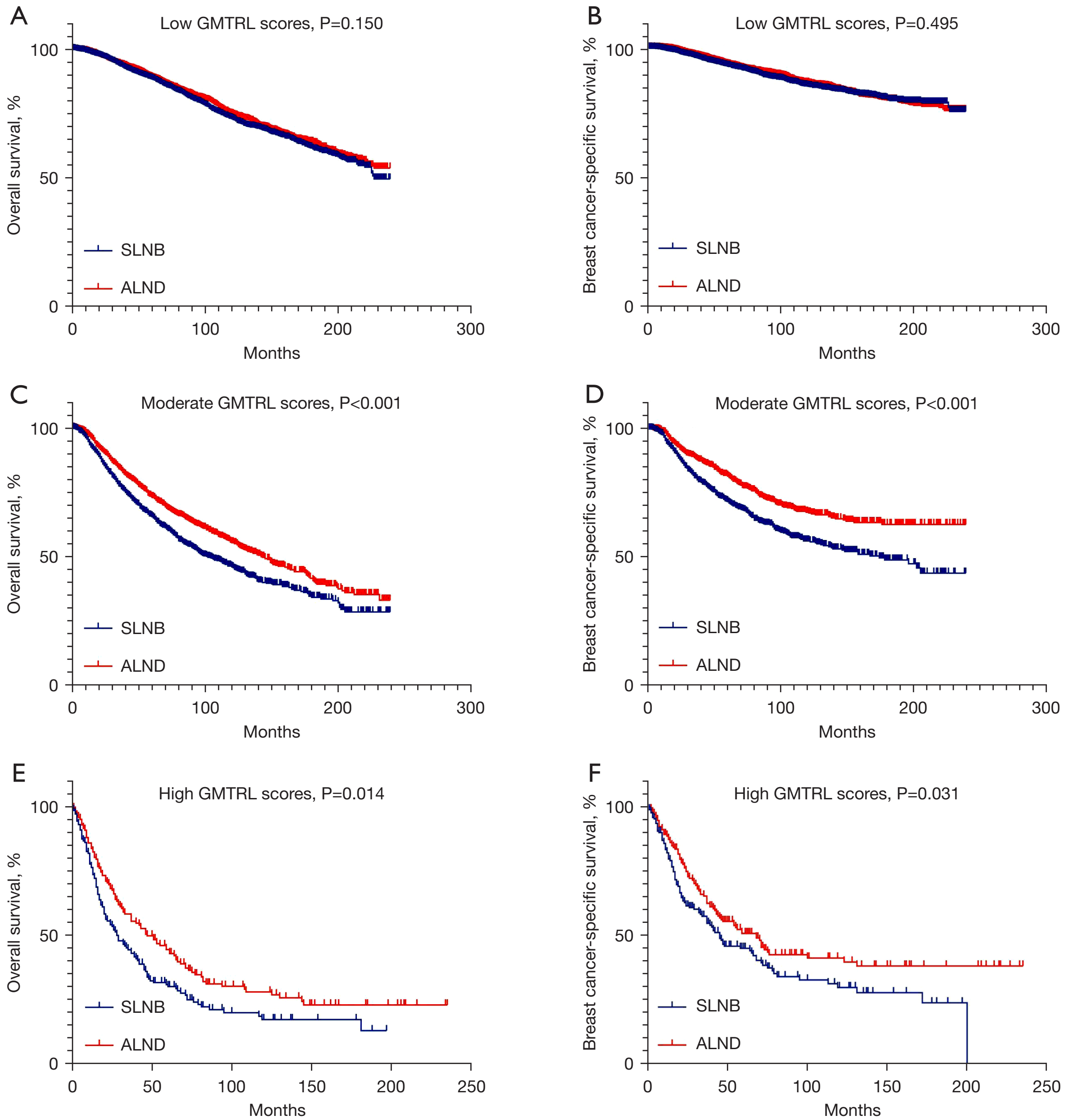

Figure 5 Survival comparison between the ALND group from the training set and all the SLNB groups after PSM in different GMTRL-score groups. (A) OS and (B) BCSS of patients with low GMTRL scores; (C) OS and (D) BCSS of patients with moderate GMTRL scores; (E) OS and (F) BCSS of patients with high GMTRL scores. PSM, propensity score matching; GMTRL, grade, marital status, T stage, radiotherapy and lymph node metastasis; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; OS, overall survival; BCSS, breast cancer-specific survival.

of positive axillary lymph nodes is an independent influential element for the outcomes of breast cancer patients and is generally accepted by medical professionals (19-21). With the improvement of radiotherapy, chemotherapy, endocrine therapy and targeted therapy for breast cancer, multiple trials have discovered that residual tumors in axillary lymph nodes are less likely to worsen a patient's prognosis, and ALND may even be avoided in certain populations. The NSABP B04 trial was the first study to investigate whether radiotherapy could replace ALND. No statistically significant

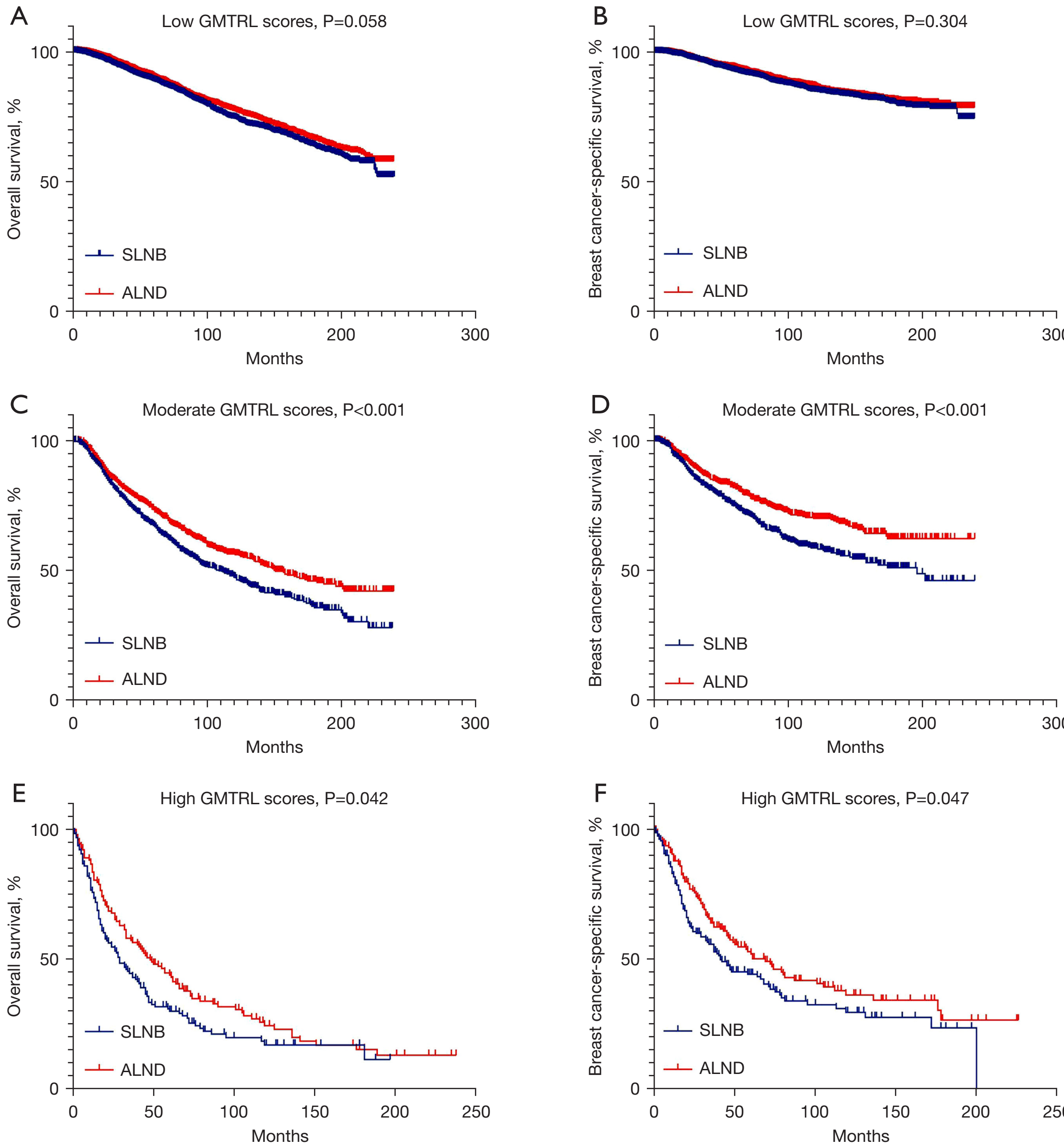

Figure 6 Survival comparison between the ALND group from the validation set and all the SLNB groups after PSM in different GMTRL-score groups. (A) OS and (B) BCSS of patients with low GMTRL scores; (C) OS and (D) BCSS of patients with moderate GMTRL scores; (E) OS and (F) BCSS of patients with high GMTRL scores. PSM, propensity score matching; GMTRL, grade, marital status, T stage, radiotherapy and lymph node metastasis; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; OS, overall survival; BCSS, breast cancer-specific survival.

differences emerged in disease-free survival (DFS) and OS among patients with clinically negative axillary lymph nodes who underwent radical mastectomy, total mastectomy combined with radiotherapy, or mastectomy alone (22). Louis-sylvestre's study enrolled patients with tumors <3 cm and clinically negative axillary lymph nodes, all of whom received breast-conserving plus whole breast radiotherapy and were randomized to ALND and radiotherapy groups. Neither group had significantly different survival rates after 10 and 15 years (73.8% *vs.* 75.5% at 15 years), nor did they

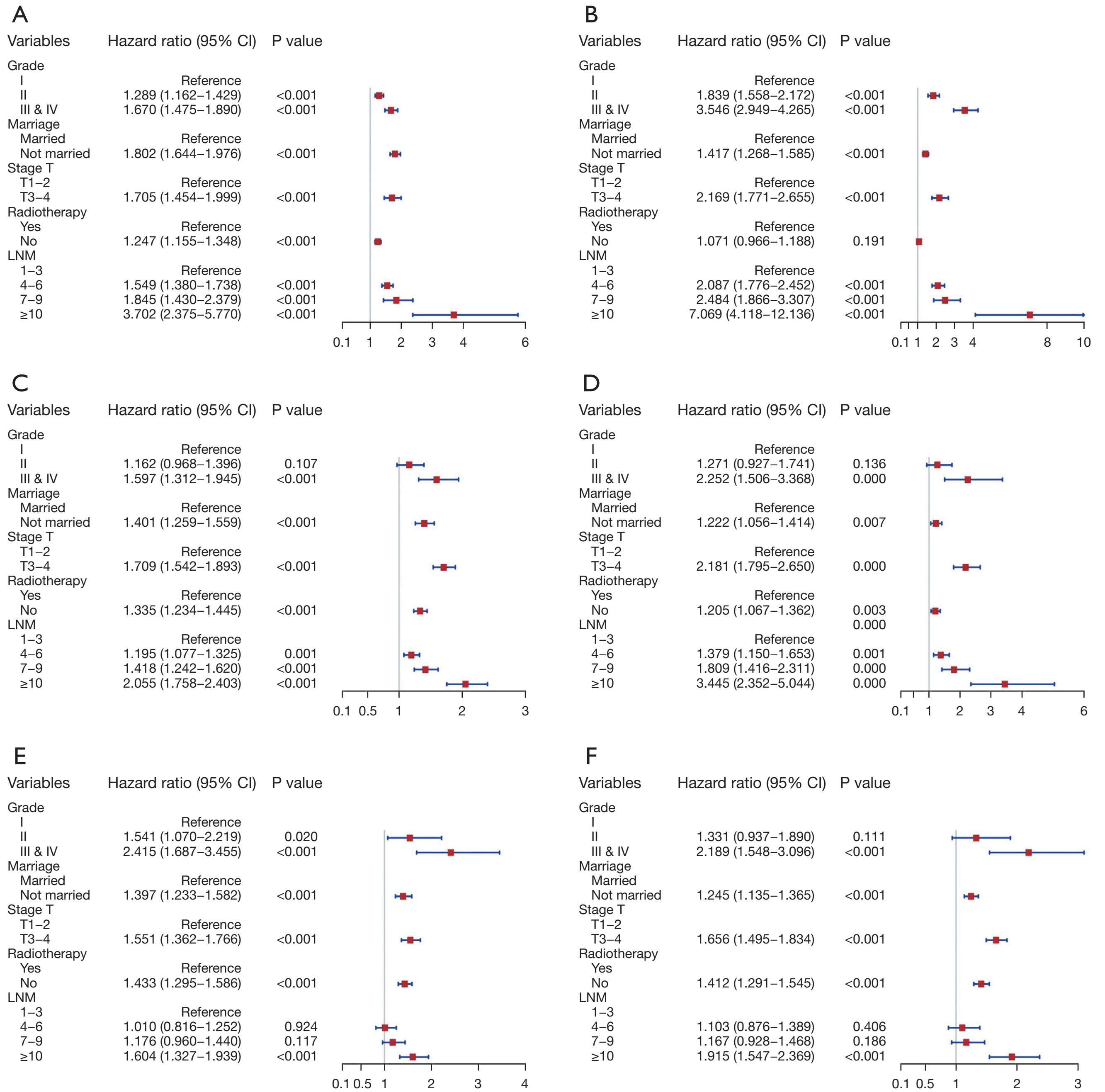

Figure 7 Forest plots of multivariate Cox regression analyses for different GMTRL-score groups. (A) OS and (B) BCSS of patients with low GMTRL scores; (C) OS and (D) BCSS of patients with moderate GMTRL scores; (E) OS and (F) BCSS of patients with high GMTRL scores. GMTRL, grade, marital status, T stage, radiotherapy and lymph node metastasis; LNM, lymph node metastasis; OS, overall survival; BCSS, breast cancer-specific survival; CI, confidence interval.

have any significant differences in breast, supraclavicular, or distant metastases (23). These two studies suggested that radiotherapy had a noninferior safety profile to ALND, whereas these studies have not truly changed clinical practice since SLNB was not widely performed at that time to obtain accurate axillary staging prior to radiotherapy.

Since the 1990s, SLNB has been the preferred axillary surgery for patients with stage T1–2 and clinically negative nodes. Whether patients with positive sentinel lymph nodes can avoid ALND remains controversial. Traditional guidelines recommend routine ALND in patients with pathologically confirmed positive nodes. Nonetheless, a few recent studies have suggested that ALND may be avoided in some instances for patients with positive sentinel lymph nodes. It was indicated through a meta-analysis that for those patients with clinically negative nodes and positive sentinel nodes, the OS (HR =1.09, 95% CI: 0.75–1.43, P=0.365) and DFS (HR =1.01, 95% CI: 0.58–1.45, P=0.144) between axillary radiotherapy (ART) and ALND were similar (24-26). Additionally, the results from different retrospective analyses showed no substantial variations in survival between patients treated with SLNB alone and those treated with ALND for early-stage and positive-node instances (27-32). It is important to note that the above results concerning the avoidance of ALND in patients who have sentinel lymph node metastases are retrospective data, whereas more convincing evidence should come from prospective randomized controlled trials.

One of the most convincing prospective randomized controlled trials was the Z0011 trial, which was a landmark in the development of axillary treatment for breast cancer and had been incorporated into guidelines. Prior to the Z0011 trial, ALND was required for patients with positive axillary lymph nodes, leading to more postoperative complications. Since the trial, however, guidelines have been changed accordingly. The National Comprehensive Cancer Network (NCCN) guidelines state that if a patient has a T_1 or T_2 tumor, one or two positive sentinel lymph nodes, receiving no neoadjuvant therapy, with breast-conserving surgery and whole breast radiotherapy, the experts recommend no further axillary surgery. The Z0011 trial is of great significance in reducing axillary surgeries. It allows some patients with positive sentinel lymph nodes to avoid ALND, thereby reducing the corresponding postoperative complications, especially the edema of the affected limb, and improving the quality of life of patients. Following the Z0011 trial, several prospective clinical trials have reached similar conclusions (33,34). However, it should be noted that patients enrolled in the Z0011 trial were older (64% >50 years old), with a high positive rate of hormone receptors, 77% of whom were positive for ER. Ninety-six percent of patients received comprehensive adjuvant therapy after surgery, and the trial did not recruit enough patients. In addition, the target area of postoperative radiotherapy was not defined for patients without ALND. These factors limited the generalization of the Z0011 results to all eligible populations to some extent. The Z0011 trial only enrolled patients undergoing breast-conserving surgery, while the EORTC 10991-22023 AMAROS trial did not restrict the surgical methods of patients, only requiring that the size of tumors was less than 3 cm. An evaluation of the 5-year axillary recurrence rate, 5-year DFS, and 5-year OS between the ALND group and the ART group found no statistically significant differences (35). Another OTOASOR study, similar to the AMAROS trial, also demonstrated no variation in the axillary recurrence rate (2% *vs.* 1.7%, P=1.00), OS (77.9% *vs.* 84.8%, P=0.060), and DFS (72.1% *vs.* 77.4%, P=0.51) among patients with positive sentinel lymph nodes who underwent either ALND or radiotherapy (36).

The innovation of this study lied in not only providing nomograms that could accurately predict the 3- and 5-year OS and BCSS of breast cancer patients but also establishing two risk-stratified prediction models to quickly determine which patients had no statistically significant differences in survival outcomes between SLNB alone and ALND. The low GMTRL risk score for predicting OS was ≤105, while that for predicting BCSS was ≤107. Independent prognostic factors for survival in the low GMTRL score groups included grade, marital status, T stage, radiotherapy, and lymph node metastasis. Patients with low GMTRL scores were almost always accompanied by lower grades and earlier stages. In addition, receiving radiotherapy and possessing spouses were also typical features. These patients could be considered free from ALND, thereby avoiding lymphedema and other complications to improve their quality of life. However, marital status, T stage and radiotherapy were the main independent prognostic factors predicting survival outcomes in the moderate and high GMTRL score groups. Patients in these groups were often accompanied with larger tumors, advanced stages and poor grades, so that they had high risks of recurrence and metastasis, with poor prognoses. If these patients had metastatic axillary lymph nodes, not performing ALND would increase the risks of recurrence and distant metastasis, ultimately affecting their survival. As for them, ALND played a crucial role and could not be replaced by any other treatment modalities. In clinical practice, another important factor affecting the prognoses of breast cancer patients is the expression of human epidermal growth factor receptor 2 (HER2) (37). Amplification or overexpression of HER2 is ultimately associated with low survival rates in breast cancer patients (38). Patients with HER2 overexpression can be treated with targeted therapy before or after the surgery. Although the positive significance of HER2 was not found in our prediction models, it is undeniable that HER2 is of great significance for the prognoses of breast cancer patients. Furthermore, chemotherapy is also an important factor affecting the prognoses of breast cancer patients. Future researches can focus on the significances of HER2 and chemotherapy in the prediction models of axillary surgeries.

Despite some advantages of our research, such as a large population, a rigorous hierarchical evaluation for the building of nomograms, and ample interior and exterior validation, several barriers prevent the interpretation of the nomograms. Initially, we did not account for some potential confounders, such as polygenic trait assessment and basic diseases (hypertension, diabetes or coronary heart disease), due to the absence of detailed information in the SEER database. The second concern was the lack of detail regarding clinical and therapeutic information, especially adjuvant therapy and physical conditions. Thirdly, as the type of lymph node surgical procedure had not been clearly defined in the SEER database, we classified the removal of 1–5 lymph nodes as SLNB and the removal of more than 10 nodes as ALND based on other study (2), excluding patients with the removal of 6–9 nodes, which might lead to some limitations in our results. Moreover, no specific information about the irradiated sites of radiotherapy was obtained in this study, and future studies need to incorporate relevant data to explore whether the effects of irradiations on different sites are consistent. Finally, since there was a high percentage of Caucasian and black patients enrolled in the study, it is imperative that the prediction models are being applied to an external cohort of patients, especially Asian patients. Only a well-designed prospective randomized trial can be the most compelling way to gather persuasive evidence. A few ongoing trials may provide insight into whether ALND is eligible to be omitted under different situations (39-41). We are looking forward to the outcomes of these medical trials to supply improved evidence that is exempt from ALND.

Conclusions

Well-validated nomogram plots and GMTRL risk scores were developed in this research to determine which breast cancer patients could safely undergo SLNB instead of ALND. It appeared that ALND could significantly improve the survival of patients with moderate and high GMTRL scores compared with SLNB. However, in the low GMTRL score groups, SLNB alone might be safely administered to avoid ALND without compromising survival. It may be beneficial for clinicians to reflect on the advantages and limitations of SLNB and ALND before developing individualized treatment strategies based on the findings of this study. We expect stronger evidence from prospective trials.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1639/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1639/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1639/coif). 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. We received permission to access the research data file in the SEER program from the National Cancer Institute, US. Approval was waived by the local ethics committee, as SEER data are publicly available and de-identified. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

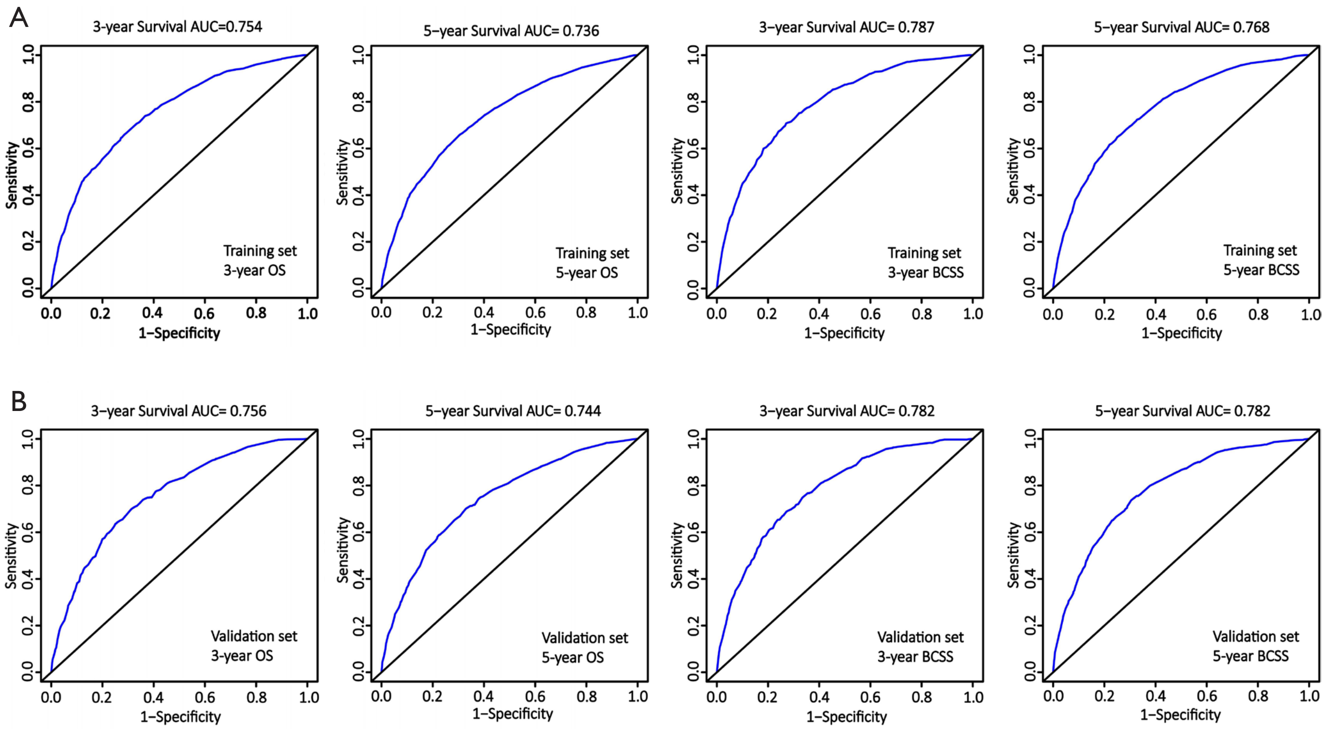

Figure S1 ROC curves for these nomograms in training set (A) and validation set (B). AUC, area under the curve; OS, overall survival; BCSS, breast cancer-specific survival; ROC, receiver operating characteristic.

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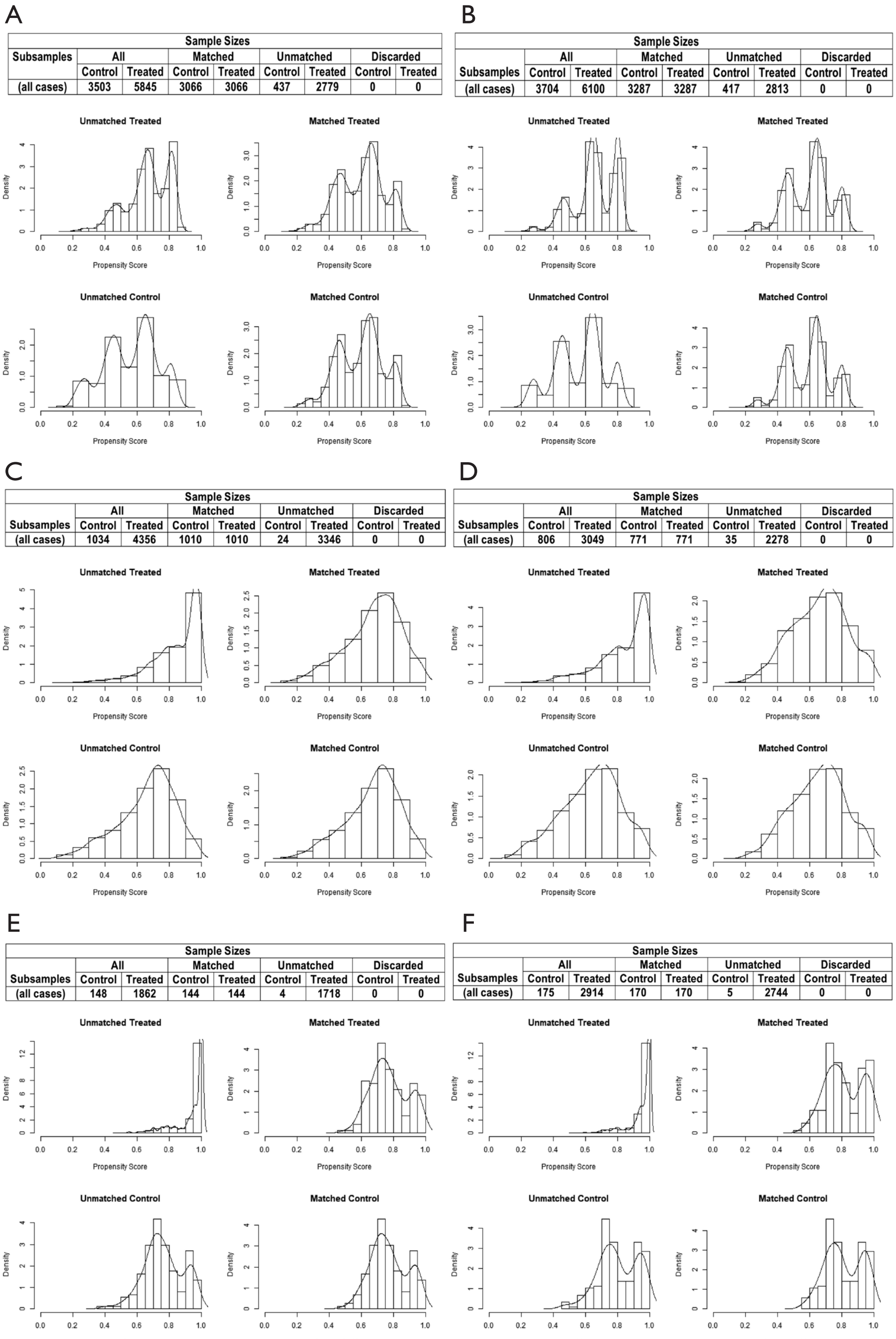

Figure S2 The distribution of propensity scores for paired and unpaired patients of the ALND group from the training set and all the SLNB groups. (A) OS and (B) BCSS of patients with low GMTRL scores, (C) OS and (D) BCSS of patients with moderate GMTRL scores, (E) OS and (F) BCSS of patients with high GMTRL scores. The control group means the SLNB group, and the treated group means the ALND group. GMTRL, grade, marital status, T stage, radiotherapy and lymph node metastasis; OS, overall survival; BCSS, breast cancer-specific survival; ALND, axillary lymph node dissection.

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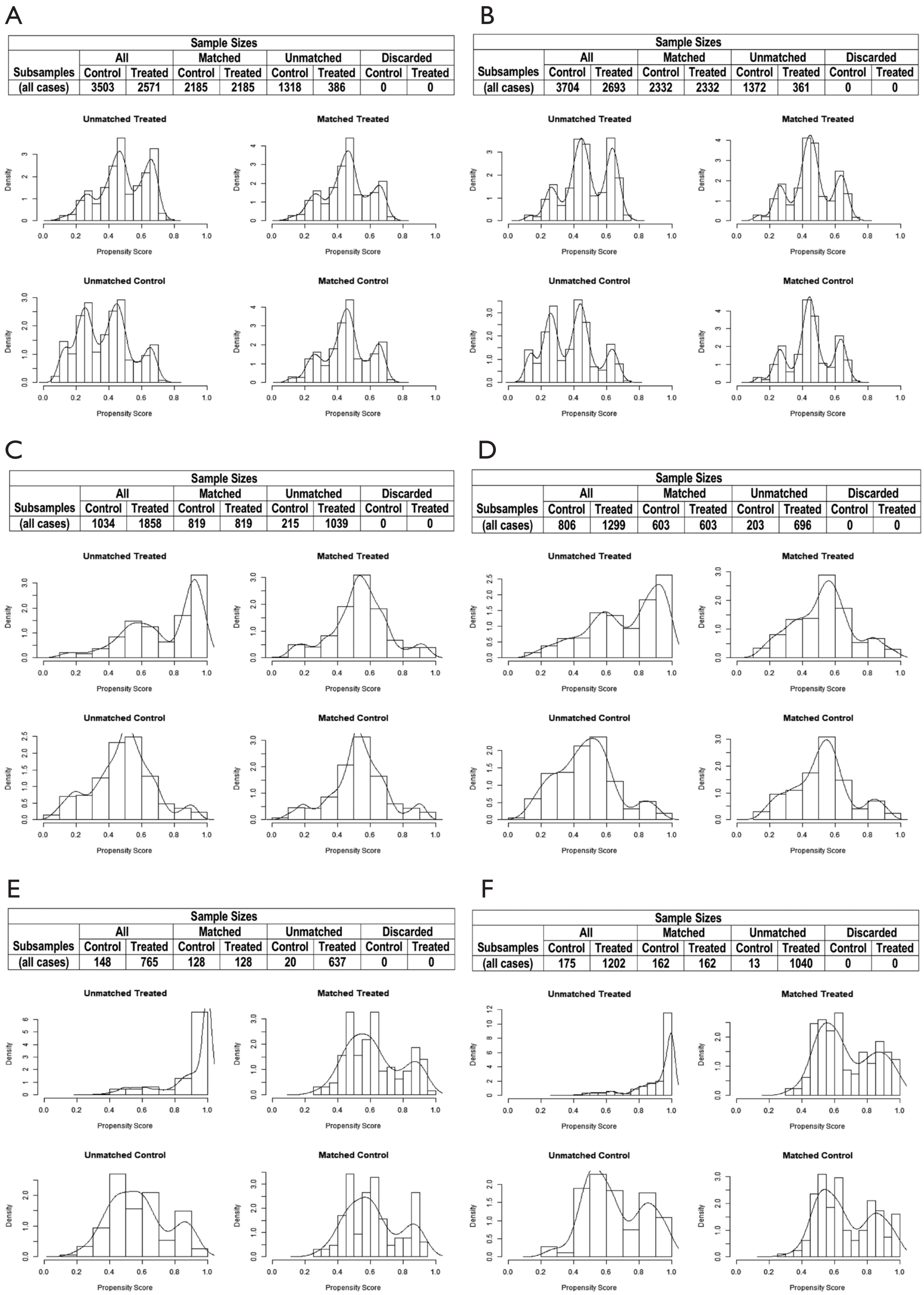

Figure S3 The distribution of propensity scores for paired and unpaired patients of the ALND group from the validation set and all the SLNB groups. (A) OS and (B) BCSS of patients with low GMTRL scores, (C) OS and (D) BCSS of patients with moderate GMTRL scores, (E) OS and (F) BCSS of patients with high GMTRL scores. The control group means the SLNB group, and the treated group means the ALND group. GMTRL, grade, marital status, T stage, radiotherapy and lymph node metastasis; OS, overall survival; BCSS, breast cancer-specific survival; ALND, axillary lymph node dissection.

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