Original Article

Comparison of three lymph node staging methods for predicting outcome in breast cancer patients with mastectomy

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Background: Axillary lymph node (ALN) staging is essential in predicting the clinical outcome of breast cancer (BC) patients. Traditionally, it follows the tumor–node-metastasis (TNM) staging, but its accuracy needs further improvement.

Methods: A total of 9,616 BC patients from the Surveillance, Epidemiology, and End Results (SEER) database and 675 patients from the First Affiliated Hospital of China Medical University underwent mastectomy together with ALN dissection were reviewed. Univariate and multivariate logistic analyses were conducted to find the most meaningful factors relevant to prognosis.

Results: After univariate and multivariate analyses, age, race, primary site, radiation, chemotherapy, grade, T-stage, estrogen receptor (ER), progesterone receptor (PR), total number of positive lymph nodes (pN), positive lymph node ratio (LNR) and log odds of positive LNs (LODDS) were found to be significantly associated with overall survival (OS). Using these non-LN risk factors, we further compared the efficacy of three different ALN staging methods in prognosis via nomograms. Harrell's concordance index (C-index) and Akaike Information Criterion (AIC) were used to measure nomogram performance of the ALN staging methods: pN: C-index=0.687 (95% CI: 0.678–0.696), AIC =61,398.24; LNR: C-index =0.691 (95% CI: 0.683–0.701), AIC =61,313.56; and LODDS: C-index =0.691 (95% CI: 0.682–0.700), AIC =61,315.60. We found that the nomogram incorporating LODDS had better predictive ability compared with other two methods. Furthermore, an external validation revealed a C-index of 0.753 (95% CI: 0.690–0.816) for the Asian population, which indicates the nomogram based on LODDS may have universality for both Western and Asian populations.

Conclusions: Compared with pN and LNR, LODDS showed higher homeostasis in LN evaluation, and showed marked efficacy in evaluating survival differences among patients with negative LN staging. We constructed a BC prognosis model by incorporating highly relevant clinical pathological factors and a new method of LN staging, which may greatly aid in guiding postoperative treatment.

Keywords: Breast cancer (BC); log odds of positive LNs (LODDS); lymph node staging; nomograms

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Introduction

The dissemination of cancer cells from the primary site of breast cancer (BC) to the axillary lymph nodes (ALN) is a critical process in tumor progression that influences early recurrence and 5- or 10-year overall survival (OS) (1). Thus, ALN status is an important prognostic factor for BC patients with modified radical mastectomy. Total number of positive lymph nodes (pN) is commonly used to determine the N stage. However, accumulating evidence shows that a positive lymph node ratio (LNR) can predict prognosis more precisely than the traditional pN stage for BC (2-5). LNR is defined as the ratio between LNs with metastasis versus the total number of LNs retrieved, and thus does not solely rely on positive LNs. Several studies have shown that LNR has greater ability to predict the OS of patients compared with traditional TNM staging, and that LNR should be considered as an alternative to pN staging (2-8). The definition of pN =0 is equal to LN R =0, indicating no LNs with metastasis. However, prognosis may vary for pN0 patients, and underestimations of severity still exist due to the shortcomings of the pN staging method. The newly issued 8th edition of the TNM system designed by the American Joint Committee on Cancer includes prognostic factors such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and grade (9-11). However, a more powerful model combining both prognostic factors and refined N staging is necessary to improve the accuracy of survival prognosis.

Nomograms are used to visually predict the prognosis of patients with various malignant tumors, including gastric, colon, prostate, and BC types, by analyzing relevant variables (12-15). A well-constructed nomogram also allows surgeons to classify patients with different levels of severity and optimize the postoperative therapeutic approach.

Currently, there are no nomograms based on the Surveillance, Epidemiology, and End Results (SEER) database that include both prognostic factors and LNR or log odds of positive LNs (LODDS) to predict prognosis. Therefore, by combining related risk predictors and lymph node staging methods, we constructed a more effective evaluation model.

We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4856).

Methods

Data retrieval

All patients met the following inclusion criteria: (I) pathologically diagnosed with invasive ductal or lobular BC, equivalent to codes 8500/3, 8521/3 or 8522/3 in the International Classification of Disease for Oncology 3rd edition (ICD-O-3) in SEER*Stat; (II) underwent mastectomy together with ALN dissection; and (III) age at diagnosis >18 years. Exclusion criteria were the following: (I) distant metastasis present at diagnosis; (II) <5 regional LNs examined; (III) incomplete information about pathology, LN status, or systemic treatment regimen; (IV) lost to follow-up; or (V) a primary malignancy apart from BC. A flowchart of the training cohort selection process is shown in Figure S1. The primary outcome was OS, defined as time from diagnosis to death. The cut-off follow-up date was December 31, 2014. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of The First Hospital of China Medical University (2019-72-2), and informed consent was obtained from all patients in validation set, while informed consent in training set was unnecessary because SEER is a public resource.

Filtering of variables associated with OS

The SEER database was used to collect age at diagnosis, race (White, Black, other), primary site grade, the edition of TNM staging used (3th, 6th, 7th), radiation record, chemotherapy record, regional LNs examined, positive regional LNs, survival months, vital status record, ER status record, and PR status record. Age was classified as ≤50 and >50 years. Poorly differentiated (grade III) and undifferentiated (grade IV) BC were considered as a group compared with well-differentiated (grade I) and moderately differentiated (grade II) groups. The SEER database does not provide detailed information about radiation and chemotherapy treatment regimens, simply showing whether a patient received those treatments. Importantly, to have a sufficient follow-up period, we enrolled the 9,616 patients from 1994 to 2004. There were three editions of TNM staging used during this period, so we re-staged patients diagnosed before 2010 according to the 7th edition of the American Joint Committee on Cancer (AJCC) TNM

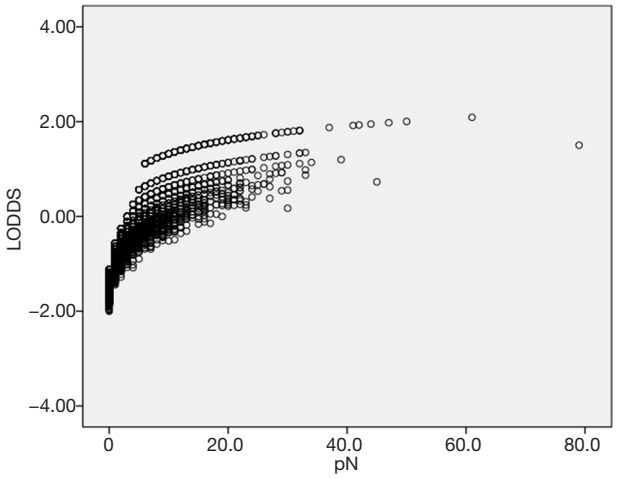

Figure 1 Distribution of log odds of positive lymph nodes (LODDS) *vs.* total number of positive lymph nodes (pN).

staging system.

LNR

LNR classification intervals were determined by comparing OS rates according to LNR with an initial interval of 0.1 (LNR =0 and 1 were considered separately, reflecting metastasis in none or all nodes retrieved), and then sorting patients with similar OS.

The LODDS system

LODDS is estimated as $\log\frac{(pnod+0.5)}{(tnod-pnod+0.5)}$, where tnod = total numbers of LNs retrieved and pnod = positive LNs in tnod, with 0.5 being added to both the numerator and denominator to avoid singularity (16,17). The classification is equivalent to the LNR method but with an initial interval of 0.5.

Construction and validation of the nomogram model

After pN, LNR, and LODDS were taken into consideration, univariate and multivariate analyses were conducted to find the most meaningful factors relevant to prognosis. Three nomograms were constructed based on pN, LNR, and LODDS, and then the C-index and Akaike Information Criterion (AIC) were used to measure the prognostic performance of the three models (18). After constructing the nomogram based on LODDS, an external validation was conducted on the 675 Asian patients from the First Affiliated Hospital of China Medical University.

Statistical analysis

All statistical analyses and visualization were performed with the IBM SPSS 21.0 statistics package (SPSS, Inc., Chicago, IL, USA) and the "rms" package on R software version 3.1.3 (http://cran.r-project.org). For all analyses, only P values <0.05 were regarded as significant. The SEER database is a reportable database in the United States, so informed consent was unnecessary for those patients, while informed consent was given by all patients involved in the external validation.

Results

Patients' characteristics

The training cohort of a total of 9,616 female BC patients from 1994 to 2004 were enrolled via SEER 18 (1973–2015), released in November 2017 with the SEER*Stat 8.3.5 software. The validation cohort consisted of 675 patients admitted to the First Affiliated Hospital of China Medical University from 2005 to 2010 and followed for 5 years after surgery. The clinicopathologic characteristics of the training cohort and validation cohort are shown in Table S1. For the 9,616 patients, an average of 14.64±6.53 LNs were retrieved, ranging from 6 to 81. An average of 2.36±0.05 LNs were metastatic, ranging from 0 to 79. After re-analyzing the N-stage according to the 7th AJCC TNM N classification for all patients, pN0–pN3 were defined as patients with 0, 1–3, 4–9 and >9 affected LNs, respectively As shown in Table S1, the distributions of training set and validation set are different. Considering that the race of validation set only obtains information about "other" group, thus we perform subgroup analysis of training set and validation set according to "other" group. The results tend out that the clinicopathological features still have difference between the "other" group of two sets (Table S2). This may be related to the fact that "other" group in SEER database includes not only Asian population, but also a considerable number of people of multiple races around the Pacific Ocean, such as American Indian/AK Native, Asian/Pacific Islander.

Relationships between LODDS and pN or LNR

Scatter plots were created for the distribution of LODDS *vs.* pN (*Figure 1*) and the distribution of LODDS *vs.* LNR (*Figure 2*). The LODDS values increased as the number of positive LNs increased (*Figure 1*), which indicated a close

relationship between LODDS and the number of metastatic LNs. Based on this nonlinear relationship, the LODDS evaluation system is better than the pN evaluation system when the number of metastatic LNs is <10. We found that LODDS also increased as the number of positive LNs increased (*Figure 2*). However, we found an interesting phenomenon with varied LODDS values at LNR =0 and 1. Traditional N staging only considers the number of positive LNs, yet OS differed for patients with LNR =0 and 1.

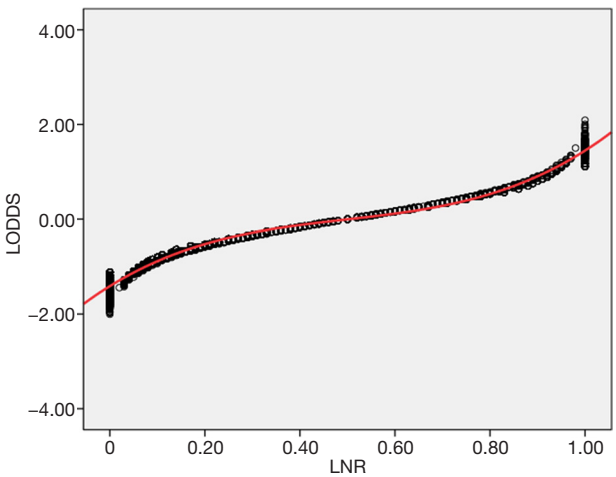

Figure 2 Distribution of log odds of positive lymph nodes (LODDS) *vs.* lymph node ratio (LNR).

Thus, we believe that LODDS may potentially discriminate between patients with the same LNR classification but different OS, although LNR =0 and 1 should be taken into special consideration.

Regrouping LODDS and LNR according to OS

After running log-rank statistical analysis, we grouped patients with similar prognoses (*Table 1*): LNR0: LNR =0; LNR1: 0< LNR1 ≤0.2; LNR2: 0.2< LNR2 ≤0.3; LNR3: 0.3< LNR3 ≤0.5; LNR4: 0.5< LNR4 ≤0.9; LNR5: 0.9< LNR5 <1.0; and LNR6: LNR6 =1. Of the 9,616 patients, 4,740 (49.3%) were LNR0, 2,618 (27.2%) were LNR1, 589 (6.1%) were LNR2, 671 (7.0%) were LNR3, 715 (7.4%) were LNR4, 97 (1.0%) were LNR5, and 186 (2.0%) were LNR6. The 10-year survival rate decreased significantly as LNR increased: LNR0 =77.8%; LNR1 =74.8%; LNR2 =63.4%; LNR3 =57.7%; LNR4 =45.2%; LNR5 =23.3%; LNR6 =29.8% (P<0.001, *Figure 3*). We then constructed a novel 7 grouping based on LODDS: LODDS1 ≤–1.5; –1.5< LODDS2 ≤–1; –1< LODDS3 ≤–0.5; –0.5< LODDS4 ≤0; 0< LODDS5 ≤0.5; 0.5< LODDS6 ≤1; LODDS7 >1. We found 10-year survival rates of 80.6%, 76.4%, 73.9%, 59.8%, 48.2%, 34.9%, and 27.7%, respectively (P<0.001, *Table 2*; *Figure 4*). In all cases, survival rate displayed an inverse relationship with LODDS stage, with lower survival rates at higher LODDS stages. In nomogram, the same LNR or LODDS categorization has been used.

Table 1 Five- and ten-year survival rates of breast cancer patients according to the value of LNR with the interval of 0.1

	No.	5-YSR	10-YSR	P[a]
LNR =0	4,740	91.3	77.8	0.144
0< LNR ≤0.1	1,410	91.2	76.5	0.069
0.1< LNR ≤0.2	1,208	88.1	72.8	<0.001
0.2< LNR ≤0.3	589	85.4	63.4	0.043
0.3< LNR ≤0.4	363	79.4	59.8	0.325
0.4< LNR ≤0.5	308	76.8	55.3	0.080
0.5< LNR ≤0.6	199	73.4	49.1	0.668
0.6< LNR ≤0.7	192	73.2	47.9	0.318
0.7< LNR ≤0.8	166	63.9	42.7	0.660
0.8< LNR ≤0.9	158	60.2	39.5	0.018
0.9< LNR <1.0	97	50.5	23.3	0.637
LNR =1.0	186	52.2	29.8	

[a], comparison between adjacent groups. No, number of patients; YSR, year survival rate; LNR, positive lymph node ratio.

Homogeneity in LODDS grouping

Table 3 shows the 10-year OS of patients with different pN and LNR stages classified by LODDS. The 10-year OS was significantly different after classifying by LODDS regardless of pN stage. However, for patients within the same LODDS stage, the 10-year OS was highly similar, indicating that the LODDS method may be superior to pN staging. Similar results are evident when comparing LODDS with the LNR staging system. Patients had varying LODDS in each LNR stage, yet the 10-year OS rates were comparable and patients with the same LODDS score showed similar prognosis, implying that LNR staging performs similarly to LODDS staging for classifying patients based on prognosis.

Number of lymph nodes required

We next compared the prognosis performance of the pN, LNR, and LODDS staging systems classified by the number of collected LNs. As shown in *Table 4*, for pN staging method, the 10-year OS varied significantly with the

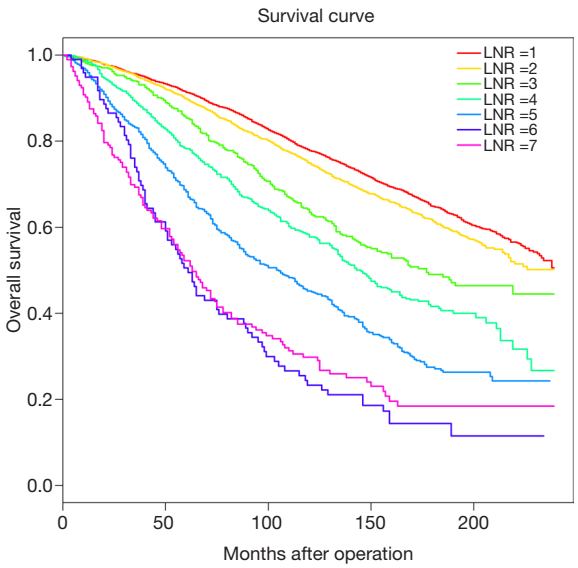

Figure 3 Survival curves of breast cancer patients according to lymph node ratio (LNR)

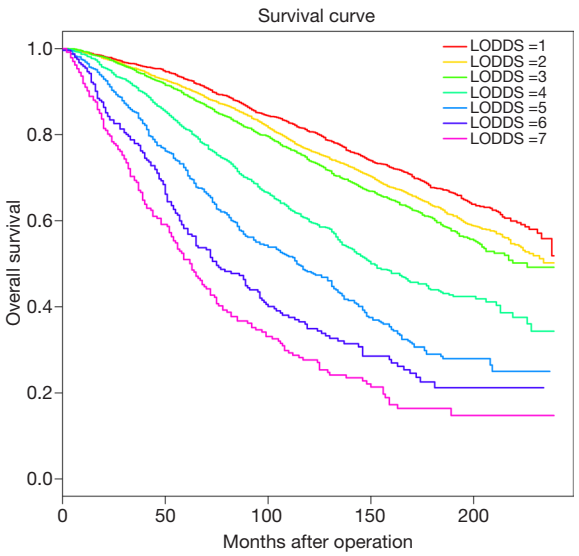

Figure 4 Survival curves of breast cancer patients according to log odds of positive lymph nodes (LODDS) stage.

Table 2 Five- and ten-year survival rates of breast cancer patients according to the value of LODDS with the interval of 0.5

	No.	5-YSR	10-YSR	P[a]
LODDS ≤−1.5	1,552	96.8	0.808	0.001
−1.5< LODDS ≤−1	3835	0.994	0.764	0.013
−1< LODDS ≤−0.5	2074	0.991	0.739	<0.000
−0.5< LODDS ≤0	1157	0.980	0.598	<0.000
0< LODDS ≤0.5	518	0.916	0.480	0.002
0.5< LODDS ≤1	244	0.783	0.347	0.030
1< LODDS ≤1.5	163	0.673	0.280	0.847
LODDS >1.5	73	0.197	<0.2	

[a], comparison between adjacent groups. LODDS, log odds of positive LNs; No, number of patients; YSR, year survival rate; LNR, positive lymph node ratio.

Table 3 Overall survival rates based on pN and LNR classification according to the LODDS staging system

	LODDS1		LODDS2		LODDS3		LODDS4		LODDS5		LODDS6		LODDS7		P[a]
	No. (%)	10-YSR	No. (%)	10-YSR	No. (%)	10-YSR	No. (%)	10-YSR	No. (%)	10-YSR	No. (%)	10-YSR	No. (%)	10-YSR	
pN															
0	1,552 (32.7)	0.806	3,118 (67.3)	0.763	–	–	–	–	–	–	–	–	–	–	0.001
1	–	–	645 (21.5)	0.766	1,919 (63.9)	0.743	440 (14.6)	0.644	–	–	–	–	–	–	<0.001
2	–	–	2 (0.2)	1.0	154 (13.1)	0.688	651 (55.4)	0.566	265 (22.5)	0.477	61 (5.2)	0.517	43 (3.6)	0.410	<0.001
3	–	–	–	–	1 (0.1)	–	66 (9.5)	0.610	253 (36.4)	0.486	183 (26.3)	0.298	193 (27.7)	0.252	<0.001
P[b]	–		0.690		0.548		0.028		0.859		0.006		0.286		
LNR															
0	1,552 (32.7)	0.806	3,188 (67.3)	0.763	–	–	–	–	–	–	–	–	–	–	0.001
1	–	–	647 (24.7)	0.766	1,971 (75.3)	0.742	–	–	–	–	–	–	–	–	0.136
2	–	–	–	–	103 (17.5)	0.674	486 (82.5)	0.626	–	–	–	–	–	–	0.412
3	–	–	–	–	–	–	671 (48.4)	0.577	518 (37.2)	0.482	197 (14.4)	0.373	–	–	<0.001
4	–	–	–	–	–	–	–	–	–	–	47 (16.6)	0.261	236 (83.4)	0.277	0.594
P[c]	–		0.825		0.220		0.009		–		0.314		–		

[a], comparison of overall survival rates between different LODDS groups; [b], comparison of overall survival rates between different pN groups; [c], comparison of overall survival rates between different LNR groups. LNR, positive lymph node ratio; LODDS, odds of positive lymph nodes; No, number of patients; YSR, year survival rate.

different numbers of LNs retrieved. Compared with >30 nodes, the OS with fewer LNs collected varied significantly. Particularly, pN =3 patients with <15 LNs collected had a significantly poor prognosis, which indicates the necessity of collecting a sufficient number of LNs for the pN staging method. For LNR and LODDS staging, the OS was highly consistent across different number of LNs retrieved, which, together with the results shown in *Table 3*, suggests that LNR and LODDS staging are more powerful for predicting prognosis than pN.

Association of LODDS with survival and ability to differentiate patients with negative lymph nodes

The correlations between log hazard ratio and pN, LNR, and LODDS are shown in *Figures 5*-7. Prognosis decreased as pN, LNR, and LODDS increased. Strikingly, more variable prognosis was seen as LODDS increased in patients with no LN metastasis (*Figure 8*), indicating that LODDS could distinguish different OS in pN0 or LNR0 patients.

Selection of variables and nomogram construction

In the univariate analysis, age at diagnosis (P=0.000), race (P=0.000), primary site (P=0.000), grade (P=0.000), radiation (P=0.000), chemotherapy (P=0.000), T-stage (P=0.000), ER (P=0.000), PR (P=0.000), pN (P=0.000), LNR (P=0.000), and LODDS (P=0.000) were all significantly relevant to prognosis. Multivariate analyses were performed with the univariate results, and all significantly correlated with

Table 4 Overall survival rates on the basis of pN, LNR, and the LODDS staging system according to the number of lymph nodes retrieved

No. of lymph node retrieved	6–10			11–15			16–20			21–25			26–30			>30		P[a]
	No.	10-YSR	P[b]	No.	10-YSR	P[b]	No.	10-YSR	P[b]	No.	10-YSR	P[b]	No.	10-YSR	P[b]	No.	10-YSR	
pN classification																		
0	1,691	0.752	0.378	1497	0.776	0.659	939	0.799	0.874	376	0.823	0.575	152	0.796	0.790	85	0.830	0.018
1	867	0.726	0.108	1027	0.732	0.192	662	0.731	0.208	265	0.763	0.253	119	0.700	0.192	64	0.821	0.638
2	302	0.471	0.176	380	0.552	0.349	297	0.592	0.818	125	0.612	0.902	45	0.714	0.444	27	0.537	0.004
3	11	0.102	0.009	167	0.277	0.034	226	0.395	0.516	142	0.483	0.939	78	0.373	0.327	72	0.446	0.003
LNR classification																		
0	1,691	0.752	0.378	1497	0.776	0.659	939	0.799	0.874	376	0.823	0.575	152	0.796	0.790	85	0.830	0.018
1	537	0.763	0.346	873	0.753	0.370	674	0.730	0.220	307	0.761	0.282	145	0.690	0.137	82	0.801	0.650
2	188	0.660	0.204	192	0.606	0.328	130	0.639	0.196	52	0.616	0.518	14	0.917	0.037	13	0.428	0.372
3	401	0.547	0.646	411	0.501	0.680	328	0.487	0.692	135	0.535	0.979	68	0.441	0.311	43	0.522	0.120
4	54	0.343	0.799	98	0.286	0.679	53	0.266	0.911	38	0.256	0.820	15	0.144	0.758	25	0.221	0.961
LODDS classification																		
1	–	–	–	–	–	–	939	0.799	0.874	376	0.823	0.575	152	0.796	0.790	85	0.830	0.877
2	1,691	0.752	0.161	1497	0.776	0.301	356	0.759	0.349	140	0.774	0.145	90	0.716	0.128	61	0.862	0.370
3	537	0.763	0.528	917	0.750	0.462	346	0.688	0.930	190	0.748	0.632	59	0.655	0.992	25	0.624	0.108
4	414	0.650	0.436	352	0.563	0.729	251	0.585	0.784	81	0.514	0.717	34	0.697	0.366	25	0.507	0.202
5	122	0.397	0.751	162	0.505	0.997	127	0.476	0.959	62	0.588	0.319	29	0.447	0.699	16	0.516	0.618
6	53	0.508	0.781	83	0.246	0.100	52	0.365	0.330	25	0.356	0.263	17	0.160	0.051	14	0.556	0.012
7	54	0.343	0.297	60	0.319	0.180	53	0.266	0.331	34	0.288	0.334	13	0.169	0.626	22	0.072	0.816

[a], comparison of overall survival rates between different groups of lymph nodes retrieved; [b], comparison of overall survival rates with the group of >30 lymph nodes retrieved. LNR, positive lymph node ratio; No, number of patients; LODDS, odds of positive lymph nodes; YSR, year survival rate.

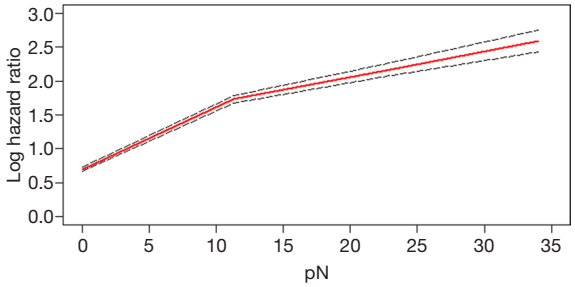

Figure 5 Log hazard ratio as a function of total number of positive nodes (pN).

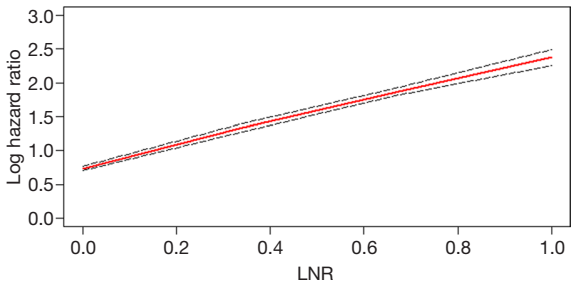

Figure 6 Log hazard ratio as a function of ratio of positive lymph nodes (LNR).

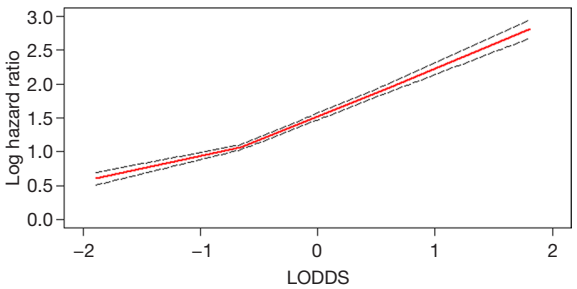

Figure 7 Log hazard ratio as a function of log odds of positive lymph nodes (LODDS).

prognosis (Table S3). We constructed three nomograms based on these factors to predict 5- and 10-year OS. Each nomogram consisted of one of the three N-staging methods, but all other risk factors were the same.

Internal and external validation

The C-index and AIC were used to measure the performance of each nomogram: (I) nomogram pN (*Figure 9*): C-index =0.687 (95% CI: 0.678–0.696), AIC =61,398.24; (II) nomogram

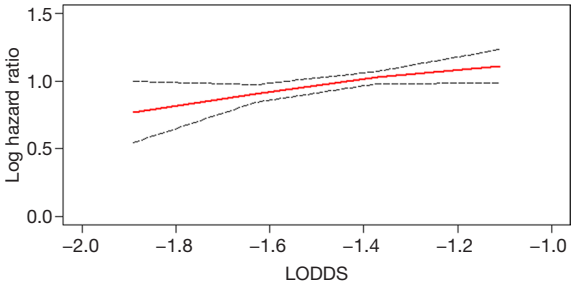

Figure 8 Log hazard ratio as a function of log odds of positive lymph nodes (LODDS) individually for patients with no lymph nodes involved (n=4,740).

LNR (*Figure 10*): C-index =0.691 (95% CI: 0.683–0.701), AIC =61,313.56; (III) nomogram LODDS (*Figure 11*): C-index =0.691 (95% CI: 0.682–0.700), AIC =61,315.6. Our results indicated that the nomogram using LODDS had the most powerful predictive ability. External validation results from the 675 BC patients revealed a C-index of 0.753 (95% CI: 0.690–0.816), and the calibration plot (*Figure 12*) also indicating fairly accurate predictive ability.

Discussion

BC is one of the most common malignant tumors and the main cause of cancer-related deaths among females worldwide (19), with the incidence rate increasing each year. In 2018, there were 266,120 patients diagnosed with invasive BC and 40,920 deaths (19). Although the BC survival rate has significantly improved with better early detection and treatment methods, proper staging is often impeded by underestimating the affected LNs, which can influence subsequent systematic treatment and prognosis, especially for patients with pN0 stage. Therefore, a more effective LN assessment method is necessary to predict prognosis and guide treatment.

The AJCC TNM classification is currently the most common method used for prognosis evaluation and treatment decision-making. However, pN staging only considers the specific number of metastatic LNs found and does not consider the effect of total LN detection on prognosis. Although several studies have shown that the LNR classification is superior to the pN classification, flaws still exist, as patients with stages LNR =0 or 1 can have varied OS. LNR staging can effectively reduce staging migration, and minimal LN detection is needed to ensure accurate prognosis evaluation.

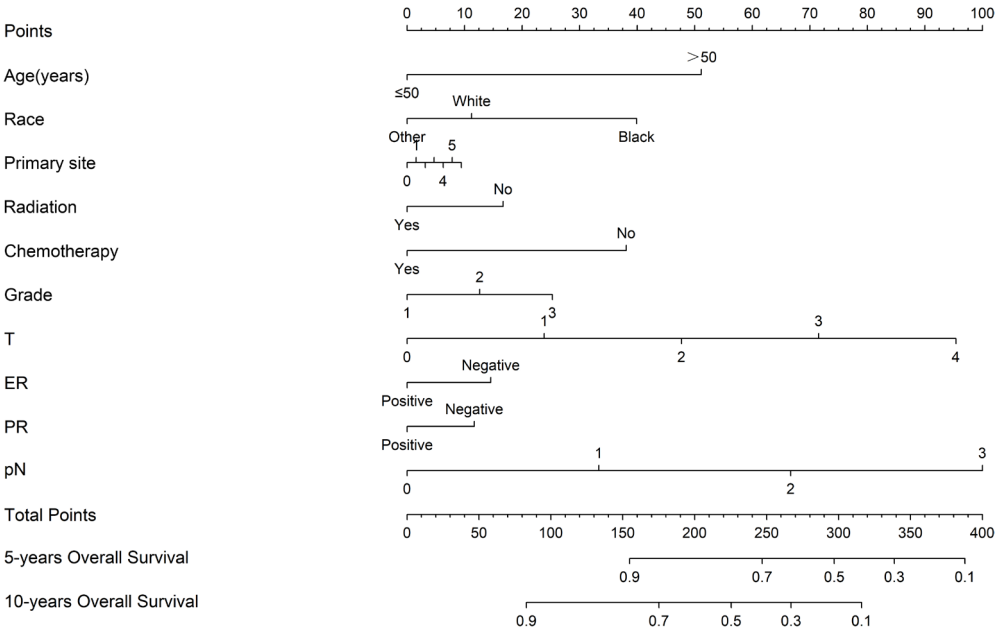

Figure 9 Nomogram constructed based on pN and other non-lymph node risk factors. ER, estrogen receptor; PR, progesterone receptor; pN, total number of positive lymph node.

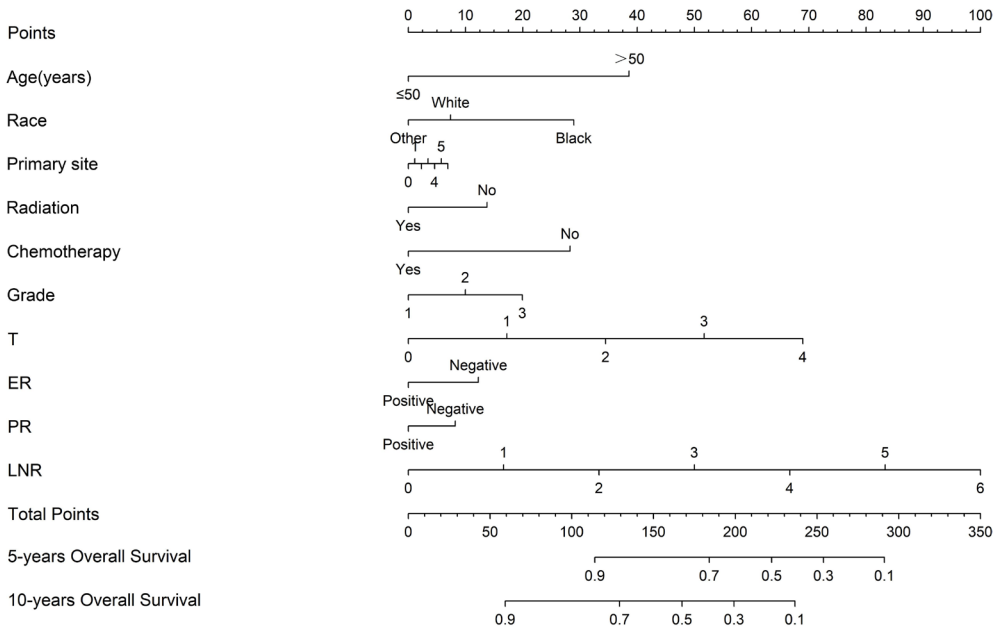

Figure 10 Nomogram constructed based on LNR and other non-lymph node risk factors. ER, estrogen receptor; PR, progesterone receptor; LNR, lymph node ratio.

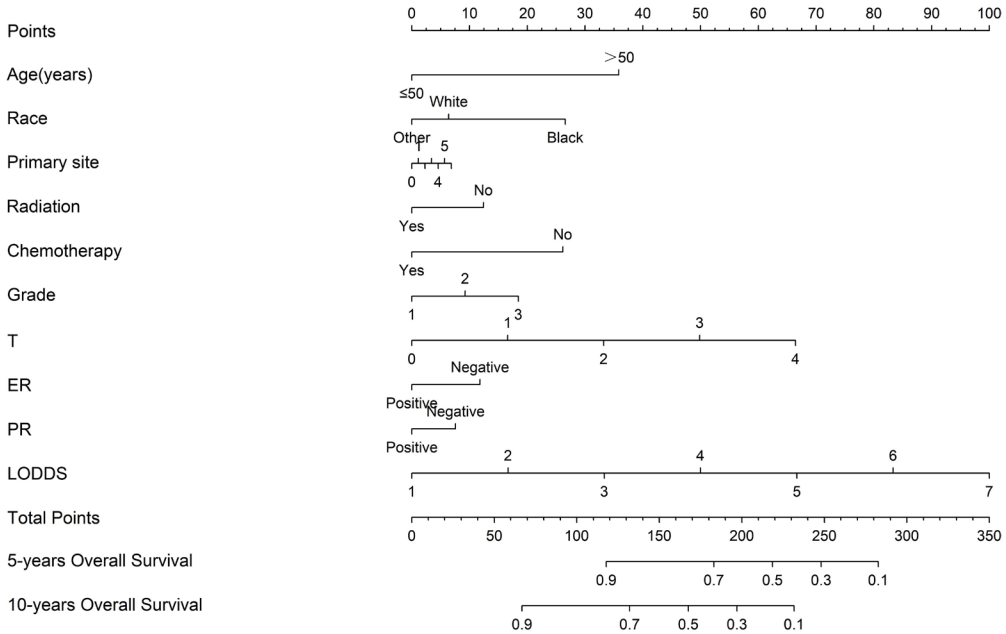

Figure 11 Nomogram constructed based on LODDS and other non-lymph node risk factors. ER, estrogen receptor; PR, progesterone receptor; LODDS, log odds of positive lymph nodes.

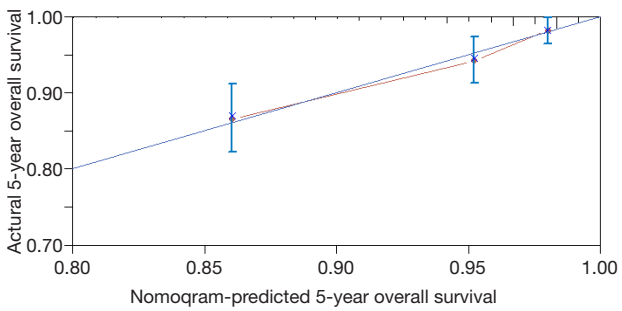

Figure 12 Calibration plot of 5-year Overall Survival associated nomograms in validation sets.

LODDS is defined as the log of the ratio between the probability of being a positive LN and the probability of being a negative LN when one lymph node is retrieved. It is a promising indicator for predicting LN status that displays greater discriminatory power than LNR in patients without metastatic LNs and may be a novel option for improving the accuracy of pN classification for prognosis evaluation. Until now, no study comparing the three lymph node staging methods for predicting outcome in BC patients with mastectomy has been reported.

In our study, non-LN factors were independent predictors of prognosis in the multivariate analysis, and three nomograms were constructed according to the different LN classifications: pN, LNR, and LODDS. The results indicated that LODDS and LNR are superior to pN classification. LODDS and LNR can effectively avoid heterogeneity within the same pN stage, and because these staging methods were highly correlated with the number of LNs removed, their staging accuracy was improved. Furthermore, our cubic splines revealed that different LODDS values indicated different survival rates even in the pN0 stage when LNR =0. By using a large sample population, we confirmed that the survival rate of patients with no LN metastasis was highly heterogeneous, so it is necessary to screen high-risk groups from this population to provide appropriate treatment.

Consistent with our results, some previous studies report that pN staging is inferior to LNR and LODDS staging (20,21). In the 8th edition of TNM staging, prognostic factors have played a pivotal role in the evaluation of individuals, but there is, to our knowledge, no existing prognostic model based on the 8th edition. By combining LN staging with other critical clinicopathologic factors, we constructed the first nomogram based on the SEER database data to predict individual survival. The predictive efficacy of our nomogram was significantly improved with the use of other clinicopathologic factors (e.g., age, race,

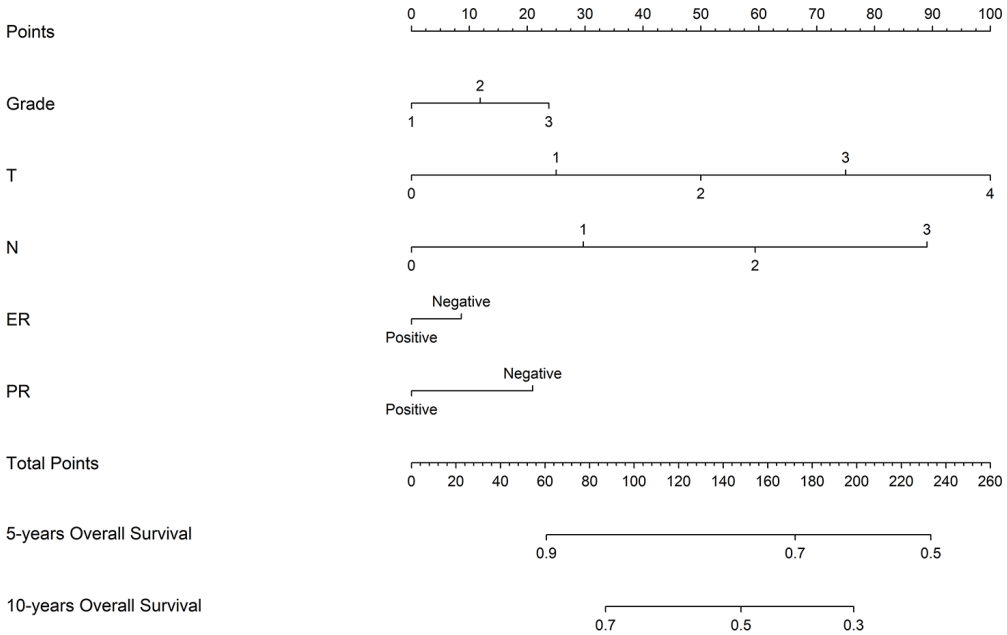

Figure 13 Nomogram constructed based on the 8th TNM classification. ER, estrogen receptor; PR, progesterone receptor.

radiotherapy, and chemotherapy) and refined LN staging (e.g., LNR, LODDS) compared with the nomogram consisting of the factors defined in the 8th TNM staging (*Figure 13*; C-index =0.635; 95% CI: 0.625–0.645; AIC =62,028.51). Finally, we verified the universality of our model using data from patients attending our medical center and found that the model that performed well for the American SEER population had an even better score for the Asian population.

Our study has some limitations that should be recognized. First, this study was retrospective. All patients included in this study were from the SEER database, creating a certain degree of selection bias despite the large sample size. Second, because the diagnostic time of the included population was between 1994 and 2004, HER2 status was not disclosed in the SEER database. Thus, although previous studies have shown that HER2 significantly correlates with prognosis (22,23), it cannot be applied to the model construction in this study. Third, radiotherapy and chemotherapy regimens for each patient are not available in the public database, so we cannot apply detailed drug categories to the prognostic models. Fourth, there is no definite surgical method for ALNs (e.g., sentinel LN biopsy or ALN dissection) in the SEER database, so we only used patients with at least five LNs collected and assumed that ALN dissection had been carried out.

In conclusion, the current study showed that LODDS and LNR have obvious advantages in discriminating patients with the same pN stage in non-distant metastatic BC compared with the AJCC pN classification. Accordingly, our nomogram consisting of both prognostic factors and LODDS or LNR classification may provide relatively accurate prognostic information compared with anatomical TNM stage. This may help to accurately screen patients with variable prognoses for the most appropriate treatment option.

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Footnotes

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4856

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4856). 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). The study was approved by the Ethical Committee of The First Hospital of China Medical University (2019-72-2), and informed consent was obtained from all patients in validation set, while informed consent in training set was unnecessary because SEER is a public resource.

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