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Modified lymph node ratio improves the prognostic predictive ability for breast cancer patients compared with other lymph node staging systems

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ABSTRACT

Background: Metastatic regional lymph nodes (LN) is a strong predictor of worse long-term outcome. Therefore, different LN staging systems have been proposed in recent years. In this study, we proposed a modified lymph node ratio (mLNR) as a new lymph node staging system and then compared the prognostic performance of mLNR with American Joint Committee on Cancer N stage, lymph node ratio (LNR) and log odds of metastatic lymph nodes in breast cancer patients.

Methods: Breast cancer patients who underwent surgery between 2004 and 2012 were identified from the Surveillance, Epidemiology, and End Results database. Restricted cubic spline functions were calculated to characterize the association between variables and the risk of death. The Cox proportional hazards models were constructed to assess the predictive ability of different lymph node staging systems using the Akaike's Information Criterion (AIC) and Harrell's concordance index (C-index).

Results: A total of 264,096 breast cancer patients were enrolled and 187,785 (71.1%) patients had a limited number of LNs harvested. In the limited LN harvest cohort, the prognostic performance of LNR decreased and mLNR could greatly solve this problem. In addition, among the entire cohort, mLNR modeled as a continuous value had the best predictive ability (AIC: 922021.9 and C-index: 0.727) than other lymph node staging systems.

Conclusions: The predictive ability of LNR is restricted by a limited LN harvest. However, mLNR shows superiority to LNR and other lymph node staging systems especially in a limited LN harvest cohort, making mLNR the most powerful lymph node staging systems.

1. Introduction

Breast cancer is the most common cancer and has the highest morbidity and mortality among women worldwide. According to the National Cancer Institute, more than 270,000 new cases and 42,000 deaths have been estimated in 2019 in the United States [1]. ` Metastatic regional lymph nodes (LNs) significantly influence the prediction of long-term breast cancer prognosis after surgery [2]. The traditional American Joint Committee on Cancer (AJCC) N stage is based on the number of positive lymph nodes (NPLNs) and is considered one of the most powerful prognostic factors in breast cancer [3]. Although the number of metastatic LNs has been demonstrated to confer a poor prognosis, the technique of axillary lymph node dissection varies across various institutions, depending on surgical expertise, patient age and co-morbidities, handling of

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List of abbreviations

LN	lymph node
mLNR	modified lymph node ratio
LNR	lymph node ratio
AIC	Akaike's Information Criterion
C-index	Harrell's concordance index
AJCC	American Joint Committee on Cancer
NPLN	the number of positive lymph node
LODDS	log odds of positive lymph nodes
NRLN	the number of removed lymph node
NNLN	the number of negative LN
SEER	the National Cancer Institute's Surveillance, Epidemiology, and End Results
ER	estrogen receptor
PR	progesterone receptor
IQR	interquartile range
RCS	restricted cubic spline
HR	hazard ratio

the surgical specimen by the pathologist [4]. In this condition, in addition to the AJCC N stage, some studies have suggested that LN status should be described by lymph node positive rate (LNR) or log odds of positive lymph nodes (LODDS) [5]. The LNR, a powerful prognostic predictor in breast cancer, is calculated as the NPLNs divided by the number of removed lymph nodes (NRLNs) [6–10]. The LODDS is defined as the logarithmic value of NPLNs divided by the number of negative LNs (NNLNs) and has demonstrated prognostic superiority in other cancers such as gastric cancer [11,12] and colorectal cancer [13–16].

However, the existing staging systems still have some disadvantages. When NRLNs is low, the prognosis evaluation of these staging systems will be affected. For example, there is a negative correlation between NRLNs and OS in breast cancer patients with low NRLNs (often < 10) [17]. Hence, it is clinically required that a certain number of axillary LNs should be resected after a mastectomy to avoid underestimating the tumor stage [18]. Apart from that, when NRLNs is too low, the variability of LNR is large, which affects its accuracy. Therefore, some studies may choose to exclude samples that do not meet a certain number of LNs [19]. To solve this problem, we have proposed mLNR which is calculated by adding 2 to the denominator of LNR, or NRLNs. Then, we studied the impact of these staging systems on prognostic accuracy when there are less or more than 10 LNs removed.

In this study, we compare the prognostic performance of the conventional AJCC N stage and the ratio-based nodal staging systems (LNR, mLNR and LODDS) in breast cancer patients and investigate differences between these staging systems in low NRLNs and high NRLNs. Calculation results show that mLNR which is based on LNR increases prognostic performance especially in patients with low NRLNs.

2. Methods

2.1. Patient selection

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was used in this study. We identified breast cancer patients in the SEER database according to International Classification of Diseases for Oncology, third revision (ICD-O-3) code C50 (breast). Patients with stage 0 disease were excluded. Patients with unclear LN data or bilateral breast cancer were also excluded from the analysis (Supplementary Fig. 1).

Standard data on the demographic information, surgical information, clinical pathology and tumor-related information of each patient were extracted. The tumor-related data included tumor size, stage, presence or absence of distant metastasis, TNM stage, and estrogen receptor (ER) and progesterone receptor (PR) expression. The date of the last follow-up and the vital status were also collected for all patients. For comparative purposes, the data on LN status was categorized into several different LN staging systems: seventh edition AJCC N categories, LNR, and LODDS. To avoid infinite values for LODDS, we added 0.5 to the numerator and denominator when calculating LODDS.

We chose OS as an outcome variable in our study to compare prognostic performance between different models. OS was calculated as the length of time until death, irrespective of the cause.

2.2. Statistical analyses

The demographic, clinical, pathological and interventional variables were reported as percentages or medians with interquartile ranges (IQRs) or as means ± standard deviations. Univariate analysis was performed for all possible confounders using Cox models. The significant confounders ($P < 0.05$) in the univariate analysis were then analyzed in the multivariate analysis. Age, race, pathological type, pathological grade, tumor size, type of surgery, and ER and PR expression were analyzed as prognostic factors. OS was estimated using the Kaplan-Meier method, and differences in survival were examined with the log-rank test. The relationship between different LN staging systems and prognosis was acquired by three-knot restricted cubic spline (RCS) functions, except for the NRLNs, which was evaluated by a four-knot RCS function.

Multivariate Cox models regarding OS were created for a limited group and a sufficient group to assess the independent prognostic value of each nodal category. To verify the selectivity and goodness-of-fit, we calculated Akaike's information criterion (AIC) and Harrell's concordance index (C-statistic) for each model. AIC illustrates the accuracy and simplicity of the model. Usually, the smaller the AIC value, the better the fit of the model. C-statistic is a generalization of the area under the receiver operating characteristic curve that quantifies the proportion of all patient pairs for whom the predicted and observed survival outcomes are concordant [20]. A value of C-statistic = 0.5 indicates no predictive ability compared with chance alone, and a value of 1 indicates perfect discrimination.

Subsequently, the patients were divided into 4 LNR risk groups: LNR1 (LNR = 0), LNR2 ($0 < LNR \leq 0.2$), LNR3 ($0.2 < LNR \leq 0.65$) and LNR4 (LNR>0.65). The chosen LNR cutoff values were based on a previously published analysis.[10] The LODDS was similarly analyzed as both a continuous and a categorical variable using cutoff values based on a previously published analysis. Four groups were created based on LODDS: LODDS1 ($LODDS \leq -1.00$), LODDS2 ($-1.00 < LODDS \leq 0$), LODDS3 ($0 < LODDS \leq 1.5$) and LODDS4 (LODDS> 1.5) [21]. To obtain a reasonable mLNR cutoff value, we selected 86,498 patients with positive LN metastasis in the cohort. A simple random sampling of 10,000 patients with replacement was repeated 1000 times. Both cutoffs were varied between 0.05 and 0.95 in steps of 0.05. The optimal cutoff values were defined as the pair of cutoffs that led to the greatest number of the minimal AIC values during the 1000 times of simple random sampling. Finally, we chose 0.20 and 0.50 as the cutoff values of mLNR (Fig. 1).

All analyses were carried out with R version 3.5.2. All tests were 2-sided, and a $P < 0.05$ was considered statistically significant.

Overall, 264,096 patients with breast cancer who underwent curative-intent resection and who met the inclusion criteria were identified.

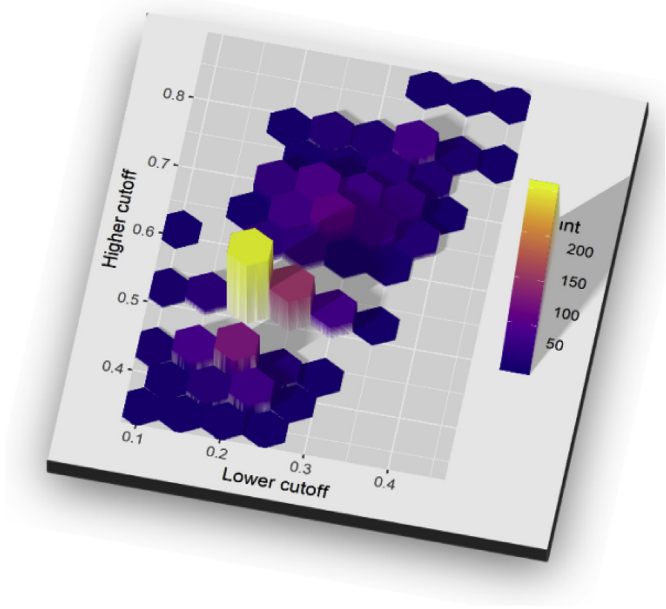

Fig. 1. Distribution of simple random sampling lymph node ratio cutoff points. The Akaike's information criterion (AIC) was used to select the optimal cutoff values in 1000 iterations.

3. Results

3.1. Patient characteristics and impact on overall survival

Initially, we identified 516,898 patients who had breast cancer diagnosed between 2004 and 2010. Finally, 264,096 M0 patients, those with only one primary breast tumor, met the inclusion criteria and were enrolled in this study (Supplementary Fig. 1). The demographic, clinical and interventional characteristics are summarized in Table 1. The ages ranged from 18 to 103 years with a median age of 59.0 years (IQR: 47–66). The patients were predominantly white (215,752, 81.2%), and of the remaining patients, 23,839 (9.0%) were black, and 24,505 (9.3%) were other races. As for pathological type, the vast majority (201,369, 76.2%) of the surgically resected samples were infiltrating ductal carcinoma. Infiltrating lobular carcinoma was the second most common pathological type with 19,443 (7.4%) samples. Most tumors (75.0%) presented with a well or moderately differentiated histological grade. The mean NRLNs, NNLNs, LNR, and LODDS were 7.1 ± 7.2, 5.9 ± 6.0, 0.1 ± 0.2 and −0.7 ± 0.5, respectively. Within the NRLNs <10 subset, the patients' pathological grade tended to be lower, the proportion of stage I patients was higher (25.8% vs 9.1%), and the number of stage III patients was significantly lower (30.5% vs 47.5%). Similarly, the NRLNs <10 subset is dominated by tumors ≤2 cm in size (71.3%) and an AJCC N stage of N0 (83.6%). These data indicate that tumors in the NRLNs <10 subset are relatively less malignant than those in the NRLNs ≥10 subset.

The median follow-up time was 73 months (IQR: 50–102). A univariate Cox regression model showed that age, race, tumor size, histological grade, histological subtype, surgery and ER/PR status were significant for OS (Table 2). As a result of the univariate survival analysis, all the significant variables were included in the Multivariate Cox models.

3.2. Relationships between different lymphatic staging systems and prognosis

The relationships between hazard ratio (HR) and LNR, LODDS, NRLNs and NNLNs were evaluated using the RCS method (Fig. 2). Fig. 2A shows the link between LNR and HR, which is nearly linearly related to $\log_2$HR and has a small confidence interval. When LODDS < −1, $\log_2$HR hardly changed, but when the LODDS > −1, the LODDS had a positive correlation with $\log_2$HR like LNR (Fig. 2B). Interestingly, as the NRLNs increase, $\log_2$HR first increases and then decreases, reaching its highest value at NRLNs = 20 (Fig. 2C). Finally, we studied the relationship between NNLNs and HR and found the relationship to be negatively correlated (Fig. 2D). However, the confidence intervals shown in both Fig. 2C and D are both large, indicating that the accuracy of NRLNs and NNLNs as prognostic factors is deficient.

3.3. Impact of the number of removed lymph nodes on the risk of death: is the lymph node ratio an ideal prognostic strategy?

Firstly, we would like to show the reasons why we want to modify LNR. Fig. 3A illustrates the distribution between the LNR and LODDS. There was a consistent agreement between the LNR and LODDS (Pearson correlation 0.821, P < 0.001). However, when the value of LNR was equal to 0 (i.e., node-negative patient) or 1, the corresponding LODDS value was quite heterogeneous. In addition, when LNR = 0, the HR of the NRLNs<10 subset and NRLNs> 10 subset in the Cox risk regression shown little change. However, when LNR = 1, the HR of the NRLNs<10 subgroup in the Cox risk regression was significantly lower than that of the NRLNs>10 subset (HR = 0.606). This result indicates that when the LNR = 1, the ability to predict risk in cases with different NRLNs is significantly heterogeneous. Due to the defect of LNR, we proposed a modified LNR and compared its ability to predict prognosis with NRLNs, LNR and LODDS in different subsets which we will show later.

Fig. 3B and C explain the principle of mLNR. We further explored the interaction between NRLNs and LNR by defining the HR of death associated with the LNR at 4 fixed LNR intervals as 0 < LNR≤0.25, 0.25 < LNR≤0.5, 0.5 < LNR≤0.75 and 0.75 < LNR (Fig. 3B). Heterogeneity was noted when analyzing different LNR groups. Although the HR of death was relatively constant for patients with LNR ranging from 0 to 0.25, there was considerable variation in HR when LNR was >0.50. The HR of death associated with mLNR in the 4 exact fixed mLNR intervals was also calculated (Fig. 3C). Compared to the LNR curve, the mLNR curve appears smoother and has less heterogeneity. This phenomenon is particularly evident in the mLNR ≥0.5 subset.

3.4. Impact of LN status on risk of death: performance of various LN staging/scoring systems

Through multivariate Cox models, the LN staging systems with the best prognostic discriminatory ability were assessed through iterative statistical models and compared using the AIC and C-statistic values. Table 3 summarizes the parameter estimates from the multivariate survival analysis that controlled for confounders. When assessed using continuous values among the entire cohort, LNR had a better prognostic performance (C-index: 0.725; AIC: 922505.5) than the LODDS (C-index: 0.720; AIC: 923355.6) and was slightly surpass the AJCC N staging system (C-index: 0.724; AIC: 923546.8) Within the NRLNs <10 subset, although the performance of LNR (C-index: 0.701; AIC: 501027.1) was better than that of the LODDS (C-index: 0.699; AIC: 501029.3), the performance of LNR was lower than that of the AJCC N staging system (C-index: 0.702; AIC: 500965.3). Within the NRLNs ≥10 subset, the predictive performance of LNR (C-index: 0.719; AIC: 367034) was still better than that of the AJCC N staging system (C-index: 0.712; AIC: 367860.3) but was not better than LODDS (C-index: 0.717; AIC: 367159.9). This

Table 1
Demographic and clinical characteristics of the study cohort.

	subset with NRLN <10 N = 187,785	subset with NRLN≥10 N = 76,311	All Patients N = 264,096	P-value[c]
Age at diagnosis, years				<0.001
<50	44,970 (23.9%)	24,474 (32.1%)	64,305 (26.3%)	
≥ 50	142,817 (76.1%)	51,837 (67.9%)	199,791 (73.7%)	
Median (IQR)	59 (50–69)	56 (47–66)	58 (49–68)	
Race				<0.001
White	154,116 (82.1%)	59,336 (77.8%)	215,752 (81.2%)	
Black	17,302 (9.2%)	10,087 (13.2%)	23,839 (9.0%)	
Others[a]	16,367 (8.7%)	6888 (9.0%)	24,505 (9.3%)	
Surgery				<0.001
BCS	126,302 (67.3%)	49,870 (65.4%)	174,936 (66.2%)	
Mastectomy	61,483 (32.7%)	26,441 (34.6%)	89,160 (33.8%)	
Histology				<0.001
IDC	143,053 (76.2%)	57,642 (76.1%)	201,369 (76.2%)	
ILC	13,568 (7.2%)	6391 (8.4%)	19,443 (7.4%)	
Others[b]	31,164 (16.6%)	12,278 (16.1%)	43,284 (16.4%)	
Grade				<0.001
I	48,470 (25.8%)	9162 (9.1%)	58,337 (22.1%)	
II	82,040 (43.7%)	30,907 (40.5%)	113,240 (42.9%)	
III	57,275 (30.5%)	36,242 (47.5%)	92,519 (35.0%)	
Tumor size (cm)				<0.001
≤ 2	133,852 (71.3%)	28,937 (37.9%)	164,872 (62.4%)	
2–5	47,745 (25.4%)	35,869 (47.0%)	83,039 (31.4%)	
> 5	6188 (3.3%)	11,505 (15.1%)	16,185 (6.1%)	
AJCC N stage				<0.001
N0	157,059 (83.6%)	15,990 (21.0%)	175,696 (66.5%)	
N1	26,867 (14.3%)	32,841 (43.0%)	62,446 (23.6%)	
N2	3502 (14.3%)	13,326 (17.5%)	17,098 (6.5%)	
N3	357 (0.19%)	14,154 (18.5%)	8856 (3.4%)	
NRLN, mean (SD)	3.3 (2.2)	16.7 (6.0)	7.1 (7.2)	<0.001
NNLN, mean (SD)	3.0 (2.1)	13.2 (4.6)	5.9 (6.0)	<0.001
LNR, mean (SD)	0.1 (0.2)	0.2 (0.3)	0.1 (0.2)	<0.001
LODDS, mean (SD)	−0.7 (0.4)	−0.7 (0.7)	−0.7 (0.5)	<0.001
ER status				<0.001
Positive	154,958 (82.5%)	57,418 (75.2%)	212,679 (80.5%)	
Negative	32,827 (17.5%)	18,893 (24.8%)	51,417 (19.5%)	
PR status				<0.001
Positive	135,269 (72.0%)	48,830 (64.0%)	184,582 (69.9%)	
Negative	52,516 (28.0%)	27,481 (36.0%)	79,514 (30.1%)	
Follow-up time				
Median (IQR)	70 (46–100)	75 (51–103)	73 (50–102)	

Abbreviations: AJCC, American Joint Committee on Cancer; BCS, breast conserving surgery; ER, estrogen receptor; PR, progesterone receptor; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; IQR, interquartile range; LN, lymph node; LNR, lymph node ratio; LODDS, log odds of metastatic lymph nodes; NNLN, number of negative lymph nodes; NRLN, number of removed lymph nodes; PR, progesterone receptor; SD, standard deviation.

[a] Including American Indian/Alaskan native and Asian/Pacific Islander.

[b] Including other breast cancer histology except IDC and ILC.

[c] P-value was calculated with the chi-square test for categorical variables and with the Kruskal-Wallis test for continuous variables.

finding shows that when the NRLNs <10, LNR is not ideal as an LN staging system, and it is difficult to predict the OS accurately.

When we adopt the mLNR as the LN staging system, the predictive power of the mLNR is much better than that of the AJCC N staging system, LNR and LODDS among all patients (C-index: 0.725; AIC: 922693.9) and the NRLNs ≥10 subset (C-index: 0.716; AIC: 367373.7). The most important aspect is that the accuracy of the mLNR in the NRLNs <10 subset (C-index: 0.702; AIC: 500827.7) was similar to that of the AJCC N staging system. All the above data indicate that in our cohort, the predictive performance of mLNR for prognosis is superior to that of other LN staging systems.

To assess whether the relative performance of the different LN staging systems would be impacted by the chosen categorical cutoff values, repeat analyses were performed using categorical variables in the statistical models. Still, mLNR had the best predictive performance, which was higher than LNR, AJCC N staging system and LODDS (Table 3).

5. Discussion

The LN staging system of breast cancer has a crucial influence and helps guide postoperative patient prognosis, treatment and surveillance. The most widely used LN staging method is the AJCC N staging system, but the reliability of this method has been recently questioned by researchers because the system considers only the NPLNs without considering the NRLNs or NNLNs [22–25]. Due to the importance of LN status for breast cancer, researchers have proposed a range of different LN staging methods over the past decade [15,26,27]. Early experiences with LNR can be traced back to the 1990s when several authors proposed that LNR had a more precise and comprehensive prognostic value than NPLNs in patients with resected gastric cancer [28–30]. Furthermore, LNR has also been widely studied as a prognostic factor in breast cancer [31,32]. However, studies using the LODDS emerged from the cancer research field approximately two decades after recognizing

Table 2
Univariate Cox proportional hazards model of breast cancer.

	All Patients N = 264,096			subset with NRLN≥10 N = 76,311			subset with NRLN <10 N = 187,785		
	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
Age at diagnosis years									
<50	1.00		<0.001	1.00		<0.001	1.00		<0.001
≥50	1.79	1.75–1.83		1.68	1.62–1.74		2.21	2.13–2.30	
Race									
White	1.00		<0.001	1.00		<0.001	1.00		<0.001
Black	1.52	1.47–1.56		1.43	1.37–1.49		1.42	1.36–1.48	
Others[a]	0.69	0.66–0.72		0.73	0.68–0.77		0.63	0.59–0.67	
Surgery									
BCS	1.00		<0.001	1.00		<0.001	1.00		<0.001
Mastectomy	2.01	1.97–2.05		1.77	1.71–1.83		1.74	1.70–1.79	
Histology									
IDC	1.00		<0.001	1.00		0.4	1.00		0.01
ILC	1.05	1.01–1.09		1.02	0.96–1.07		1.06	1.00–1.11	
Others[b]	0.96	0.94–0.99		0.98	0.94–1.02		0.97	0.93–1.00	
Grade									
I	1.00		<0.001	1.00		<0.001	1.00		<0.001
II	1.49	1.44–1.54		1.41	1.33–1.50		1.40	1.34–1.45	
III	2.45	2.38–2.53		2.29	2.17–2.43		2.09	2.02–2.18	
Tumor size (cm)									
≤ 2	1.00		<0.001	1.00		<0.001	1.00		<0.001
2–5	2.29	2.25–2.34		1.98	1.91–2.05		2.14	2.08–2.21	
> 5	4.31	4.18–4.44		3.33	3.19–3.47		4.10	3.90–4.30	
AJCC N stage									
N0	1.00		<0.001	1.00		<0.001	1.00		<0.001
N1	1.73	1.69–1.77		1.05	1.00–1.09		2.01	1.94–2.07	
N2	3.23	3.14–3.33		1.83	1.74–1.91		5.23	4.95–5.52	
N3	5.59	5.40–5.78		3.51	3.35–3.67		6.44	5.48–7.58	
ER status(P)	1.87	1.83–1.92	<0.001	1.85	1.79–1.91	<0.001	1.73	1.68–1.78	
PR status(P)	1.83	1.80–1.87	<0.001	1.87	1.81–1.93	<0.001	1.68	1.63–1.73	
LNR	5.77	5.60–5.94	<0.001	5.86	5.60–6.13	<0.001	4.43	4.24–4.62	<0.001
LODDS	2.21	2.18–2.25	<0.001	1.95	1.92–1.99	<0.001	2.35	2.28–2.42	<0.001

Abbreviations: N, number; HR, hazard ratio; CI, confidence interval; P, positive; NRLN, number of removed lymph nodes; BCS, breast conserving surgery; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; LNR, lymph node ratio; LODDS, log odds of metastatic lymph nodes.
[a] Including American Indian/Alaskan native and Asian/Pacific Islander.
[b] Including other breast cancer histology except IDC and ILC.

the prognostic utility of the LNR [33].

In our article, we found that there is a deficiency in LNR. To explore the relationship between the LODDS and LNR, this article studied the scatter plot between LNR and LODDS. As shown in Fig. 2, there is a high degree of consistency between the LNR and LODDS. However, when LNR = 0 or LNR = 1, the LODDS value becomes extremely heterogeneous. This finding shows that the accuracy of the predictive power for prognosis is significantly reduced when the LNR equals 0 or 1. For an extreme example, the prognosis of a patient with 1 LN removed and 1 positive LN is clearly expected to have a better prognosis than patients with 20 LNs removed and 20 positive LNs.

Based on the above results, we have proposed a modified LNR to improve the predictive power of LNR. We add 2 to the NRLNs, the denominator of LNR to adjust the value of LNR under different NRLNs. Our results show that when utilized as categorical variables, both LNR and LODDS are superior to the traditional AJCC N staging system. However, in the NRLNs<10 subgroup, the prognostic predictive ability of both LODDS and LNR was slightly lower than that of the AJCC N staging system. Moreover, the predictive power of LODDS and LNR were basically equal to each other, which is different from the results shown in previous studies [11]. For the NRLNs ≥10 subgroup, both LNR and LODDS were found to be significantly better than the AJCC N staging system, and the predictive power of LNR was better than that of LODDS. It is worth mention that when mLNR was added to the comparison, the data indicated that within the overall patient group or the NRLNs <10 subgroup, mLNR showed superior predictive power over LNR, LODDS and AJCC N staging system. In addition, within the NRLNs ≥10 subgroup, the predictive power of the mLNR was basically equal to LNR. Furthermore, when mLNR was compared as a continuous variable, mLNR was clearly superior to other LN staging systems in our model. Taken together, our results demonstrate that the introduction of mLNR can greatly increase the predictive power of the model, therefore we suggest that mLNR can be considered when performing LN staging.

There are still some disadvantages to our research. As ratio values, LNR and mLNR are not as convenient to calculate as the AJCC N stage, which makes these ratios difficult to popularize and implement in clinical applications. In addition, it is well known that the state of HER2 expression is an important factor, which significantly influences the prognosis of breast cancer. Since HER2 was introduced in the SEER database after 2010, we did not include data after 2010 in order to obtain more information about prognostic events. Therefore, the HER2 expression status is missing in our data and future work should include HER2 expression designed to evaluate whether mLNR still performs better than other LN staging systems.

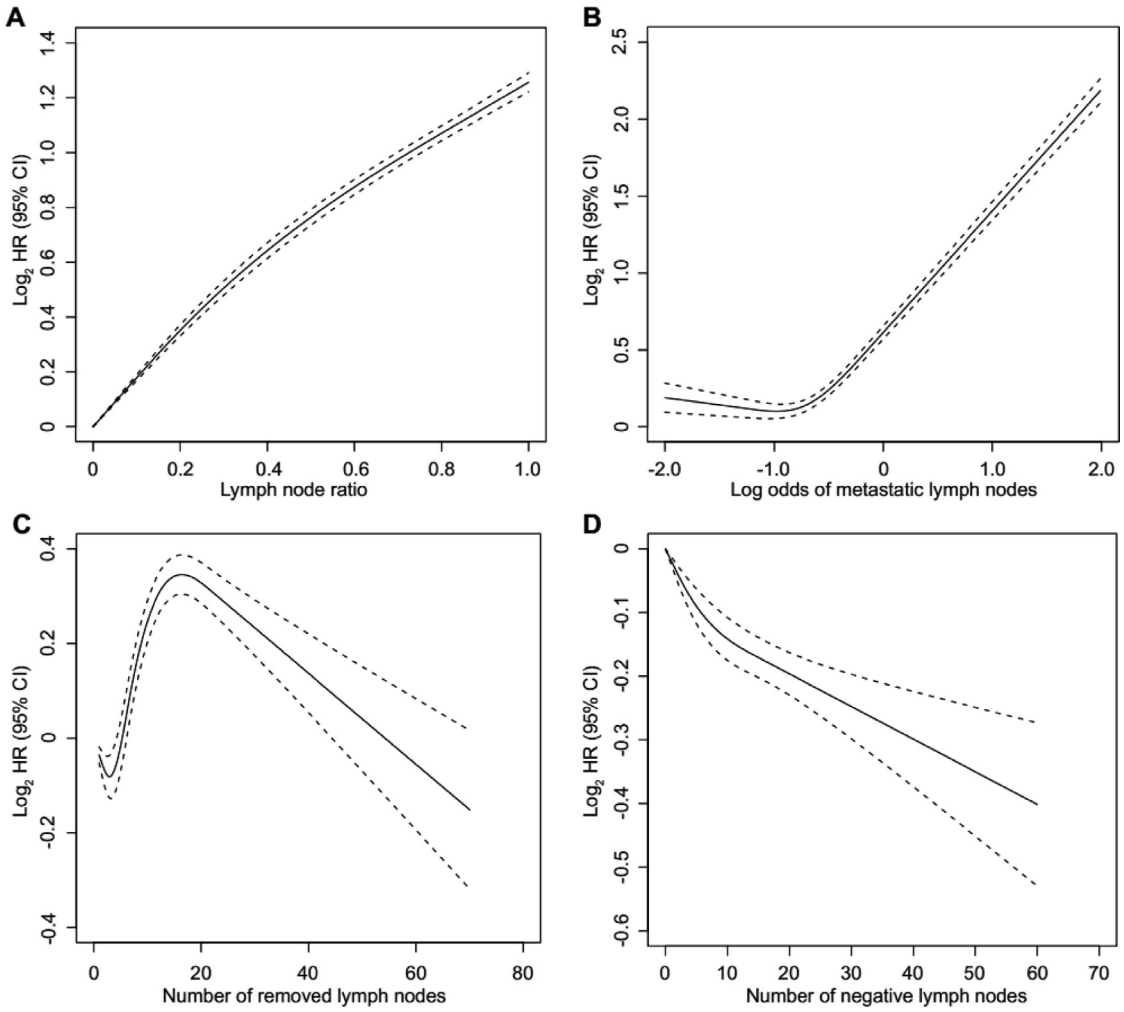

Fig. 2. Association between different lymph nodes staging and hazard ratio (HR), allowing for non-linear effects, with 99% CI. A, B, C and D are respectively for lymph node ratio, log odds of metastatic lymph nodes, number of removed lymph nodes and number of negative lymph nodes.

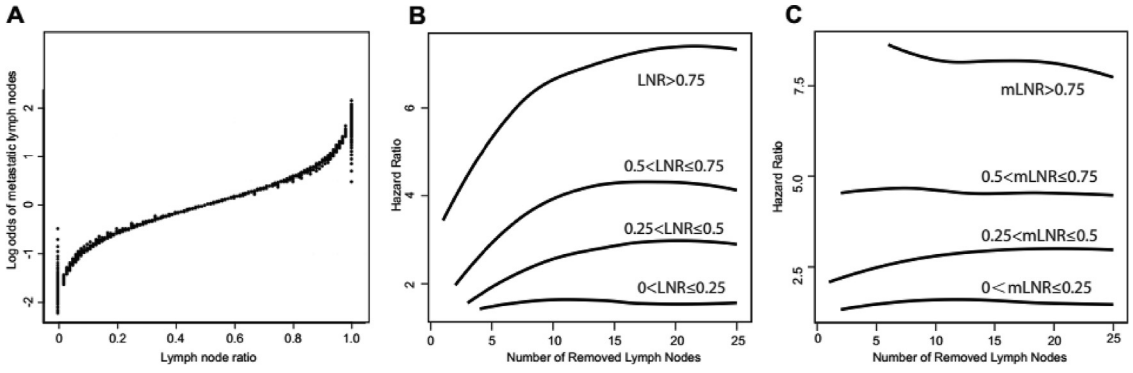

Fig. 3. (A) A scatter plot of lymph node ratio (LNR) and log odds of metastatic lymph nodes (LODDS). The distribution shows a one-to-one correspondence and positive correlation between the two curves (except LNR = 1 or LNR = 0 [node-negative]). (B) Hazard ratio according to the number of removed lymph nodes examined (NRLN) for different LNR intervals. The hazard ratio varies considerably for a given LNR, especially for LNR >50%, and increases as the number of removed lymph nodes increases. (C) Hazard ratio according to NRLN for different modified lymph node ratios (mLNR) intervals. The hazard ratio varies little with the increase of NRLN compared with Figure B in different mLNR intervals.

6. Conclusion

Our results indicate that mLNR shows superiority to LNR and other lymph node staging systems especially in a limited LN harvest cohort, making mLNR the most powerful lymph node staging systems in our data. Therefore, we believe mLNR can be considered in clinical practice.

Table 3
Prognostic performance of the models describing the relationship between different lymph node staging systems and mortality, adjusted for other clinical and demographic variables.

Model	Among the entire training cohort		Among NRLN<10 subset		Among NRLN≥10 subset	
	OS		OS		OS	
	AIC	C-Index	AIC	C-Index	AIC	C-Index
1- Clinical and demographic Variables (without LN staging systems)	927679	0.709 (0.706–0.711)	502769.5	0.690 (0.686–0.693)	369972	0.692 (0.688–0.696)
2- Model 1 + AJCC N staging	923546.8	0.724 (0.721–0.726)	500965.3	0.702 (0.698–0.705)	367860.3	0.712 (0.709–0.716)
3- Model 1 + LNR (continuous)	922505.5	0.725 (0.722–0.727)	500868.5	0.701 (0.697–0.705)	367034	0.719 (0.715–0.722)
4- Model 1 + mLNR (continuous)	922021.9	0.727 (0.724–0.729)	500539.3	0.702 (0.699–0.706)	367036.8	0.719 (0.715–0.723)
5- Model 1 + LODDS (continuous)	923355.6	0.720 (0.717–0.723)	501065.1	0.699 (0.695–0.702)	367159.9	0.717 (0.713–0.720)
6- Model 1 + LNR (categorical)	922699.4	0.725 (0.722–0.728)	501027.1	0.701 (0.698–0.705)	367353.8	0.716 (0.712–0.720)
7- Model 1 + mLNR (categorical)	922351.2	0.726 (0.723–0.729)	500827.7	0.702 (0.698–0.706)	367373.7	0.717 (0.713–0.720)
8- Model 1 + LODDS (categorical)	923212.7	0.724 (0.721–0.726)	501116	0.698 (0.695–0.702)	367363	0.715 (0.711–0.719)

Abbreviations: AJCC, American Joint Committee on Cancer; BCSS, breast cancer-specific survival; LN, lymph node; LNR, lymph node ratio; mLNR, modified lymph node ratio; LODDS, log odds of metastatic lymph nodes; OS, overall survival.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The clinic data of breast cancer patients that support the findings of this study are available from the National Cancer Institute's Surveillance, Epidemiology, and End Results database, https://seer.cancer.gov/

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Authors' contributions

Conception and design: MGJ, YG, YCP, XH and ZMS. Development of methodology: MGJ, YG, YCP, XH and ZMS. Acquisition of data: MGJ, YG and YCP. Analysis and interpretation of data: MGJ, YG, YCP, XH and ZMS. Writing, review, and/or revision of manuscript: MGJ, YG, YCP, XH and ZMS. Study supervision: XH and ZMS. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.11.003.

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