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Prediction of non-sentinel lymph node metastases in T1–2 sentinel lymph node-positive breast cancer patients undergoing mastectomy following neoadjuvant therapy

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Abstract

Background Axillary lymph node dissection (ALND) is the standard axillary management for breast cancer patients with positive sentinel lymph node biopsy (SLNB) after neoadjuvant therapy. Nevertheless, when that happens, the frequency of additional positive nodes is not properly evaluated. We aim to develop a prediction model to assess the frequency of additional nodal disease after a positive sentinel lymph node following neoadjuvant therapy.

Methods We retrospectively analyzed the ultrasound and clinicopathological characteristics of breast cancer patients with 1–3 positive sentinel lymph nodes (SLN) undergoing mastectomy after neoadjuvant therapy (NAT) at our institution, and performed univariate and multivariate logistic analyses to confirm the factors affecting non-SLN metastasis. These factors were included to establish a nomogram, and the area under receiver operating characteristic curve (AUC) and decision curve analysis (DCA) were utilized to assess the validity of this model.

Results A total of 126 breast cancer patients were ultimately included in our study, 38 (53.5%) patients were diagnosed with non-SLN metastases of all 71 patients in training set. The results of multifactorial logistic analysis suggested that lymph node metastasis ratio (LNR), short axis of lymph node and progesterone receptor (PR) were strongly associated with non-SLN metastasis. We established a nomogram using the above three variables as predictors, which yielded an area under the curve of 0.795, and validated with a favorable AUC of 0.876.

Conclusion The nomogram we constructed can accurately predict the likelihood of non-SLN metastasis in our patients with 1–3 positive SLN after NAT, which may help guide decision making regarding axillary management.

Keywords Breast cancer, Nomogram, non-SLN metastases, Neoadjuvant therapy

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Introduction

Neoadjuvant therapy (NAT) for breast cancer can help to descent the stage of breast tumors, achieve breast conservation and axillary downstaging, and reduce the scope of surgery [1]. Axillary lymph node dissection (ALND) is the recognized axillary management for mastectomy and has long been considered an important part of breast cancer surgery [2]. ALND provides an accurate assessment of a patient's axillary status in order to develop a more appropriate treatment plan [3]. However, ALND may affect the patients' quality of life, as patients often experience complications such as sensory abnormalities, activity limitations, and edema after ALND [4]. For patients undergoing NAT, SLNB is recommended when patients are cN0. SLN-negative patients exhibited similar rates of regional recurrence, disease-free survival (DFS), and overall survival (OS) following SLNB and ALND according to the NSABP B32 trial [5]. SLN-negative patients who underwent ALND did not reveal a significant survival benefit compared to those who underwent SLNB alone. More than 50% of patients with cN0 who receive NAT have no detectable ALN involvement postoperatively [6]. However, the feasibility of SLNB after NAT in cN+patients remains controversial, and ALND remains the standard treatment for patients with the positive lymph nodes after NAT. For the breast cancer patients with ALNs assessed as cN1 prior to neoadjuvant therapy, neoadjuvant therapy resulted in approximately 40% of patients being negative, especially for patients with cN1 breast cancer with specific molecular typing, and two-thirds of breast cancer patients were free of axillary lymph node metastases (ALNM) after NAT [7]. The above results suggest that supplemental ALND can be avoided in this subset of patients with negative ALNs after NAT if SLNB results are negative [8]. Most of the patients with ALN metastasis after NAT enrolled in the relevant study were at the stage of cN1, and SLNB after NAT should be implemented for cases with cN1 stage turn to ycN0, and those with cN2 stage down to ycN0 should be performed with caution [7, 9, 10]. As for cases in which ALNs remain positive after NAT, the standard treatment is undoubtedly still ALND [11]. Therefore, to ensure the accuracy and safety of implementation of SLNB after NAT, the main focus should be on patients with cN1 down to ycN0 after NAT. The results of the classic Z0011 study were first published in 2010 [12]. After 5 and 10 years of follow-up, it was confirmed that patients with 1 to 2 SLN metastases can be exempted from axillary dissection if they undergo breast-conserving surgery and subsequently complete radiotherapy and systemic therapy. There was no statistical difference between patients with axillary dissection in terms of regional control and long-term survival [13]. Z0011 is a study to rewrite the guidelines. The SENOMAC trial demonstrated that in patients with stage T1 to T3 breast cancer who are clinically lymph node-negative and have macroscopic metastases in 1 or 2 sentinel lymph nodes, the majority of whom undergo lymph node radiotherapy, it is safe to omit complete axillary lymph node dissection [14]. While for mastectomy surgery, patients with T1-2 primary breast cancer and no palpable lymphadenopathy were enrolled in AMAROS trial. The AMAROS study proved that patients with 1–2 macrometastases in SLN, whether undergoing breast-conserving surgery or total resection, can be exempted from ALND if they receive axillary radiotherapy after surgery [15]. However, the clinical study included relatively few mastectomy patients, only about 17%. Therefore, it is currently more controversial whether to exempt axillary dissection after mastectomy.

The objective of our research was to recognize the predictors of non-SLN metastasis in patients receiving NAT with 1–3 SLN-positive after mastectomy and to use these predictors to construct a nomogram to guide clinicians in the choice of treatment.

Materials and methods

Study design and data collection

We retrospectively investigated 353 patients diagnosed as invasive breast cancer from the Second Affiliated Hospital of Chongqing Medical University during 2016 to 2023. The inclusion standards of our research were: (1) all patients were at the stage of T1-T2 of AJCC 8th T stage, (2) all received NAT, (3) all patients underwent mastectomy after NAT, (4) all underwent SLNB and following completed ALND, (5) 1–3 positive SLN detected by SLNB (In our study, Macro-metastasis and micrometastasis were defined as SLN positive, ITCs and no metastasis were defined as SLN-negative.). The study excluded the following groups: (1) patients with clinical staging of lymph nodes as N2 after NAT, (2) those with specific pathological types, (3) cases with incomplete NAC for any reason, (4) patients with a history of breast cancer in either the ipsilateral or contralateral breast, and (5) individuals with incomplete medical records. Neoadjuvant therapy indications were determined according to the National Comprehensive Cancer Network (NCCN) guidelines [16]. The indications of the neoadjuvant therapy are as follow: 1.HER2-positive disease and TNBC, if≥cT2 or ≥cN1; 2.Large primary tumor relative to breast size in a patient who desires breast conservation; 3.cN+disease likely to become cN0 with preoperative systemic therapy. Finally, 126 patients who met the eligibility criteria were included in the study. For patients categorized as Luminal A, we opt for neoadjuvant treatment when tumor reached T3 or N+. In our center, the dye method (nanocarbon) is mainly used for sentinel lymph node tracing. Among the included patients, 76.24% had

3 to 6 sentinel lymph nodes biopsied. These patients were divided into two groups: a training group ($n=71$) and a validation group ($n=55$). The training group consisted of patients who consulted between January 2016 and December 2021, with a total of 71 cases. The validation group comprised cases from January 2022 to December 2023, with a total of 55 cases (Fig. 1). And we collected clinicopathological factors of these patients, including side, menopause, number of positive SLN, LNR, histological grade, estrogen receptor (ER), progesterone receptor (PR), clinical T stage (cT), clinical N stage (cN), human epidermal growth factor receptor 2 (HER-2), ki-67, treatment response, and the color doppler ultrasound characteristics: tumor location, long axis of lymph node, short axis of lymph node (The long axis of a lymph node is the longest diameter in any plane, while the short axis refers to the maximum diameter of a lymph node perpendicular to its long axis.), blood flow, lymphatic hilum, calcification, and cortex.

Statistical analysis

The relationship of the clinicopathological factors between the non-SLN-positive groups and non-SLN-negative groups were explored. Categorical variables were investigated by using fisher exact test or Pearson chi-square test. In our research, specific clinical parameters were analyzed using Student's t-test. The predict items were dug out by univariate and multivariate logistic regressions. The multivariate model had these variables that the univariate analysis found to be statistically significant. Additionally, We used the risk of non-SLN metastasis as an outcome indicator and the significant factors in the multivariate COX regression analysis as covariates, and based on their correlation with the impact of non-SLN metastasis, we plotted a nomogram using the "rms" package, summed the scores based on patient-specific variables to obtain the total score, and drew a vertical line between the total points axis and the risk axis to predict the probability of developing additional positive lymph nodes after neoadjuvant treatment for patients with T1-T2 staging of 1–3 positive sentinel lymph nodes. To evaluate the nomogram's predictive value, calibration curves and a decision curve analysis (DCA) curve were constructed. All our analyses were performed by using SPSS26 and R4.2.1 software.

Results

Clinicopathologic characteristics

We counted the clinicopathologic characteristics of 71 breast cancer patients from the screened training set (Table 1) and categorized the patients into two subgroups based on whether or not the non-SLNs were positive. Among the patients finally included in the analysis, Luminal A accounted for 42.8%, Luminal B accounted for 31.1%, HER2-enriched accounted for 14.2%, and triple-negative accounted for 10.3%. And 76.24% had 3 to 6 sentinel lymph nodes biopsied. We found that the value of LNR was higher in non-SLN-positive patients, lymph nodes were longer in long and short axes, and cortical thickening was more likely to be detected under Doppler color ultrasound.

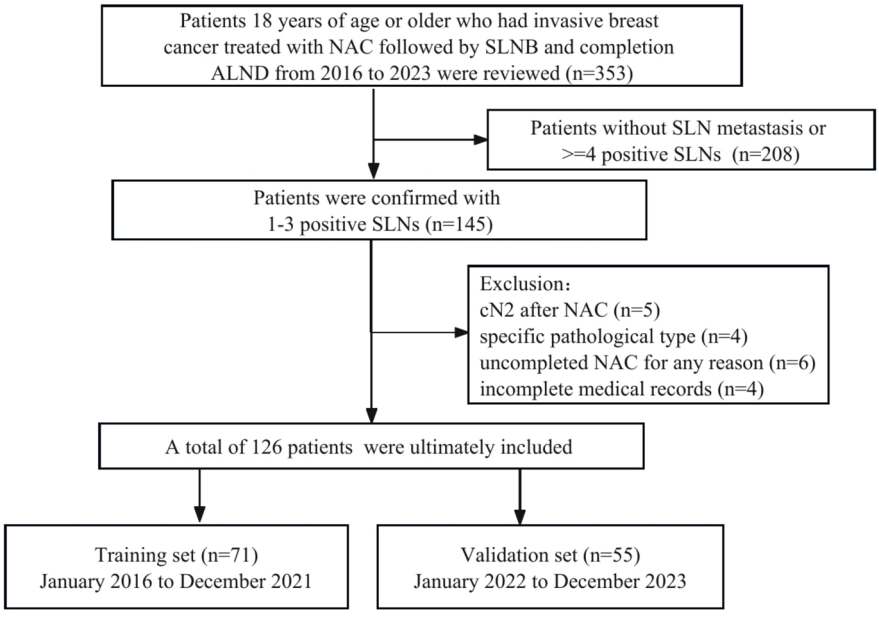

Fig. 1 The patients selection process for the study

Table 1 Baseline characteristics of non-SLN positive and non-SLN negative patients

Variables	Subgroup	No. of patients		
		Non-SLN negative	Non-SLN positive	P
		(*n* = 34, 47.9%)	(*n* = 37, 52.1%)	
Side	Left	18(52.9%)	20(54.1%)	0.925
	Right	16(47.1%)	17(45.9%)	
Menopause	No	21(61.8%)	18(48.6%)	0.267
	Yes	13(38.2%)	19(51.4%)	
Number of positive SLN	1	20(58.8%)	14(37.8%)	0.189
	2	9(26.5%)	13(35.1%)	
	3	5(14.7%)	10(27.0%)	
LNR		0.41(± 0.21)	0.63(± 0.31)	< 0.001
Tumor location	Upper outer quadrant	23(67.6%)	21(56.8%)	0.421
	Upper inner quadrant	3(8.8%)	4(10.8%)	
	Lower inner quadrant	1(2.9%)	0(0.0%)	
	Lower outer quadrant	5(14.7%)	5(13.5%)	
	Central	2(5.9%)	7(18.9%)	
Long axis of LN(Mean ± SB, mm)		6.6(± 7.6)	12.4(± 8.8)	0.004
Short axis of LN(Mean ± SB, mm)		3.4(± 4.2)	6.9(± 4.8)	0.002
Blood flow	No	20(58.8%)	22(59.5%)	0.957
	Yes	14(41.2%)	15(40.5%)	
Calcification	No	32(94.1%)	33(89.2%)	0.456
	Yes	2(5.9%)	4(10.8%)	
Cortex	Normal	21(61.8%)	12(32.4%)	0.013
	Thickening	13(38.2%)	25(67.6%)	
Lymphatic hilum	Normal	22(64.7%)	18(48.6%)	0.173
	Disappear	12(35.3%)	19(51.4%)	
Histological grade	1	13(38.2%)	6(16.2%)	0.103
	2	19(55.9%)	29(78.4%)	
	3	2(5.9%)	2(5.4%)	
ER	<=10%	10(29.4%)	13(35.1%)	0.607
	> 10%	24(70.6%)	24(64.9%)	
PR	<=20%	21(61.8%)	16(43.2%)	0.119
	> 20%	13(38.2%)	21(56.8%)	
HER-2	Negative	27(79.4%)	29(78.4%)	0.915
	Positive	7(20.6%)	8(21.6%)	
KI-67(Mean ± SB)	< 10%	1(2.9%)	3(8.1%)	0.640
	10–30%	7(20.6%)	7(18.9%)	
	> 30%	26(76.5%)	27(73.0%)	
cT	1	11(32.4%)	8(21.6%)	0.308
	2	23(67.6%)	29(78.4%)	
Response	SD + PD	22(64.7%)	24(64.9%)	0.989
	CR + PR	12(35.3%)	13(35.1%)	
cN	0	10(29.4%)	7(18.9%)	0.301
	1	24(70.6%)	30(81.1%)	

Baseline characteristics of non-SLN positive and non-SLN negative patients after NAT. LNR: lymph node ratio; ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor receptor 2; *c*T: clinical T stage; cN: clinical N stage; SD: stable disease; PD: progressive disease; CR: complete response; PR: partial response

Unifactorial and multifactorial logistic analysis

Calcification, cortex, lymphatic hilum, histological grade, ER, PR, HER-2, KI-67, cT, treatment response and cN were subjected to univariate and multivariate logistic regression analyses, and ultimately we found that LNR ($p=0.009$) and PR ($p=0.032$) were the independent prognostic factors affecting 1–3 SLN-positive breast cancer patients after NAT, and the short axis of lymph node reached marginal significance ($p=0.072$) (Table 2).

The construction and validation of a nomogram

We then constructed a nomogram (Fig. 2A) using these predictors on the outcomes of multifactorial logistic regression to assess prognostic risk of patients. The

Table 2 Univariate and multivariate logistic regression analysis of the patients with non-SLN positive lymph nodes in T1-2 breast cancer with 1–3 positive SLNs after NAT

Variables	Subgroup	Univariable		Multivariable	
		Hazard ratio	*P*	Hazard ratio	*P*
Side	Left	1	0.925		
	Right	0.956(0.376, 2.432)			
Menopause	No	1	0.269		
	Yes	0.586(0.228, 1.510)			
Number of positive SLN	1	1	0.196		
	2	2.063(0.694, 6.139)			
	3	2.857(0.800, 10.198)			
LNR		24.566(3.273, 184.411)	0.002	21.896(1.170, 220.929)	0.009
Tumor location	Upper outer quadrant	1	0.636		
	Upper inner quadrant	1.460(0.292, 7.303)			
	Lower inner quadrant	NS			
	Lower outer quadrant	1.095(0.277, 4.325)			
	Central	3.833(0.715, 20.550)			
Long axis of LN(Mean ± SB, mm)		1.090(1.024, 1.159)	0.007	0.924(0.782, 1.091)	0.351
Short axis of LN(Mean ± SB, mm)		1.192(1.059, 1.342)	0.004	1.319(0.976, 1.782)	0.072
Blood flow	No	1	0.957		
	Yes	0.974(0.378, 2.511)			
Calcification	No	1	0.462		
	Yes	1.939(0.332, 11.337)			
Cortex	Normal	1	0.015	1	0.591
	Thickening	3.365(1.268, 8.929)		1.562(0.307, 7.955)	
Lymphatic hilum	Normal	1	0.175		
	Disappear	1.935(0.745, 5.024)			
Histological grade	1	1	0.158		
	2	2.706(0.979, 7.478)			
	3	6.195(0.173, 10.592)			
ER	<=10%	1	0.607		
	> 10%	0.769(10.283, 2.091)			
PR	<=20%	1	0.121	1	0.032
	> 20%	2.120(0.820, 5.479)		3.780(1.125, 12.702)	
HER-2	Negative	1	0.915		
	Positive	1.064(0.340, 3.333)			
KI-67(Mean ± SB)	< 10%	1	0.662		
	10–30%	0.333(0.028, 4.036)			
	> 30%	0.346(0.034, 3.545)			
cT	1	1	0.310		
	2	1.734(0.599,5.017)			
Response	SD + PD	1	0.989		
	CR + PR	0.993(0.375,2,632)			
cN	0	1	0.304		
	1	1.786(0.591,5.391)			

Univariate and multivariate logistic regression analysis of 71 patients with non-SLN positive lymph nodes in T1-2 breast cancer with 1–3 positive SLNs after mastectomy

calibration curve (Fig. 2B) suggested that the mean absolute error of the training model was 0.062.The nomogram has a good ability of prediction, with an AUC value of 0.795 (Fig. 3A) in the training set and 0.789(Fig. 3B) in the validation set I and 0.876 (Fig. 3C) in the validation set II. Then the decision curve analyses (DCA) were plotted to assess the effectiveness of our model and verified our nomogram with good clinical impact (Fig. 3D).

Discussion

There have been some studies about SLNB after NAT, such as SENTINA and ACOSOG Z1071, and the SN FNAC study [9, 10, 17], the ACOSOG Z1071 study enrolled patients with cN1, and the detection rate of SLNB was 92.9%, with a FNR of 12.6% [10]. The results of the SENTINA study also showed that the number of

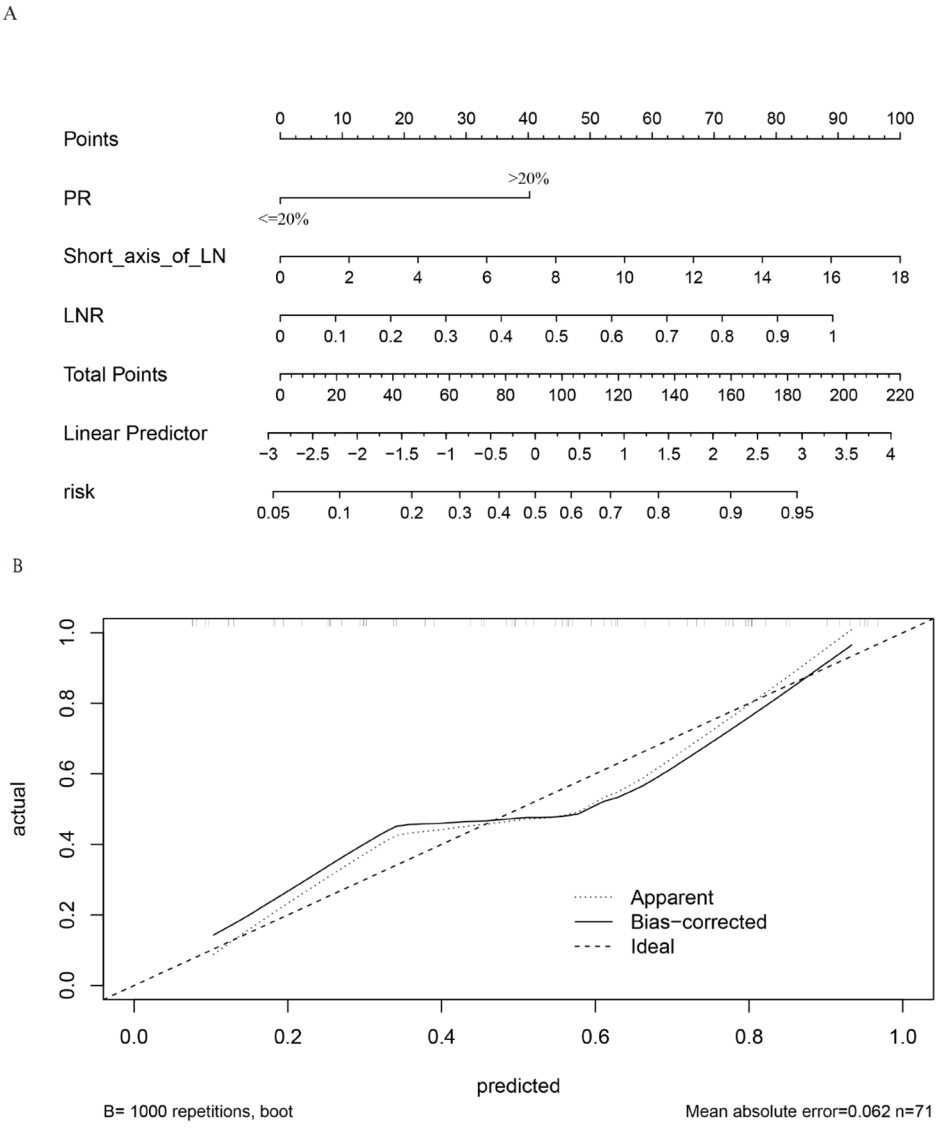

Fig. 2 (**A**) Clinical factor-based nomogram for predicting the likelihood of non-SLN metastasis in T1-2 breast cancer patients with 1–3 positive SLNs after NAT. (**B**) The calibration curves in the training cohort

patients with cN1 descending to cN0 had a SLNB detection rate of 80.4% and a FNR of 14.2% [9]. However, lower detection rates and higher FNR were shown in these studies compared to SLNB performed before NAT. The effect of SLNB after chemotherapy could not be confirmed for the whole group of breast cancer patients with positive lymph nodes confirmed by pathologic biopsy who underwent adjuvant chemotherapy. Because their FNRs all exceeded the prespecified value. Whereas, on the result of the NSABP B04 study, axillary management did not affect the final survival outcome of patients. The Alliance 11,202 study was designed to evaluate the potential for axillary preservation in sentinel-positive patients after neoadjuvant chemotherapy. The objective of this study was to compare patients with a positive SLN after NAT with patients who received ALND and axillary radiotherapy to elucidate the difference in recurrence rates between the two groups. This clinical study will provide new explorations and research directions for the management of the axilla after NAT [18]. Whether regional radiotherapy can be used as an alternative to surgical treatment for the purpose of minimizing the scope of surgery or even safely avoiding surgery. Therefore, further exploring the risk of ALNM in SLN-positive patients after NAT can effectively assess the prognostic risk of the patients, select appropriate treatment options for the patients, and reduce unnecessary treatment. Yu et al. explored the accuracy of SLNB after NAT in patients with ALNM from breast cancer. The results suggest that SLNB is feasible only for patients with cN0. In contrast, for patients with a positive result of ALN biopsy, a high FNR may occur with SLNB after NAT, so ALND is still

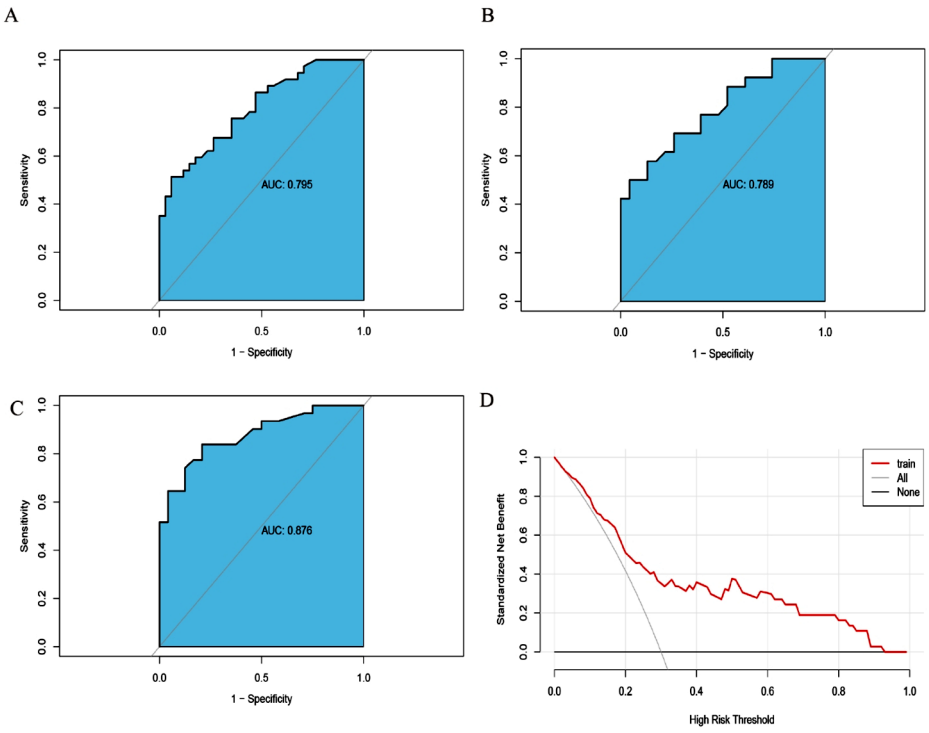

Fig. 3 The receiver operating characteristics (ROC) curve and area under the ROC curve (AUC). (**A**) The ROC in the training cohort, (**B**) The ROC in the first validating cohort; (**C**) The ROC in the second validating cohort. (**D**) The calibration curves to assess the accuracy of the nomogram and determination of decision points through Decision Curve Analysis (DCA)

routinely recommended in this situation [19]. Meanwhile, several studies have shown that the number of SLN metastases is an independent predictor of non-SLN metastases in breast cancer. Cheng et al. explored the metastatic factors of non-SLN in 179 patients who accepted NAT for downgrading from cN+to cN0. The results indicated that the quantity of positive SLNs and clinical lymph node stage that achieved pathologic complete remission (CR) were the independent predictors of the metastasis of non-SLN [20]. And they analyzed the factors influencing SLN positivity in early breast cancer with negative ALNs that received NAT for their non-SLN metastasis. The results showed that the number of positive SLNs, macroscopic metastasis of SLNs, and lymphovascular invasion were associated with non-SLN positivity in breast cancer. Zhang et al. found that pre-NAT lymph node status, post-NAT axillary ultrasonographic status, number of SLNs, and distribution of lymph nodes in breast cancer patients after NAT were the independent factors of non-SLN metastases [21].

To date, this is the largest study exploring non-SLN metastasis in patients with positive SLN after NAT. We finally found that LNR, short axis of lymph node, and PR were significantly associated with the risk of non-SLN metastasis in breast cancer patients with 1–3 SLN-positive after NAT, and created a nomogram based on these predictors. Breast cancer usually occurs lymph node metastasis first, and tumor cells drain from all levels of alveoli to subareolar and periprosthetic drainage along the mammary lymphatic ducts, whereas lymph node metastasis of breast cancer mainly focuses on axillary metastasis [22], and the first stop of axillary metastasis of breast cancer is the SLN, so the metastasis of SLN with or without it is more important for the metastasis of non-SLN [23]. The absolute number of ALNs involved is considered the most important prognostic factor in breast cancer [24]. The involved LNR refers to the number of positive lymph nodes to the total number of lymph nodes removed. Involved lymph nodes have prognostic value in both oral cavity and cervical cancer [25, 26]. Several studies have shown that the LNR is a more objective indicator of lymph node positivity in breast cancer than the number of positive lymph nodes, and is superior to the number of positive lymph nodes in outcome prediction [27–30], while no study have enrolled LNR in predicting non-SLN metastasis in neoadjuvant setting. As a parameter in addition to the traditional clinicopathologic factors, LNR has an important prognostic value for patients who have the positive lymph nodes, we first introduced this parameter and verified its importance in predicting non-SLN metastasis. Ultrasound plays an important role in the diagnosis of breast diseases because

it is radiation-free, inexpensive, and can be observed continuously and dynamically [31]. Axillary ultrasonography (AUS) can easily and conveniently evaluate the ALNs and has been routinely used in the preoperative examination of breast cancer, combined with ultrasound-guided ALN aspiration biopsy, it can be a good judgement of ALNM, which is helpful for clinical decision on whether or not to carry out ALND. The likelihood of finding non-SLN metastases in cT1 and AUS-negative cases is low or may be a clue not to proceed with ALND [32]. In addition to the number of lymph nodes, the size of the lymph nodes is the primary basis for determining positive lymph nodes. Ultrasound is able to accurately assess the size of lymph nodes, thus aiding in the diagnosis of metastasis of the lymph nodes. When ALNM occurs in breast cancer, the characteristic manifestation is firstly morphological changes, and localized thickening of the lymph node cortex, which is considered to be a morphological feature in the early stage of tumor metastasis [33]. There was a trend of significant thickening of lymph node cortex in the non-SLN positive group in our study. Abnormally enlarged lymph nodes can be seen when lymph node metastasis develops further. The short axis of lymph node is an important basis for determining lymph node enlargement and is also used as an important index for tumor efficacy assessment [34, 35]. The results of multifactorial logistic analysis in our study suggest that short axis of lymph node is an independent predictor of non-SLN metastasis. Hormone receptor (HR) status, including ER and PR, is one of the most significant prognostic and predictive factors for breast cancer [36]. PR is a target gene for ER upregulation, and its expression is dependent on estrogen, and PR modulates ER action [37]. PR-negative is one of the high-risks for recurrence in ER-positive breast cancer. And patients with PR > 20% have longer disease-free survival [38]. Decreased PR expression is positively correlated with overall survival and recurrence in breast cancer patients. However, in our research we found that the increasing expression of PR may indicate the higher risk of non-SLN metastasis after NAT. Petruolo et al. investigated HR + breast cancer patients and evaluated the rates of pathologic complete response (pCR) and they drew a conclusion that a lower rate of pCR was presented in PR + patients [39]. And Tu et al. found that the patients who were confirmed the low expression of PR had higher possibility of pCR than high expression of PR [40], which is consistent with our research. Thus, the expression of PR may be correlated with treatment response for HR + breast cancer patients. The ICARO study is a relatively large-sample randomized controlled study with a higher level of evidence-based medical evidence. However, it focuses on invasive recurrence rate and only focuses on the sentinel lymph node ITC population. It cannot predict the status of non-sentinel lymph nodes. Our study is a retrospective study focused on the possibility of non-sentinel metastasis in patients with sentinel lymph node macro-metastasis and micro-metastasis.

There are still limitations to our study. Selection bias may exist since we conducted a single-center retrospective study in this study. We need more external validation cohorts to further assess the accuracy of our research. Randomized controlled trials need to be supplemented to verify the prognosis of patients with SLN positive after NAT.

Conclusion

Our research indicates that larger LNR, longer lymph node short diameter, and high PR expression are strongly correlated to non-SLN metastasis in breast cancer patients after NAT. This nomogram may benefit our clinicians in speculating the likelihood of non-SLN metastasis after NAT and identifying low-risk patients of additional lymph nodes involvement, who ALND can be omitted carefully.

Author contributions

L and C contributed to the study conception and design. Material preparation, data collection and analysis were performed by F. The first draft of the manuscript was written by T. Z and C were involved in the revision of the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical approval was waived by the local Ethics Committee of the Chongqing Medical University in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no competing interests.

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