Intraoperative frozen section can reduce unnecessary second operation in breast cancer patients that failed to be diagnosed by previous core needle biopsy: a retrospective analysis of Chinese clinical practice

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Abstract

Objective: The value of frozen section in the intraoperative diagnosis of breast cancer that failed to be diagnosed by previous core needle biopsy (CNB) is indeterminate. To evaluate and improve the clinical utility of frozen section on this kind of breast cancer, we conducted a retrospective data analysis and constructed a prediction model.

Method: We reviewed data of breast cancer patients that failed to be diagnosed by previous CNB (CNB-undiagnosable) in Fudan University Shanghai Cancer Center (FUSCC) from May 1, 2006 to December 31, 2019. Clinical characteristics of patients were collected. the correlation between clinical features and false negative rate (FNR) of frozen sections was explored with logistic regression analysis, after which a nomogram was constructed to predict the probability of false negative.

Result: The diagnostic sensitivity of frozen section on CNB-undiagnosable breast cancer was 67.18%, and the FNR was 32.82%. In multivariate analysis, papillary lesion (OR, 4.251; 95% CI, 2.804-6.492; P<0.0001) and sclerosing adenosis (OR, 3.727; 95% CI, 1.897-7.376; P= 0.0001) on CNB were risk factors of false negative, while clustered microcalcifications on mammography (OR, 0.345; 95% CI, 0.216-0.543; P < 0.0001) and ultrasonic BI-RADS category 4C-5 (OR, 0.250; 95% CI, 0.081-0.777; P = 0.0157) were favorable factors of true positive. The false negative rate of frozen section could be controlled at about 11% or less by the prediction of nomogram.

Conclusion: Frozen sections are valuable in the intraoperative diagnoses of CNB-undiagnosable breast cancers. It is recommended to implement the intraoperative frozen sections for high-risk breast lesions with a low probability of false negative indicated by prediction, so as to minimize the occurrence of unnecessary second operation.

Introduction

Ultrasound-guided core needle biopsy (CNB) is the main diagnostic method for breast cancer [1]. Previous research that reported by our institute showed that the accuracy of CNB could reach 92.4%, but due to the sampling limitation, it still has possibility of false negative (FN) for diagnosis of breast cancer [2]. Previous reports have shown that high-risk breast lesion diagnosed by CNB may be upgraded to malignancy in excision biopsy [3, 4], which is bound to undergo radical surgery after definite diagnosis, we called it CNB-undiagnosable breast cancer. In practice, if the diagnosis of cancer and the radical surgery can be completed in one operation, the efficiency of treatment will be greatly improved. Frozen section is the most common method for immediate pathological diagnosis intraoperatively, and were widely used in China. However, its sensitivity in the diagnosis of very early breast cancer has been controversial. According to previous reports, the diagnostic accuracy of frozen section for invasive breast cancer is high [5–7], but lower for carcinoma in situ [8–10]. So far, as far as we know, there is no study that investigated the role of frozen section in the diagnosis of CNB-undiagnosable breast cancer, therefore, its practical utility in CNB-undiagnosable breast cancer is indeterminate. What kind of breast cancer can be diagnosed by frozen biopsy, and what are the characteristics of this type of breast cancer, there is no answer? So, we conducted a retrospective analysis of clinical data, hoping to provide some reference and help for clinical practice.

Materials And Methods

Study Population and Data Collection

Our subjects were collected from the database of Fudan University Shanghai Cancer Center (FUSCC) from May 1,2006 to December 31,2019. The eligibility criteria were as follows: 1). The final pathological diagnosis must be breast cancer;

2). CNB was taken preoperatively, but malignancy was not confirmed; 3). Frozen section must be performed for pathological assessment after excisional biopsy immediately.

We collected the baseline characteristics of patients by referring to the electronic medical record system. False negative was defined as that was diagnosed non-malignant by FS but malignant by PS. 11 clinically relevant candidate variables were selected from the database, include age, physical examination symptoms(whether the mass could be palpable, and whether there is nipple discharge), ultrasonographic features(type of ultrasonic image, ultrasonic maximum diameter, whether there is dense punctate strong echo (DPSE) on ultrasonic image, the category of the BI-RADS on ultrasonography (US-BI-RADS)), mammography features(whether there is clustered microcalcifications on mammography, the category of the BI-RADS on mammography (MG-BI-RADS)), pathological features(whether the core needle biopsy contained papillary lesions (PL-CNB) and/or sclerosing adenosis (SA-CNB)).

The need for informed consent was waived because of the retrospective nature of the study, and the study design was approved by the appropriate Ethics Review Board.

Statistical Method

Univariate logistic regression was used to test the associations between FNR of frozen section and clinical characteristics. Multivariable logistic regression with backward selection was performed to identify independent covariates. Factors at the 0.05 level were considered statistically significant. The performance of the nomogram was quantified with respect to discrimination and calibration [11]. The receiver operating characteristic (ROC) curve was drawn, and the predictive accuracy was assessed by calculating the area under the ROC curve (AUC). The Harrell C-index was used to evaluate discriminatory power [12]. Calibration was performed using the bootstrapping method and was used to illustrate the relation between the predicted and observed FNR of frozen sections [13]. Statistical analyses were performed using the rms, Hmisc, pROC, and ggplot2 packages in R version 3.4 (R Foundation for Statistical Computing), including bootstrapping and drawing of the nomogram to visually represent the model.

Result

Baseline Characteristics of Study Population

From May 1,2006 to December 31,2019, a total of 1036 patients with 1039 breast cases (3 of whom had simultaneity bilateral breast malignancies) met the inclusion criteria. 698 (696 patients) were diagnosed by frozen sections and 341 (340 patients) by paraffin sections. Based on the above data, we calculated that the diagnostic sensitivity of frozen section was 67.18%, the FNR was 32.82%.

After removing patients with incomplete image data, 876 patients (876 cases) had complete image data and were selected for logistic regression analysis and nomogram construction, and randomly assigned to the training set and testing set in a ratio of 7:3. The characteristics of the patients are shown in Table 1.

Table 1
Baseline characteristics of the training set and the testing set

Patient Characteristic			No. of Patients					
			Total, n = 876	%	Training Set, n = 613	%	Testing Set, n = 263	%
Age at diagnosis		Median(y)	53(28–86)		54(30–86)		51(28–83)	
		<45y	183	20.9%	127	20.7%	56	21.3%
		45 ~ 59y	410	46.8%	286	46.6%	124	47.1%
		≥ 60y	283	32.3%	200	32.6%	83	31.6%
ultrasonographic features	Ultrasound echo image	cystic-solid echo	82	9.4%	55	9.0%	27	10.3%
		solid echo	764	87.2%	538	87.8%	226	85.9%
		glands echo disorderly	9	1.0%	7	1.1%	2	0.7%
		normal echo	21	2.4%	13	2.1%	8	3.0%
	Ultrasonic maximum diameter	≤ 10mm	111	12.7%	75	12.2%	36	13.7%
		>10mm	765	87.3%	538	87.8%	227	86.3%
	DPSE on ultrasonic image	Yes	298	34.0%	201	32.8%	97	36.9%
		No	578	66.0%	412	67.2%	166	63.1%
	US-BI-RADS	1 ~ 3	29	3.3%	18	2.9%	11	4.2%
		4a or 0	192	21.9%	136	22.2%	56	21.3%
		4b	344	39.3%	240	39.2%	104	39.5%
		4c or 5	311	35.5%	219	35.7%	92	35.0%
mammographic features	microcalcifications on MG	Yes	420	47.9%	297	48.5%	123	46.8%
		No	456	52.1%	316	51.5%	140	53.2%
	MG-BI-RADS	1 ~ 3	71	8.1%	45	7.3	26	9.9%
		4a or 0	269	30.7%	182	29.7%	87	33.1%
		4b	247	28.2%	171	27.9%	76	28.9%
		4c or 5	289	33.0%	215	35.1%	74	28.1%
physical examination symptoms	whether the mass could be palpable	Palpable	812	92.7%	571	93.1%	241	91.6%
		unpalpable	64	7.3%	42	6.9%	22	8.4%

Abbreviation: DPSE, dense punctate strong echo; US-BI-RADS, the category of the BI-RADS on ultrasonography; MG, mammography; MG-BI-RADS, the category of the BI-RADS on mammography; PL-CNB, core needle biopsy contained papillary lesions; SA-CNB, core needle biopsy contained sclerosing adenosis.

	nipple discharge	Yes	96	69	11.3%	27	10.3%	
		No	780	89.0%	544	88.7%	236	89.7%
pathological features	PL-CNB	Yes	252	28.8%	174	28.4%	78	29.7%
		No	624	71.2%	439	71.6%	185	70.3%
	SA-CNB	Yes	61	7.0%	45	7.3%	16	6.1%
		No	815	93.0%	568	92.7%	247	93.9%
	Frozen section assessment	Failure diagnosis	283	32.3%	203	33.1%	80	30.4%
		Correct diagnosis	593	67.7%	410	66.9%	183	69.6%

Abbreviation: DPSE, dense punctate strong echo; US-BI-RADS, the category of the BI-RADS on ultrasonography; MG, mammography; MG-BI-RADS, the category of the BI-RADS on mammography; PL-CNB, core needle biopsy contained papillary lesions; SA-CNB, core needle biopsy contained sclerosing adenosis.

Logistic Regression Analysis

In the training set, of 613 patients, 205 (33.44%) were false negative. In the univariate logistic regression analysis, for patients who were sixty years and older (OR, 1.653; 95% CI, 1.029–2.686; P = 0.0396), patients who have PL-CNB (OR, 5.037; 95% CI, 3.468–7.366; P < 0.0001), or patients who have SA-CNB (OR, 2.133; 95% CI, 1.161–3.917; P = 0.014), the FNR of frozen section was higher, but lower for those that showed solid image on ultrasonography (OR, 0.286; 95% CI, 0.158–0.505; P < 0.0001), DPSE on ultrasonic image (OR, 0.205; 95% CI, 0.128–0.319; P < 0.0001), US-BI-RADS 4C-5 (OR, 0.273; 95% CI, 0.101–0.737; P = 0.0094), clustered microcalcifications on mammography (OR, 0.203; 95% CI, 0.138–0.294; P < 0.0001), and MG-BI-RADS 4C-5 (OR, 0.203; 95% CI, 0.190–0.750; P = 0.0049).

In multivariate logistic regression analysis with backward stepwise selection, US-BI-RADS 4C-5 (OR, 0.250; 95% CI, 0.081–0.777; P = 0.0157), clustered microcalcifications on mammography (OR, 0.345; 95% CI, 0.216–0.543; P < 0.0001) were associated with lower FNR, but for DPSE on ultrasonic image, the correlation is slightly weaker (OR, 0.595; 95% CI, 0.335–1.044; P = 0.0727). On the contrary, PL-CNB (OR, 4.251; 95% CI, 2.804–6.492; P < 0.0001) and SA-CNB (OR, 3.727; 95% CI, 1.897–7.376; P = 0.0001) were associated with higher FNR (show in Table 2).

Table 2
Multivariate Logistic Regression Analysis of Factors Associated with the diagnostic failure risk of frozen section in the Training Set, n = 613

Variable	FN/total	FNR	OR	95% CI	P-value
DPSE on ultrasonic image					
No	176/412	42.7%	Reference	-	-
Yes	27/201	13.4%	0.595	0.335–1.044	0.073
US-BI-RADS					
1–3	9/18	50.0%	Reference	-	-
0 or 4a	61/136	44.9%	0.601	0.195–1.861	0.372
4b	88/240	36.7%	0.434	0.143–1.321	0.137
4c-5	45/219	20.5%	0.250	0.081–0.777	0.015
microcalcifications on MG					
No	155/316	49.1%	Reference	-	-
Yes	48/297	16.2%	0.345	0.216–0.543	< 0.001
PL-CNB					
No	98/439	22.3%	Reference	-	-
Yes	105/174	60.3%	4.251	2.804–6.492	< 0.001
SA-CNB					
No	180/568	31.7%	Reference	-	-
Yes	23/45	51.1%	3.727	1.897–7.376	< 0.001
Abbreviation: DPSE, dense punctate strong echo; US-BI-RADS, the category of the BI-RADS on ultrasonography;					
MG, mammography; PL-CNB, core needle biopsy contained papillary lesions;					
SA-CNB, core needle biopsy contained sclerosing adenosis; FN, false-negative; FNA, false-negative rate; OR, odds ratio.					

Nomogram Development

On the basis of results from multivariable logistic regression analysis, a nomogram was developed to predict the FNR of frozen section. In the nomogram, the total score is calculated by using clinical and pathologic features, contain BI-RADS category on ultrasonography, DPSE on ultrasonic image, clustered microcalcifications on mammography, PL-CNB, and SA-CNB. This total score can then be used to assign a probability of FN to individual patient using the scale at the bottom of Fig. 1.

Nomogram Validation

The resulting nomogram was internally validated using the bootstrap method. We use formula to determine the cutoff value of the validation: $f(x) = \frac{nx(1-FNRx)}{N-nx(1-FNRx)}$, x represents the total score, nx represents the number of patients with this score and below, FNRx represents the actual false negative rate of patients with this score and below, and N represents the total number of patients. The best cutoff value is obtained at the peak of the formula value curve, that represents the best clinical utility. The cutoff value we set was the total score 135 points (Fig. 2), the prediction model had an AUC of 0.794 (95% CI: 0.756–0.831) in the training set, indicating that the multivariate logistic regression model had potentially promising predictive power (Fig. 3A). The model demonstrated an adequate level of accuracy for predicting the FNR of frozen section.

The independent testing set of 263 patients also showed good discriminatory ability, with an AUC of 0.800 (95% CI: 0.736–0.865), indicating that the multivariate logistic regression model in a separate, individual data set of patients had potentially promising predictive power (Fig. 3B).

The calibration was good for the training and testing cohorts and showed no significant difference between the predicted and observed probabilities of failure diagnosis (P = 1.000), indicating that the nomogram was well calibrated (Fig. 4).

On the basis of the predicted probability of FN, we calculated the practical FNR of different cutoff points in total patients (876 patients). When predicting the probabilities of patients who were more likely to be FN, the patients with practical FNR accounted for 10% and 10.16% of those who had a predicted probability of FN ≤ 10% and ≤ 15%, respectively. Among patients with a predicted probability of FN ≥ 60%, ≥ 70%, and ≥ 80%, the practical FNR accounted for 71.7%, 73.4%, and 87.5%, respectively (show in Table 3).

Table 3
The Nomogram Applied to Data Sets at Different Predicted Probability Cutoff Values

Cutoff Value		**No. of Patients (%)**		**FNR, %**
Total score (points)	**Predicted probability of FN**	**Total**	**False negative**	
≤ 40	≤ 10%	220(25.1)	22(7.8)	10.0%
≤ 76	≤ 15%	246(28.1)	25(8.8)	10.2%
≤ 135	≤ 30%	459(52.4)	52(18.4)	11.3%
> 135	> 30%	417(47.6)	231(81.6)	55.4%
≥ 190	≥ 50%	235(26.8)	152(53.7)	64.7%
≥ 220	≥ 60%	159(18.2)	114(40.3)	71.7%
≥ 251	≥ 70%	60(6.8)	44(15.5)	73.3%
≥ 288	≥ 80%	8(0.9)	7(2.5)	87.5%
Abbreviation: FN, false negative; FNR, false negative rate				

These results demonstrated that the individual probability of FN of frozen section could be predicted accurately by combining information from routinely available clinicopathologic variables.

Discussion

In most countries, frozen sections are often omitted, and paraffin sections are used for post-resection pathological assessment of breast lesions those have risks of upgrading from atypical to malignant. But in a few countries, such as China, frozen section is still utilized in clinical practice, mainly for making intra-operational decision and avoiding unnecessary second operation. This may be related to the low acceptance of second operation in Chinese patients. Of course, minimizing unnecessary second operations is beneficial for both patients and doctors. Our research showed that, in total patients, the diagnostic sensitivity of frozen section for CNB-undiagnosable breast cancer was 67.18%, and the false-negative rate was 32.82%. This suggests that frozen section is valuable in the diagnosis of these patients, but further screening is needed to reduce the false negative rate. According to the nomogram, we find that the FNR is more than 50% when the total score exceeds 135, and even reach 87.5% when the total score exceeds 288. For such patients, frozen section should be omitted. On the contrary, when the total score is lower than 135, the diagnostic sensitivity of frozen section can reach nearly 90%, the incidence of second operation is significantly reduced.

Previous research showed that the diagnostic sensitivity of frozen section for ductal carcinoma in situ (DCIS) was only about 50% [8], the main reason was that some DCIS appear as non-mass lesions, which could not be identified by macroscopic examination, that may be leading to sampling errors [8, 9]. In our study, the diagnostic sensitivity of frozen section for pure DCIS was 50.62% (papillary carcinomas are not included), which similar to previous study. In our study, interestingly, malignancies with microcalcifications on mammography were more likely to be diagnosed by frozen sections, that seems to contradict earlier researches. Previous reports had shown that pure microcalcifications on mammography may increase the FNR of frozen section [6, 14]. However, in these reports, invasive cancer and DCIS were not distinguished, and the proportion of DCIS was significantly higher in patients presenting as pure microcalcifications without mass, leading to significant imbalance of tumor stage, which may be the real reason for the difference in FNR. In our study, the staging of patients was very different from previous reports. All the subjects underwent preoperative core needle biopsy, patients diagnosed as malignant were excluded. As a result, the vast majority of invasive cancers had been excluded, resulting in a higher percentage of DCIS in our patients. The proportion of DCIS and DCIS with microinvasive carcinoma (DCIS-M) in our study was nearly 60% (include papillary carcinomas), and the percentage of DCIS + DCIS-M between the microcalcification and non-calcification groups was very similar (57.3% vs 59.7%). Cheng's report also suggested that DCIS with microcalcifications is more likely to be diagnosed in frozen section, probably because microcalcifications are more common in high-grade DCIS with comedo-necrosis, and the intraoperative diagnosis rate of such lesions is higher. In addition, the microcalcifications may help in localizing the lesion and aids in accurate sampling [8].

We found a higher FNR of frozen section for papillary carcinoma (PC), which is consistent with previous studies [5, 8]. PC is considered to be a rare type of breast cancer with a favorable prognosis, most of which are confined to ducts [15]. In the past decades, PC was considered a variant of intraductal carcinoma. The latest World Health Organization (WHO) Working Group’s classification of breast tumors defines PC as a separate subtype of breast carcinoma, which is classified into encapsulated papillary carcinoma and encapsulated papillary carcinoma with invasion [16, 17]. Previous studies have reported that the final diagnosis of PC often requires immunohistochemical examination to differentiate it from benign papilloma [15]. In the preoperative evaluation, ultrasonic images of PC more show solid-cystic lesion, and appearances of mammography more show dense masses without conspicuous microcalcification, due to the limited sampling, preoperative core needle biopsy are usually visible only to a small amount of papillary hyperplasia or atypical hyperplasia lesions, it is coinciding with one of this study results that papillary lesion can increase the FNR of FS.

Our study inevitably has some limitations. First of all, this is a retrospective study, and there are some unavoidable bias factors. Secondly, breast magnetic resonance imaging (MRI) was not included in the preoperative evaluation factors, this is because the large patients base in China and the lack of MRI equipment, most of the patients do not have enough time for preoperative MRI scan. In addition, Patients in this study all received core needle biopsy, instead of vacuum assisted biopsy (VAB), mainly because VAB is not covered by medical insurance in China, and its cost is high. Surgeons usually use VAB to remove small benign lesions, while rarely used in suspected malignant lesions [2, 18].

Conclusion

Frozen section is valuable in the intraoperative diagnosis of CNB-undiagnosable breast cancer. Although the overall false negative rate is relatively high, but it can be significantly reduced through prediction. It is recommended to implement the intraoperative frozen section for high-risk breast lesion with a low probability of false negative indicated by prediction, so as to minimize the occurrence of unnecessary second operation. Of course, prospective studies are needed to verify this conclusion.

Abbreviations

FS, frozen section; PS, paraffin section; DCIS, ductal carcinoma in situ; PC, papillary carcinoma; US, ultrasonography; DPSE, dense punctate strong echo; US-BI-RADS, the category of the BI-RADS on ultrasonography; MG, mammography; MG-BI-RADS, the category of the BI-RADS on mammography; CNB, core needle biopsy; PL-CNB, core needle biopsy contained papillary lesions; SA-CNB, core needle biopsy contained sclerosing adenosis. FN, false negative; FNA, false negative rate; OR, odds ratio; MRI, magnetic resonance imaging; VAB, vacuum assisted biopsy.

Declarations

Ethics approval and consent to participate

The need for informed consent was waived because of the retrospective nature of the study, and the study design was approved by the appropriate Ethics Review Board.

consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests

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Not applicable

Author Contributions

JX: Conceptualization, methodology, data collection, investigation, writing–original draft, and writing–review and editing. **JL:** Conceptualization, methodology, resources, and data interpretation. **YG:** Statistical analysis and data interpretation. **QC** and **LD**: Data collection and writing–original draft. **TG:** Data collection and data interpretation. **ZL** and **GL:** Supervised the study planning and design; data collection; statistical analysis and data interpretation, full access to all the data in the study and responsibility for the integrity of the data and the accuracy of the data analysis, and article review, revision, and reporting. All authors read and approved the final manuscript.

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Figures

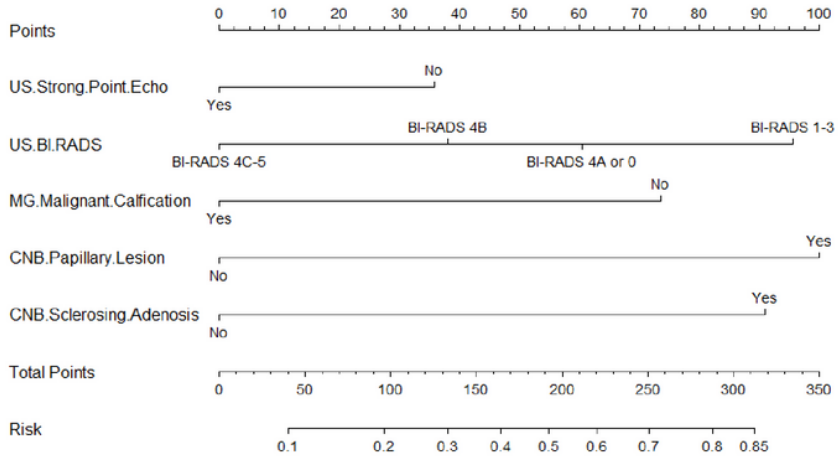
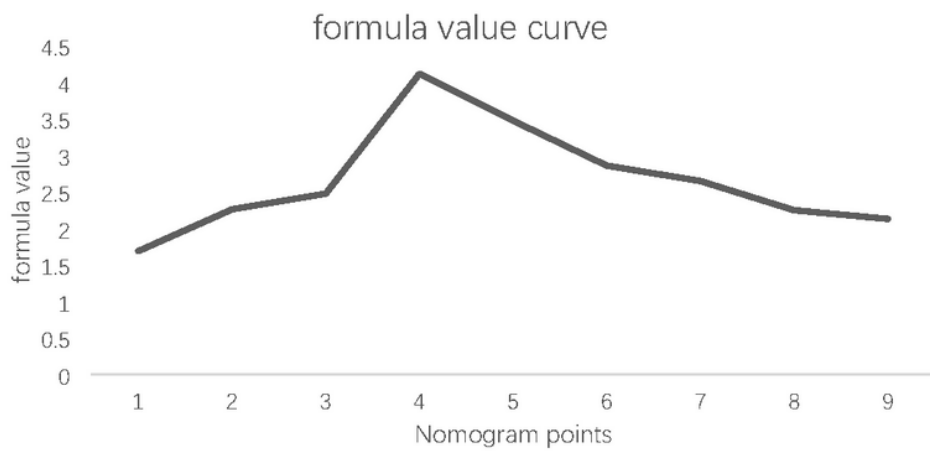


Figure 1

This is the nomogram for predicting the probability of false negative of frozen section in patients with breast malignancies that failed to be diagnosed by CNB. To calculate the probability, identify the predictor points on the uppermost point scale that correspond to each patient variable and sum them. The total points projected in the bottom scale indicate the probability of false negative.



1=0p	2≤40p	3≤76p	4≤135p	5≤165p	6≤190p	7≤220p	8≤251p	9≤288p

Figure 2

formula value curve shows the best cutoff value is 135.

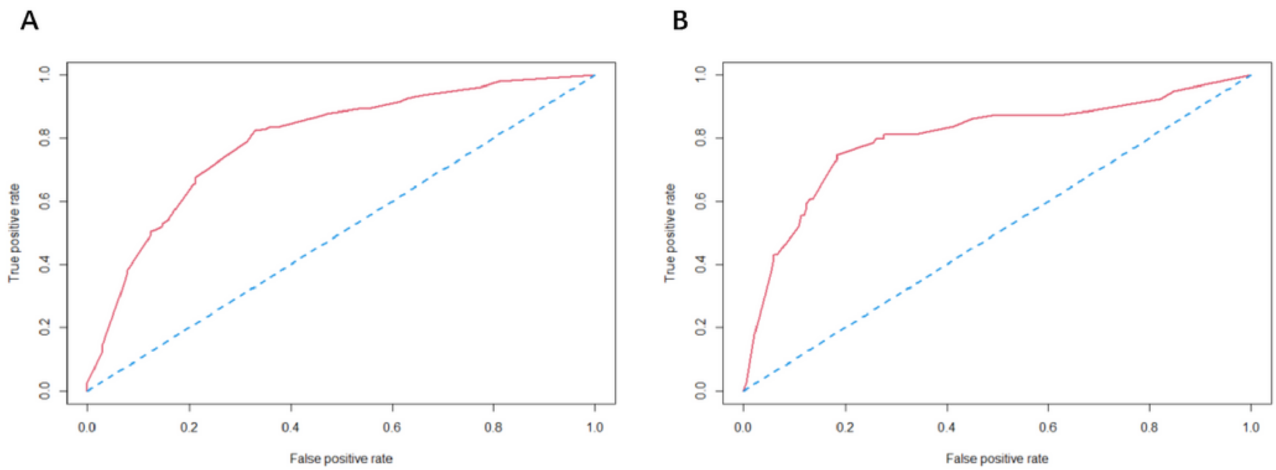


Figure 3

Receiver operating characteristic curves (ROCs) are shown for the prediction model in the training and validation cohorts. (A) The ROC curve in the training set indicates an area under the curve (AUC) of 0.7.94 (95% CI, 0.756- 0.831). (B) For discrimination in the validation set, the ROC indicates an AUC of 0.800 (95% CI, 0.736-0.865).

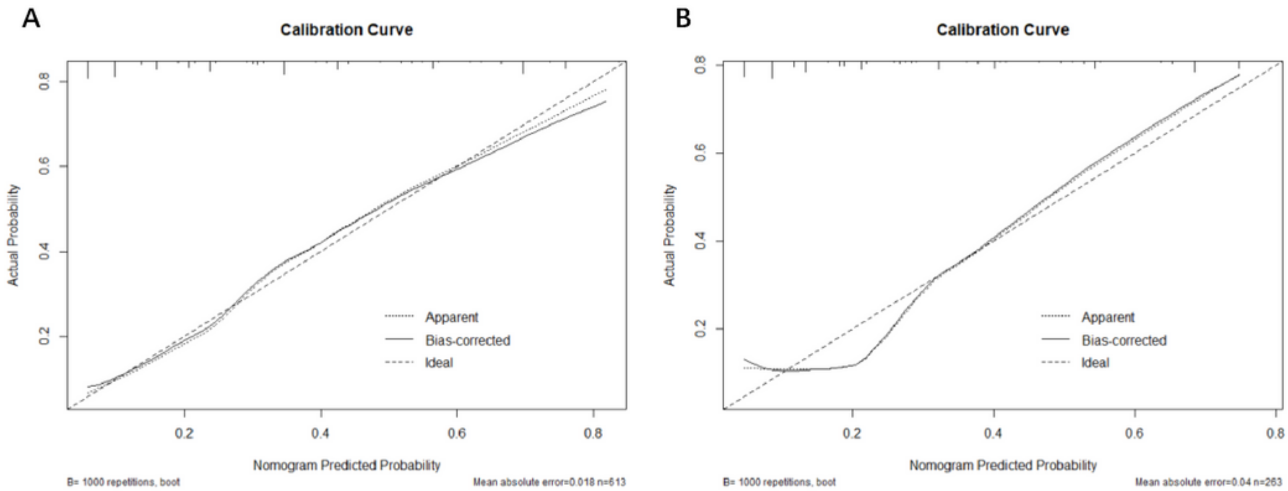


Figure 4

Calibration curves illustrate the observed and predicted false negative rates for patients with high risk breast lesion. (A) the training cohort and (B) the validation cohort. The horizontal axis indicates the predicted probabilities measured by the nomogram, and the vertical axis indicates the actual probabilities. For the calibration plot, P = 1.000.