Predictive Model for the Pathological Complete Response of Axillary Lymph Nodes After Neoadjuvant Therapy for Breast Cancer

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Research Article

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Abstract

Background: Accurately assessing the efficacy of neoadjuvant therapy (NAT) for breast cancer may predict patient outcomes. Axillary pathological complete response (apCR) after NAT is considered to indicate survival benefit, allowing initially cN+ patients to avoid axillary lymph node dissection (ALND) by turning ALNs (axillary lymph node) negative. Therefore, there has been an increasing interest in accurately predicting apCR post-NAT. Here, we integrated the clinicopathological characteristics of patients with breast cancer and positive ipsilateral ALNs who underwent NAT and surgery. Statistical methods were used to screen for predictors of apCR and design a model to predict apCR rate post-NAT, thereby guiding surgeons' decision-making and improving patients' quality of life.

Methods: Female patients (n=157) with locally advanced breast cancer and positive ALNs, diagnosed by a pathologist and treated via NAT and surgery between January 2016 and June 2020 at our hospital, were enrolled. Patients received a complete and standardized neoadjuvant regimen. Their clinicopathological characteristics were retrospectively analyzed, the factors of apCR post-NAT analyzed by logistic regression, and a nomogram used to construct a predictive model for apCR post-NAT.

Results: Sixty-two patients (39.5%) achieved apCR. Univariate analysis demonstrated that apCR was significantly associated with pathological grading, molecular typing, stroma-tumor ratio (STR), clinical N staging, and response to chemotherapy (all $P < 0.05$). A multivariate binary logistic regression equation was established, and the variables were entered into the model via forward stepwise selection; results indicated that the possibility of apCR post-NAT was higher in these cases. A predictive model for apCR post-NAT—consisting of four independent predictors: pathological grading of the aspiration specimen, STR, clinical N staging, and response to chemotherapy—was constructed using statistically significant variables in the logistic regression equation. The model had good accuracy and showed good clinical utility when both ROC curves and internal validation were performed.

Conclusion: The predictive model combined clinical and pathological features; the pathological grading of the aspiration specimen, STR, clinical N staging, and response to chemotherapy were found to be independent predictors of apCR post-NAT. The model had good applicability regarding apCR prediction post-NAT, contributing to the option of individualized de-escalation of axillary surgery.

Background

Neoadjuvant therapy (NAT) is a significant part of comprehensive breast cancer treatment and the preferred treatment modality for patients with locally advanced, HER2-positive, or triple-negative breast cancer. Through preoperative NAT, surgery is performed after tumor and axillary lymph node (ALN) downstaging. Axillary pathological complete response (apCR) is defined as the absence of tumor remnants in the ALNs[1]; it is believed to indicate survival benefit.[2–4] It has been shown that the apCR rate after NAT can reach 30–63.[5–6]

In patients with breast cancer and negative ALNs before neoadjuvant chemotherapy, a sentinel lymph node biopsy can be performed instead of axillary lymph node dissection (ALND) after chemotherapy, while in patients with positive ALNs before and after chemotherapy, ALND can be performed directly. In patients with locally advanced breast cancer and positive ALNs (cN+), preoperative NAT can lead to different degrees of ALN downstaging, and after completing a certain cycle of NAT, the clinician will assess the patients' ALNs. Sentinel lymph node biopsy has been recommended as an alternative to ALND in patients with preoperative assessment of the complete response (CR) of ALNs. The safety and reliability of sentinel lymph node biopsy have been confirmed by the ACOSOG Z0010[7] and NSABP B-32[8] trials, and is now a routine procedure in patients with negative ALNs (cN0). NAT can cause some of the initial cN+ to turn to negative ALN or downstage them, as well as decrease the incidence of ALND-induced complications, such as axillary web syndrome, wound infection, decreased ipsilateral shoulder range of mobility, and postoperative edema of the affected upper limb; therefore, studies that accurately predict apCR post-NAT have received increasing attention.

The treatment modality for breast cancer has developed into precise, minimally invasive, and individualized treatment aimed at prolonging the survival time of patients, as well as improving their quality of life. Therefore, through a comprehensive analysis of the clinicopathological characteristics of female breast cancer patients treated with NAT and surgery, we employed statistical methods to screen for the predictors of apCR, developed a predictive model, and performed internal validation, thereby providing a basis for the rational selection of axillary treatment modalities post-NAT.

Methods

Clinical data

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Jinzhou Medical University (Approval No. 202109). We retrospectively analyzed female patients who underwent breast mass and ALN aspiration at the Department of Breast Surgery of the First Affiliated Hospital of Jinzhou Medical University between January 2016 and June 2020, and were treated with neoadjuvant chemotherapy and surgery. Inclusion criteria were as follows: a diagnosis of breast cancer by preoperative coarse needle biopsy and definite molecular typing by immunohistochemistry; clinical stage T1-4N1-3M0; having tolerated and received neoadjuvant chemotherapy, and undergone surgery. Exclusion criteria were as follows: clinical stage N0 or Nx; male breast cancer patients; having undergone neoadjuvant chemotherapy without surgery, or sentinel lymph node biopsy without ALND; stage IV breast cancer with disease progression during neoadjuvant chemotherapy; and patients with incomplete data.

In total, 157 patients with breast cancer were included in this study. All patients were females aged 32–72 (median, 52) years (65 patients were aged ≤50 years, and 92 were aged >50 years); 71 women were premenopausal, and 86 were postmenopausal. Clinical staging was as follows: stage T1-2 in 113 patients, T3-4 in 44, N1 in 80, N2 in 45, and N3 in 32. Pathological grading was as follows: G3 in 89 patients and G1-G2 in 68. Molecular typing was as follows: luminal A in 15 patients, luminal B in 42,

HER2+ in 65, and triple negative in 35, and response to chemotherapy was a complete in 60 patients, partial (PR) in 28; 69 patients had stable disease (SD).

Study methods

Neoadjuvant therapy and surgical methods

All patients underwent NAT at our hospital. The treatment plan was developed considering the patient's physical condition, in accordance with the clinical practice guidelines for breast cancer issued by the Chinese Society of Clinical Oncology. Modified radical mastectomy or breast-conserving surgery was performed in our hospital following NAT, with standard ALND for axillary management. All resected tissue specimens were subjected to pathological examination.

Histopathological determination

Histological grading was based on the Scarff-Bloom-Richardson grading method modified by Elston and Ellis.[9] On immunohistochemistry, a positive estrogen receptor (ER) and/or progesterone receptor (PR) ≥1% was defined as HR positive, while a positive ER and PR <1% was defined as HR negative.[10] HER-2 positivity was determined by immunohistochemistry for HER-2 protein (3+) and/or fluorescence in situ hybridization for HER-2 gene amplification.[11] The stroma-tumor ratio (STR) was determined according to the method proposed by Mesker et al.,[12] and the stroma of the selected area had to be surrounded by tumor tissue. The carcinoma percentage (CP) in each field of view was evaluated at 100× magnification, and the remaining portion was considered the stroma percentage (SP). In the case of heterogeneity, the highest amount of stroma was considered conclusive. The carcinoma percentage in each field of view was evaluated at 10% intervals; tumor tissue with SP ≤50% was placed in the low-stroma group, and those with SP >50% in the high-stroma group. Tumor-infiltrating lymphocytes (TILs) were assessed using the method recommended by the International Tumor-Infiltrating Lymphocytes Working Group in 2014,[13] and classified into three groups according to the degree of infiltration: low/no infiltration (<10%), moderate infiltration (10–39 %), and high infiltration (40–90 %); apCR was defined as the absence of tumor cells in the ALNs.

Statistical methods

The data from this experiment were analyzed using Rstudio (embedded R3.6.3) and SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). For the count data, the Chi-squared test was used to analyze variance. The apCR was used as the dependent variable, and the statistically significant variables in the univariate analysis were used as independent variables to establish a multivariate binary logistic regression equation. The variables were entered into the model using the forward stepwise selection method with the OR values used as the risk assessment parameters, and a nomogram was applied to predictive modeling; after the consistency index (C-index) was calculated and ROC curves plotted, internal validation was performed and the calibration curves were plotted. Statistical significance was set at $P < 0.05$, and all tests were two-tailed.

Results

Of the 157 patients, 62 achieved apCR (39.5%) post-NAT. Univariate analysis demonstrated a statistically significant correlation between apCR and the pathological grading of aspiration specimens, molecular typing, STR, clinical N staging, and response to chemotherapy (Table 1). The apCR rate was higher in: patients with pathological grade 3 of the aspiration specimen, rather than grades 1-2 (51.7% vs. 23.5%, P <0.001); patients with HER2+/TNBC, rather than luminal A/B (48.0% vs. 24.6%, P <0.05); the low-stroma group, rather than the high-stroma group (60.3% vs. 23.6%, P <0.001); patients with clinical stage N1 rather than stages N2-3 (52.2% vs. 26.0%, P <0.05); the CR/PR group rather than the SD group, after NAT (60.2% vs. 13.0%, P <0.001). A multivariate binary logistic regression equation was established, and a forward stepwise selection method was used to enter variables into the model. The results showed that the likelihood of apCR post-NAT was greater in patients with histological grade III (Figure 1-A), low stroma (Figure 1-B), clinical stage N1, and PR or CR to chemotherapy (Table 2).

Table 1
Univariate analysis of post-NAT apCR

Variate	Group	apCR		*P*-value
		No	yes	
Age	≤50	39	26	0.913
	>50	56	36	
Molecular typing	Luminal A	12	3	**0.036**
	Luminal B	31	11	
	HER2+	34	31	
	TNBC	18	17	
Pathological grading	1-2	52	16	**0.001**
	3	43	46	
cT	cT1	17	5	0.314
	cT2	51	40	
	cT3	19	13	
	cT4	8	4	
cN	cN1	38	42	**0.003**
	cN2	32	13	
	cN3	25	7	
RECIST	SD	60	9	**0.001**
	PR	19	9	
	CR	16	44	
STR	High group	68	21	**0.001**
	Low group	27	41	
TILs	High	7	10	0.084
	Low-medium	88	52	
Menopause	no	42	29	0.752
	yes	53	33	

Table 2
Multivariate logistic regression analysis of post-NAT apCR

	level	β	SE	Wald	*P*-value	OR	95% CI for OR	
							Lower	upper
Pathological grading	**1-2 (ref)**	**0.000**				**1.000**		
	3	**1.164**	**0.500**	**5.419**	**0.020**	**3.203**	**1.202**	**8.533**
cN	**cN3 (ref)**	**0.000**				**1.000**		
	cN1	**1.440**	**0.686**	**4.403**	**0.036**	**4.220**	**1.100**	**16.194**
	cN2	**0.467**	**0.773**	**0.366**	**0.545**	**1.596**	**0.351**	**7.257**
RECIST	**SD (ref)**	**0.000**				**1.000**		
	PR	**2.338**	**0.716**	**10.663**	**0.001**	**10.356**	**2.546**	**42.125**
	CR	**3.599**	**0.634**	**32.184**	**0.001**	**36.571**	**10.546**	**126.814**
STR	**High group (ref)**	**0.000**				**1.000**		
	Low group	**2.049**	**0.539**	**14.456**	**0.001**	**7.759**	**2.698**	**22.309**
Constant		-5.142	0.977	27.682	0.001	0.006		
Note: Chi-squared goodness of fit = 89.698, P<0.05; C-S R-square = 0.601 shows a good model fit.								

Statistically significant variables in the logistic regression equation were used to build a predictive model for apCR; that is, a nomogram. The first row in the nomogram shows the reference score for each variable. For each patient, we could find the respective points according to the condition or value of the independent variable, calculate the total points, and find the mapping of the total points in the penultimate row of the nomogram, which corresponds with the risk probability; i.e., to obtain the probability value of apCR predicted by the independent variable. It is clear from the nomogram that when a patient has a tumor with histological grade 3, clinical stage N1, CR to chemotherapy, and low stroma, the total points are higher and the possibility of apCR greater (Figure 2).

The final model test showed a C-index=0.898, SD=0.049, and P <0.05, indicating that the consistency test was statistically significant, and that the model had good predictive ability. The area under the ROC curve was 0.898 (Figure 3), implying that the model had strong predictive ability. This experiment adopted an internal validation method to test the robustness of the predictive model, using bootstrap sampling with 1,000 replicate samples; additionally, the calibration curve was similar to the ideal curve (Figure 4), suggesting that the model had good calibration and predictive abilities.

Discussion

This study integrated the clinicopathological characteristics of female patients with breast cancer and positive ipsilateral ALNs, who were treated with NAT and surgery. Statistical methods were used to screen for predictors of apCR and design a predictive model to predict the apCR rate post-NAT. The results of univariate analysis showed that apCR was significantly associated with the pathological grading of aspiration specimens, molecular typing, STR, clinical N staging, and response to chemotherapy (all P <0.05). A multivariate binary logistic regression equation was established, and a forward stepwise selection method was adopted to enter variables into the model. The findings demonstrate a greater possibility of apCR post-NAT in cases of histological grade III, low stroma, clinical N1 stage, and PR or CR to chemotherapy. A predictive model for apCR post-NAT was developed using statistically significant variables in the logistic regression equation. The predictive model consisted of four independent predictors: pathological grading of the aspiration specimen, STR, clinical N staging, and response to chemotherapy. The predictive model had good accuracy and demonstrated good clinical utility when both ROC curves and internal validation were performed, which contributed to the option of individualized de-escalation of axillary surgery.

With the concept of multimodal treatment for breast cancer, NAT transforms locally advanced, inoperable patients into operable ones; i.e., it results in downstaging of the breast cancer focus and ALNs.[14] This study focused on ALN management after NAT. According to previous studies, the effective use of NAT and targeted therapy has enabled the post-NAT apCR rate to reach 30–63 %.[5–6] The National Comprehensive Cancer Network guidelines previously recommended that ALND remain the standard of care in patients with positive clinical lymph nodes after NAT, regardless of lymph node outcome; recently, however, the feasibility of replacing ALND with sentinel lymph node biopsy in initially cN+ patients turning to negative ALN and undergoing NAT, has been confirmed. Based on the results of the Z1071 and SENTINA trials,[15–16] for initial cN+ patients who achieved ycN0 after NAT, follow-up ALND may not be considered when a combined tracer detected >2 negative sentinel lymph nodes. Clinicians therefore need to be cautious when assessing if the patient has achieved apCR preoperatively; incorrect clinical judgment may otherwise result in residual localized metastatic lymph nodes. The predictive model for apCR post-NAT constructed in this study indicated that patients with pathological grade 3, low stroma, clinical stage N1, and CR/PR to chemotherapy achieved apCR more easily.

While the most commonly used noninvasive tool for clinical judgment of the status of ALNs after NAT is imaging, imaging data only assesses tumor burden and not the biological behavior of the tumor or its response to chemotherapeutic agents; therefore, imaging alone cannot predict the probability of pathological complete response of ALN with maximum accuracy. The predictive model of ALN status in breast cancer was first developed by the Memorial Sloan-Kettering Cancer Center in the USA in 2003.[17] Scholars at the center incorporated nine types of clinical and pathological data into the model, including tumor size, histological grade, whether it was a rapid pathological section, number of positive sentinel lymph nodes, number of negative sentinel lymph nodes, detection method of sentinel lymph nodes, estrogen receptors, vascular cancer thrombi, and multifocal tumors. The AUC values obtained from the

validation of this model at different institutions varied considerably from 0.58–0.86.[18, 19] Other institutions have also attempted to build different predictive models, such as the SCH model, constructed by Fudan University Shanghai Cancer Hospital in China[20]; the Olga predictive model, constructed using data from the US National Cancer Database[21]; the Tenon score in France[22]; the M.D. Anderson score[23]; the Cambridge score in the UK.[24] These scoring systems have shown good accuracy regarding internal validation; however, they remain to be tested regarding external validation.

In this study, we included STR—the ratio of tumor cells to stroma in the tumor tissue, which indirectly reflects the relationship between the tumor cells and microenvironment—for the first time. Sophie et al.,[25] demonstrated that patients with high-stroma, HER2-negative, early breast cancer have a lower rate of pCR and MP response after NAT. Similar to primary tumor cells in the breast, tumor cells in ALNs are affected by STR. This study revealed that the high-stroma group had a lower apCR rate than the low-stroma group, suggesting that STR may also be a predictor of post-NAT apCR. The significantly higher apCR rate after NAT indicated that ALND can be selectively avoided after NAT in some patients with initially positive ALNs, especially those with pathological grade 3, low stroma, clinical stage N1, and CR/PR to chemotherapy when >2 negative sentinel lymph nodes were detected. Still, for patients in the initial cN2-3 group, the apCR rate was only 26% due to the high tumor burden, and ALND was recommended. The nomogram predictive model constructed in this study can predict the possibility of apCR based on patient and disease characteristics, which is useful for guiding both physicians and patients in selecting further treatment options; however, the predictive model is not intended to replace the clinician's judgment but assist the physician's decision by providing more objective probability estimates to complement other relevant clinical data.

This study has some limitations. First, this was a single-center study, and further analysis and modeling with a larger data are needed to refine the model and its application. Second, the predictive model is based on the treatment modality of the disease over a certain period; with the development of medical standards and treatment techniques, the predictive model becomes inaccurate over time and needs to be updated.

Conclusions

In summary, by integrating the clinicopathological characteristics of female patients with breast cancer and positive ipsilateral ALNs who were treated with NAT and surgery, as well as constructing a predictive model for apCR post-NAT, we predicted the pathological response of ALNs in breast cancer post-NAT. This therefore contributes to the option of individualized de-escalation of axillary surgery based on NAT efficacy.

Abbreviations

NAT
Neoadjuvant therapy

apCR
Axillary pathological complete response
ALND
Axillary lymph node dissection
TSR
Tumor-stroma ratio
ALN
Axillary lymph node
CR
Complete response
PR
Partial response
SD
Stable disease
ER
Estrogen receptor
PR
Progesterone receptor

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee of the First Affiliated Hospital of Jinzhou Medical University (approval no. 2020) and was conducted in accordance with the 1964 Helsinki Declaration; patient consent was not required due to the retrospective nature of the study.

Consent for publication: Not applicable.

Availability of data and materials: The analyzed data sets generated during the current study are available from the corresponding author upon reasonable request. Inquiries for data access may be sent to the following e-mail: lixinyue913@163.com.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: JY performed the experiments, analyzed the data, and wrote the manuscript. XL contributed to statistical analyses. All authors read and approved the final manuscript.

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Figures

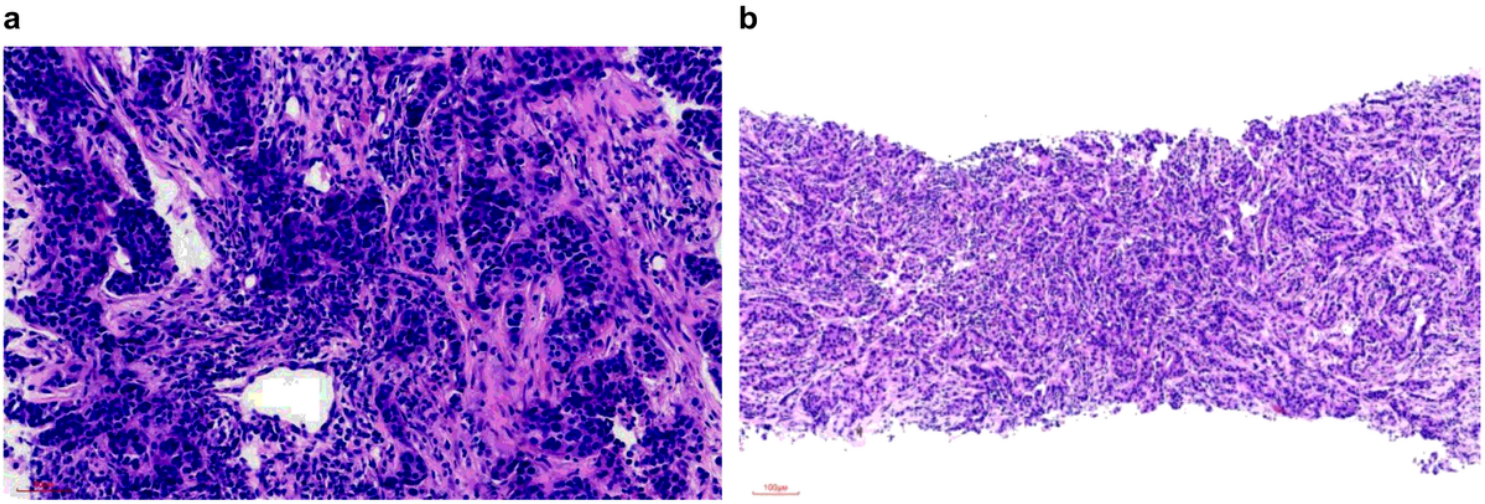

Figure 1

A. Breast cancer pathological grade III; B. Breast cancer low stroma (H&E ×100)

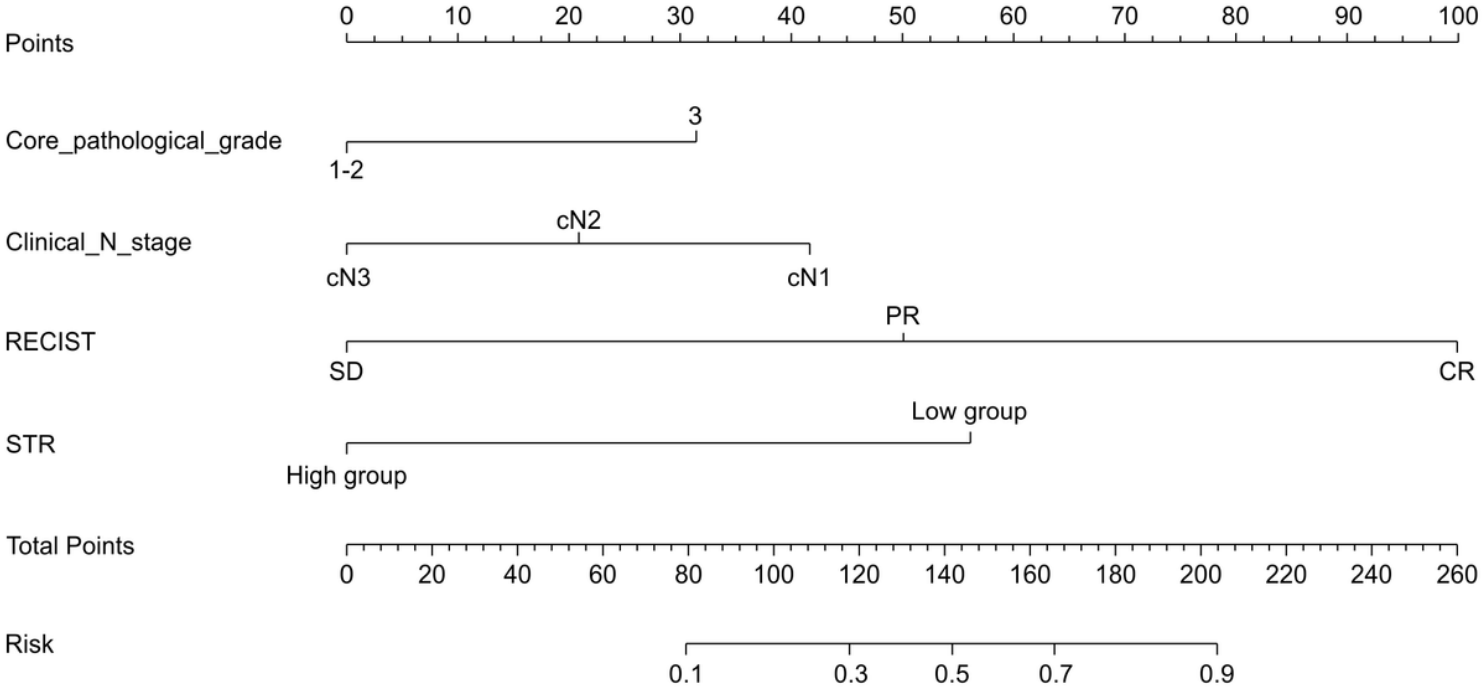

Figure 2

Predictive model for post-NAT apCR (nomogram

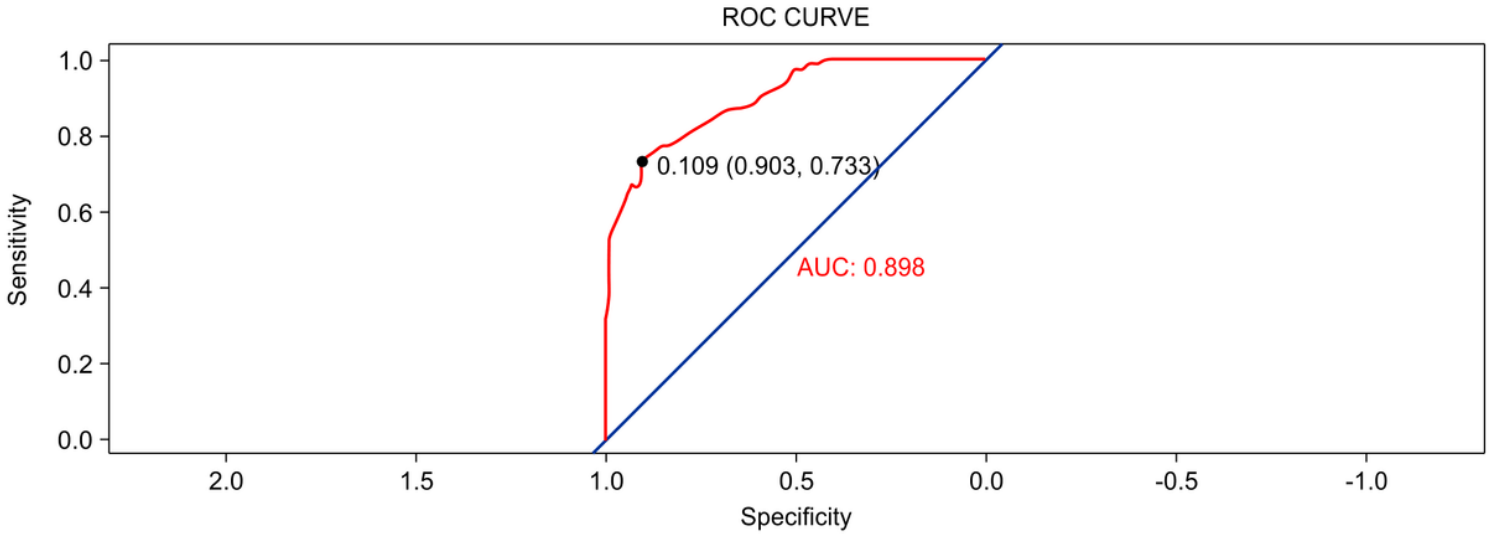

Figure 3

Predictive model for post-NAT apCR AUC = 0.898

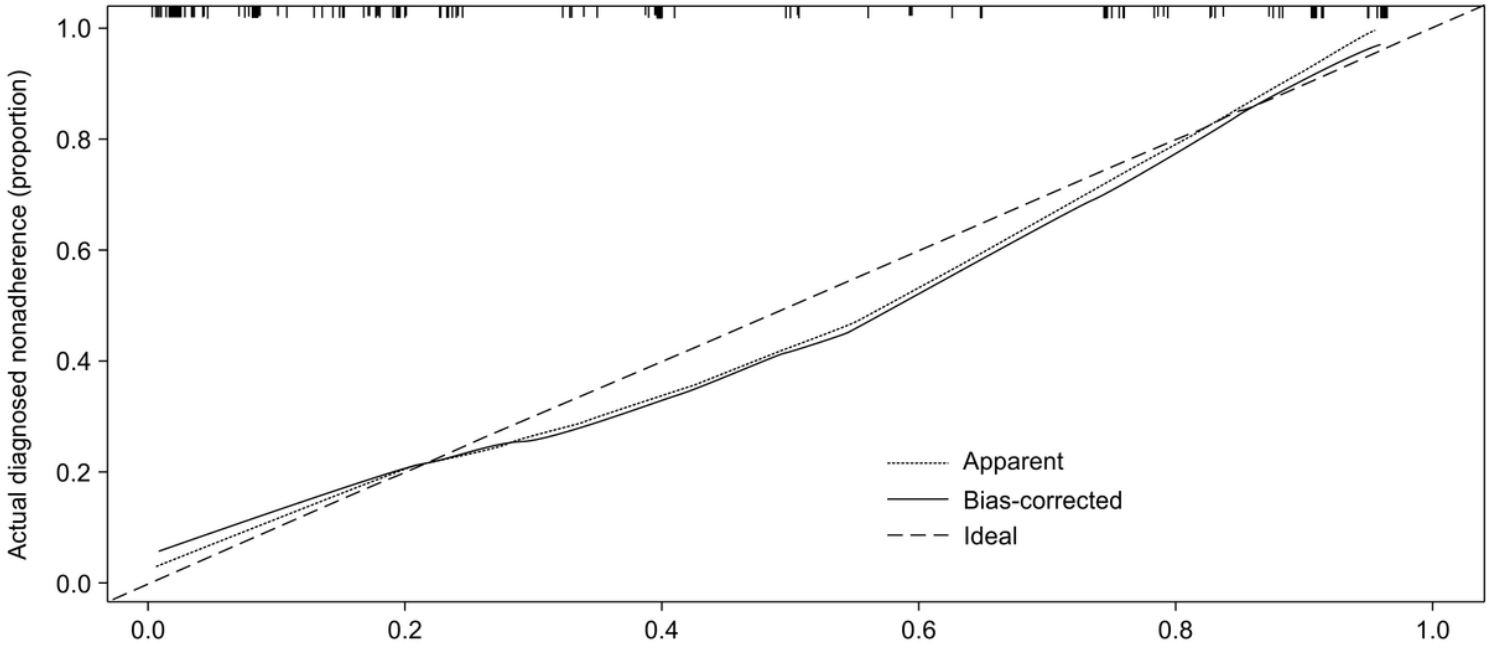

Figure 4

Nomogram-predicted probability of nonadherence