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ORIGINAL RESEARCH

A Nomogram Based on S100A7 and Clinicopathological Characteristics to Predict the Efficacy of Neoadjuvant Chemotherapy in Breast Cancer: A Retrospective Study

Tianqi Zhang[1], Xin Yu[1], Xiaolu Yang[1], Yilun Li[1], Xiaolong Li[2], Li Ma[1]

[1]Department of Breast Disease Center, The Fourth Hospital of Hebei Medical University, Shijiazhuang, People's Republic of China; [2]Department of Breast Surgery, The Fourth Hospital of Shijiazhuang, Shijiazhuang, People's Republic of China

Correspondence: Li Ma, Email 47500562@hebmu.edu.cn

Background: We have previously found that S100 calcium-binding protein A7 (S100A7) is strongly associated with chemoresistance in breast cancer (BC). In this study, we investigated whether S100A7 can be used to predict the efficacy of neoadjuvant chemotherapy (NAC) and assessed its relationship with clinicopathological characteristics in BC.

Methods: We retrospectively analyzed the clinicopathological data of patients with BC who underwent NAC at the Fourth Hospital of Hebei Medical University between January 2021 and December 2021. The *t*-test, Wilcoxon test, and chi-square test were used to compare clinicopathological characteristics between the NAC-sensitive and NAC-insensitive groups and assess the relationship between S100A7 expression and clinicopathological characteristics. Binomial logistic regression analysis was used to identify the predictors of NAC efficacy. A prediction model was constructed and visualized using a nomogram for clinical prediction of NAC efficacy.

Results: A total of 76 patients with BC who underwent NAC were included in this study; of these patients, 49 were sensitive to NAC, whereas 27 were insensitive to NAC. Statistically significant differences were observed in age, menstrual status, histological grade, T stage, Ki67, and S100A7 expression between the NAC-sensitive and NAC-insensitive groups. Regression analysis showed that age, histological grade, Ki67, subtype, menstrual status, TILs and S100A7 expression were predictors of NAC efficacy. However, only histological grade III (OR, 25.613; 95% CI, 1.254–523.077; $P = 0.035$), Ki67 (OR, 9.781; 95% CI, 2.022–47.317; $P = 0.005$), TILs (OR, 1.227; 95% CI, 1.064–1.415; $P = 0.005$), and S100A7 expression (OR, 0.042; 95% CI, 0.010–0.174; $P<0.001$) were independent predictors. Therefore, we constructed a model incorporating these four characteristics and visualised the model in a nomogram to predict NAC efficacy in clinical settings, with a model prediction accuracy of 0.927.

Conclusion: S100A7 may serve as a predictor of NAC efficacy in patients with BC.

Keywords: neoadjuvant chemotherapy, breast cancer, S100A7, predictor

Background

Breast cancer is the most prevalent malignant tumour among women worldwide, with 2,308,897 new cases in 2022, and its incidence continues to rise annually.[1,2] Chemotherapy is the primary treatment for BC. Neoadjuvant chemotherapy (NAC) is administered to patients with BC before localized treatments such as surgery or radiation.[3] The original purpose of NAC is to shrink tumors so that patients with larger tumors can undergo surgical treatment.[4] Later, clinicians found that, unlike adjuvant chemotherapy, in which changes in lesions cannot be measured because it is administered after surgery or radiation, NAC provides the opportunity to assess clinical response by observing tumor regression or enlargement via imaging or the naked eye, which helps assess drug sensitivity in patients.[5] Consequently, NAC is widely used in clinical practice.[3] However, not all patients are sensitive to NAC. According to data from two large clinical trials, <30% of patients with BC who receive NAC achieve pathological complete response (pCR).[6] Moreover, studies have shown that 40–80% of patients with BC who undergo NAC

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experience a delay in subsequent treatment.[5] Therefore, it is necessary to identify biomarkers that can easily, accurately, and effectively predict the efficacy of NAC in BC.

S100 calcium-binding protein A7 (S100A7) is an important constituent protein of the S100 family and was initially identified from the epidermal squamous epithelial cells of patients with psoriasis.[7,8] Studies have shown that S100A7 promotes the progression of various tumors.[9–11] We have previously found that S100A7 promotes the proliferative, migratory, and invasive abilities of BC cells and its knockdown increases the sensitivity of BC cells to paclitaxel in vitro.[12] These findings suggest that S100A7 plays an oncogenic role in BC and is strongly associated with the sensitivity of BC cells to chemotherapy. However, previous studies have been conducted on public databases or cell lines and lacked clinical data support. Therefore, we conducted this retrospective study to investigate the relationship between S100A7 and the efficacy of NAC for BC and to explore its potential as a biomarker for predicting the efficacy of NAC.

In this retrospective study, we analyzed various clinicopathological characteristics to evaluate their potential in predicting NAC efficacy, identified S100A7 as one of the predictors, and constructed a model to predict NAC efficacy in clinical settings. In addition, we investigated the relationship between S100A7 expression and clinicopathological characteristics.

Methods

Study Design and Patients

We retrospectively reviewed the clinicopathological data of patients with BC who underwent NAC at the Fourth Hospital of Hebei Medical University between January 2021 and December 2021. Patients with incomplete medical records, those requiring anti-human epidermal growth factor receptor-2 (HER-2) therapy, those with comorbidities with other cancers, and those with bilateral BC were excluded.[13] Eventually, a total of 76 patients with BC who underwent NAC were included in this study. These patients had not received any anti-cancer therapy before NAC.

Data Collection

We collected and analyzed the following variables: age at diagnosis, menstrual status, histological grade, tumor size, lymph node metastasis status, AJCC stage,[14] estrogen receptor (ER) status, progesterone receptor (PR) status, tumor infiltrating lymphocytes (TILs), S100A7 expression, and Miller–Payne (MP) grade after NAC.

MP grading is currently the most commonly used pathological evaluation system in China. It helps assess the efficacy of NAC based on the degree of reduction in the number of primary tumor cells.[15] MP grade 1 refers to no reduction in the number of primary tumor cells, MP grade 2 refers to <30% reduction in the number of primary tumor cells, MP grade 3 refers to a 30%–90% reduction in the number of primary tumor cells, MP grade 4 refers to >90% reduction in the number of primary tumor cells, and MP grade 5 refers to the complete disappearance of infiltrating tumor cells. We defined patients with MP grades 1–3 as insensitive to NAC and those with MP grades 4–5 as sensitive to NAC.

Immunohistochemical Staining

S100A7 expression was assessed via immunohistochemical (IHC) staining. We collected perforated tumor tissues from all patients with BC included in this study. These tissues were obtained before NAC. Formalin-fixed, paraffin-embedded tumor tissues were cut into 4-μm-thick sections, placed on gelatin-coated slides, and incubated in an oven at 65°C for 1 h. The sections were dewaxed, immersed in hydrogen peroxide for 10 min, and subjected to antigen repair in diluted EDTA. Subsequently, the sections were rinsed with PBS and incubated with a primary antibody overnight. The following day, the sections were washed with PBS, incubated with a secondary antibody for 30 min, and stained with DAB. The sections were washed with PBS after both antibody incubation and DAB staining.

The stained tissue sections were examined using the LEICA DM 2000 LED biomicroscope, and 4 random images of the tumour region at a magnification of 200x were captured using the Leica Application Suite (version 4.9). Staining intensity was analyzed using the Image-Pro Plus (version 6.0) (Copyright © 1993 MediaCybernetics. All rights reserved) software. Protein expression was expressed as the mean optical density, calculated as the integrated optical density (IOD) of positively stained areas divided by the tumor area in each image.[16] The average expression of S100A7 was used as the cut-off. Above-average expression was defined as high expression, whereas below-average expression was defined as low expression.

Statistical Analysis

The SPSS (version 25.0) and R (version 4.3.1) software were used for statistical analysis. The *t*-test, Wilcoxon test, and chi-square (x^2) test were used to compare clinicopathological characteristics between the NAC-sensitive and NAC-insensitive groups and assess the relationship between S100A7 expression and clinicopathological characteristics. Furthermore, binomial logistic regression analysis was used to identify predictors of NAC efficacy. The independent predictors were used to construct a prediction model and visualized by plotting a nomogram. The receiver operating characteristic (ROC) curve was plotted to assess the predictive performance. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological and Treatment Characteristics

A total of 76 patients with BC who underwent NAC were included in this study. Of these 76 patients, 49 (64.5%) were sensitive to NAC and 27 (35.5%) were insensitive to NAC. IHC staining revealed an average staining intensity of 0.85 for S100A7 in BC tissues. According to the classification criteria, 48 and 28 patients were found to have low and high expression of S100A7, respectively (Figure 1A and B).

On comparing clinicopathological characteristics between the NAC-sensitive and NAC-insensitive groups (Table 1), we found statistically significant differences in age, menstrual status, histological grade, T stage, Ki67, TILs and S100A7 expression between the two groups ($P<0.05$). However, no differences were observed in the AJCC stage, N stage, ER status, PR status, subtype, or chemotherapy regimen. In the NAC-sensitive group, 39 (80%) patients had low S100A7 expression, whereas 10 (20%) patients had high S100A7 expression. On the contrary, a majority of patients in the NAC-insensitive group had high S100A7 expression (high expression, n = 18; low expression, n = 9). S100A7 expression was significantly different between the two groups ($P<0.001$), indicating its close relationship with the efficacy of NAC.

Univariate and Multivariate Analyses

Univariate logistic regression analysis was used to identify clinicopathological characteristics significantly associated with NAC efficacy. The results showed a significant correlation between S100A7 expression and NAC efficacy.

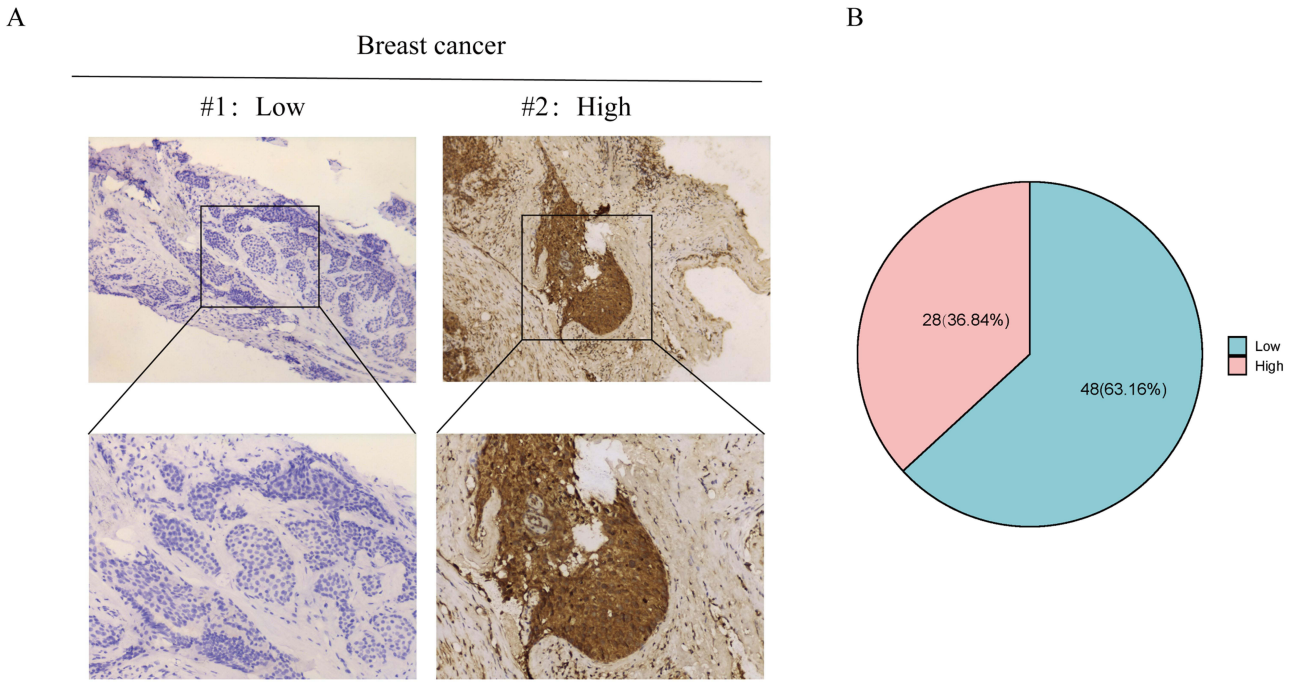

Figure 1 Expression of S100A7 in BC. (**A**) Low and high expression of S100A7 in BC. (**B**) Compositional pie charts of low- and high-expression S100A7.
Abbreviation: S100A7, S100 calcium-binding protein A7.

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Table 1 Relationship Between NAC Efficacy and Clinicopathological Characteristics

	Total	NAC Efficacy		*P*-Value
		Sensitive (N = 49)	Insensitive (N = 27)	
Age				0.014*
<50	37 (48.7%)	29 (38.2%)	8 (10.5%)	
≥50	39 (51.3%)	20 (26.3%)	19 (25.0%)	
Menstrual status				0.001*
Premenopausal	47 (61.8%)	37 (48.6%)	10 (13.2%)	
Postmenopausal	29 (38.2%)	12 (15.8%)	17 (22.4%)	
AJCC stage				0.289
II	36 (47.4%)	21 (27.7%)	15 (19.7%)	
III	40 (52.6%)	28 (36.8%)	12 (15.8%)	
Histological grade				<0.001*
I	16 (21.1%)	4 (5.3%)	12 (15.8%)	
II	44 (57.9%)	30 (39.5%)	14 (18.4%)	
III	16 (21.0%)	15 (19.7%)	1 (1.3%)	
T stage				0.035*
T1	13 (17.1%)	7 (9.2%)	6 (7.9%)	
T2	41 (53.9%)	28 (36.8%)	13 (17.1%)	
T3	11 (14.5%)	10 (13.2%)	1 (1.3%)	
T4	11 (14.5%)	4 (5.3%)	7 (9.2%)	
N stage				0.632
N0	4 (5.2%)	3 (3.9%)	1 (1.3%)	
N1	44 (57.9%)	26 (34.2%)	18 (23.7%)	
N2	15 (19.8%)	10 (13.2%)	5 (6.6%)	
N3	13 (17.1%)	10 (13.2%)	3 (3.9%)	
ER status				0.102
Negative	32 (42.1%)	24 (31.6%)	8 (10.5%)	
Positive	44 (57.9%)	25 (32.9%)	19 (25%)	
PR status				0.159
Negative	42 (55.3%)	30 (39.5%)	12 (15.8%)	
Positive	34 (44.7%)	19 (25%)	15 (19.7%)	
Ki67				0.005*
<30%	40 (52.6%)	20 (26.3%)	20 (26.3%)	
≥30%	36 (47.4%)	29 (38.2%)	7 (9.2%)	
Subtype				0.250
Triple-negative	32 (42.1%)	24 (31.6%)	8 (10.5%)	
Luminal A	29 (38.2%)	16 (21.1%)	13 (17.1%)	
Luminal B	15 (19.7%)	9 (11.8%)	6 (7.9%)	
Chemotherapy regimen				0.072
TA	61 (80.2%)	39 (51.3%)	22 (28.9%)	
AC-T	10 (13.2%)	5 (6.6%)	5 (6.6%)	
dAC-T	5 (6.6%)	5 (6.6%)	0	
TILs (%)		15±5.89	7.8±4.75	<0.001*
S100A7 expression				<0.001*
Low	48 (63.1%)	39 (51.3%)	9 (11.8%)	
High	28 (36.9%)	10 (13.2%)	18 (23.6%)	

Notes: *$P < 0.05$.

Specifically, patients with high S100A7 expression had worse NAC efficacy than those with low S100A7 expression (OR = 0.128; 95% CI, 0.044–0.370; $P<0.001$). In addition, age, histological grade, Ki67, subtype, menstrual status and TILs were significantly associated with NAC efficacy. However, AJCC stage, T stage, N stage, ER status, PR status, and chemotherapy regimen did not show a significant relationship with NAC efficacy (Table 2).

Table 2 Univariate and Multivariate Analyses of the Predictors of NAC Efficacy

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* Value
S100A7				
Low-S00A7	Reference		Reference	
High-S100A7	0.128(0.044–0.370)	<0.001*	0.042(0.010–0.174)	<0.001*
Age				
<50	Reference		Reference	
≥50	0.290(0.106–0.792)	0.016*	0.225(0.018–2.833)	0.248
Histological grade				
I	Reference		Reference	
II	6.429(1.757–23.524)	0.005*	3.232(0.559–18.685)	0.19
III	45(4.426–457.475)	0.001*	25.613(1.254–523.077)	0.035*
Ki67				
<30%	Reference		Reference	
≥30%	4.143(1.476–11.630)	0.007*	9.781(2.022–47.317)	0.005*
Subtype				
Triple-negative	Reference		Reference	
Luminal A	0.303(0.130–0.707)	0.006*	0.301(0.052–1.750)	0.181
Luminal B	0.333(0.125 −0.892)	0.029*	0.335(0.048 −2.347)	0.271
Menstrual status				
Premenopausal	Reference		Reference	
Postmenopausal	0.191(0.069–0.527)	0.001*	0.510(0.042–6.218)	0.598
AJCC stage				
II	Reference			
III	1.667(0.647–4.296)	0.29		
T stage				
T1	Reference			
T2	1.326 (0.502 −3.502)	0.569		
T3	4.941 (0.924–26.413)	0.062		
T4	0.385(0.114–1.301)	0.124		
N stage				
N0	Reference			
N1	0.462(0.093 −2.291)	0.344		
N2	0.568 (0.102–3.156)	0.518		
N3	0.852(0.144–5.032)	0.86		
ER status				
Negative	Reference			
Positive	0.439(0.162–1.190)	0.106		
PR status				
Negative	Reference			
Positive	0.507(0.196–1.313)	0.162		
Chemotherapy regimen				
AC-T	Reference			
TA	1.17(0.478–2.864)	0.731		
TILs	1.277(1.129–1.444)	<0.001*	1.227(1.064–1.415)	0.005*

Notes: *P<0.05.

The variables significantly associated with NAC efficacy were included in multivariate analysis. The results showed that S100A7 expression (OR = 0.042; 95% CI, 0.010–0.174; P<0.001), histological grade III (OR = 25.613; 95% CI, 1.254–523.077; P = 0.035), Ki-67 (OR = 9.781; 95% CI, 2.022–47.317; P = 0.005), and TILs (OR = 1.227; 95% CI, 1.064–1.451; P = 0.005) were independent predictors of NAC efficacy (Table 2).

Prediction Model for NAC Efficacy

The four independent predictors identified via univariate and multivariate analyses were used to construct a nomogram for clinical prediction of NAC efficacy (Figure 2A). The accuracy and clinical benefit of the model were estimated using ROC and DCA curves. The ROC curve showed that the model predicted NAC efficacy with an AUC value of 0.927 (95% CI, 0.865–0.989), a sensitivity of 89.8%, and a specificity of 88.9%, which indicated that the model had high predictive accuracy (Figure 2B). To further assess the reliability of the nomogram, we produced calibration curves, which

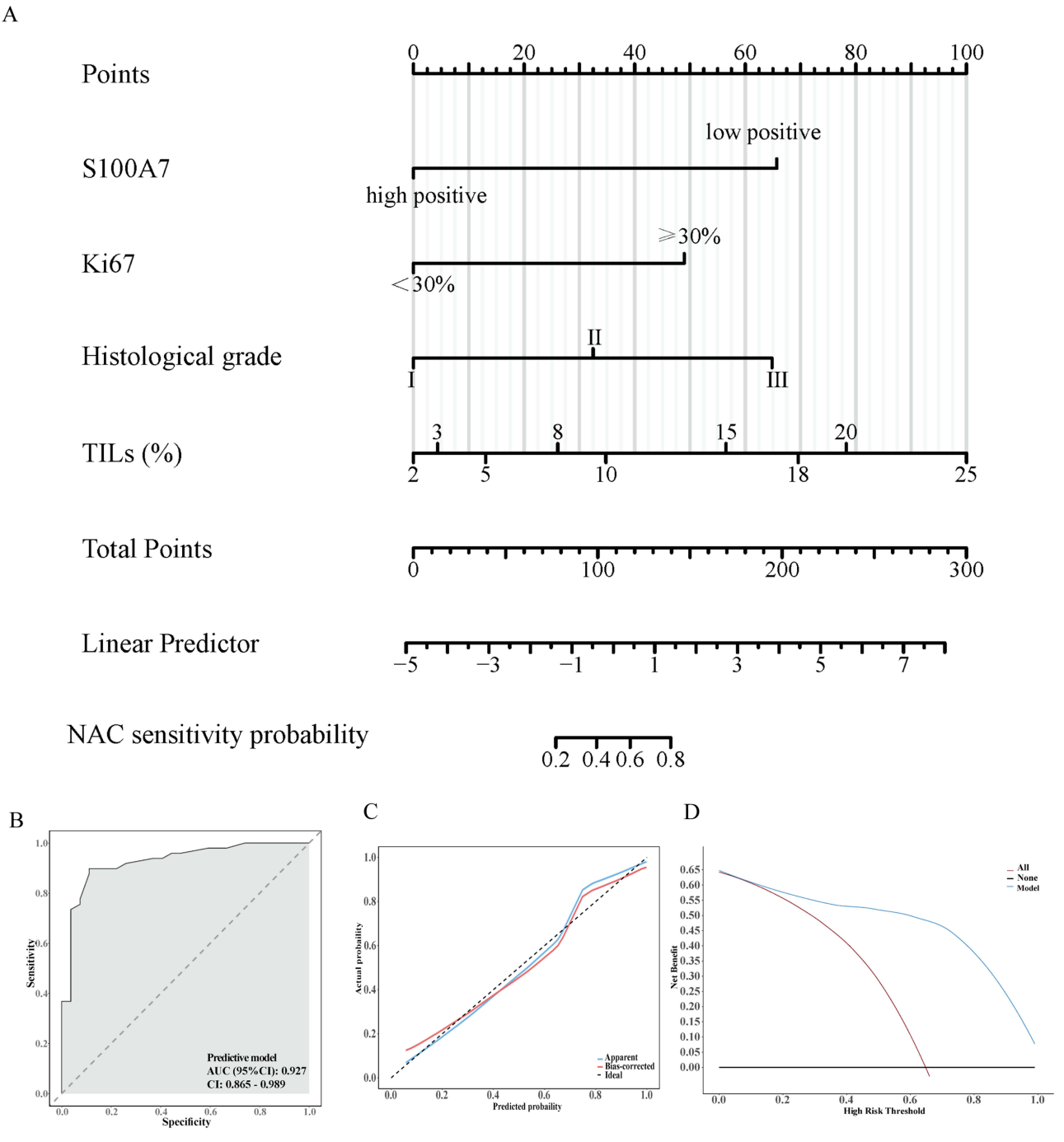

Figure 2 Establishment of predictive models for NAC efficacy. (**A**) Nomogram for predicting NAC efficacy. (**B**) ROC curves of the model. (**C**) Calibration curve for the nomogram. **(D)** DCA curve of the model.

Abbreviations: NAC, neoadjuvant chemotherapy; ROC, receiver operating characteristic; DCA, decision curve analysis; TILs, Tumor Infiltrating Lymphocytes; AUC, area under curve; CI, confidence interval.

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showed that the prediction of NAC efficacy by our nomogram was in close agreement with the actual results (Figure 2C). Moreover, the DCA curve showed that the model had a large net benefit in predicting NAC efficacy (Figure 2D).

Relationship Between S100A7 Expression and Clinicopathological Characteristics

The above-mentioned results suggest that S100A7 can be used as a predictor of NAC efficacy in BC. To further assess the influence of S100A7 on BC, we compared clinicopathological characteristics between the high- and low-S100A7-expression groups. The results showed differences in the N stage and ER status between the two groups. In addition, patients with BC with high S100A7 expression had a high AJCC stage ($P = 0.042$), indicating more advanced disease (Table 3).

Table 3 Relationship Between S100A7 Expression and Clinicopathological Characteristics

	Total	S100A7		*P*-Value
		Low (N = 48)	High (N = 28)	
Age				0.211
<50	37 (48.7%)	26 (34.2%)	11 (14.5%)	
≥50	39 (51.3%)	22 (28.9%)	17 (22.4%)	
Menstrual status				0.105
Premenopausal	47 (61.8%)	33 (43.4%)	14 (18.4%)	
Postmenopausal	29 (38.2%)	15 (19.8%)	14 (18.4%)	
AJCC stage				0.042*
II	36 (47.4%)	27 (35.5%)	9 (11.9%)	
III	40 (52.6%)	21 (27.6%)	19 (25.0%)	
Histological grade				0.157
I	16 (21.1%)	7 (9.2%)	9 (11.9%)	
II	44 (57.8%)	29 (38.1%)	15 (19.7%)	
III	16 (21.1%)	12 (15.8%)	4 (5.3%)	
T stage				0.089
T1	13 (17.1%)	9 (11.8%)	4 (5.3%)	
T2	41 (53.9%)	29 (38.1%)	12 (15.8%)	
T3	11 (14.5%)	5 (6.6%)	6 (7.9%)	
T4	11 (14.5%)	5 (6.6%)	6 (7.9%)	
N stage				0.044*
N0	4 (5.3%)	3 (3.8%)	1 (1.3%)	
N1	44 (57.9%)	32 (42.1%)	12 (15.8%)	
N2	15 (19.7%)	6 (7.9%)	9 (11.8%)	
N3	13 (17.1%)	7 (9.2%)	6 (7.9%)	
ER status				0.043*
Negative	32 (42.2%)	16 (21.1%)	16 (21.0%)	
Positive	44 (57.8%)	32 (42.1%)	12 (15.7%)	
PR status				0.227
Negative	42 (55.3%)	24 (31.6%)	18 (23.7%)	
Positive	34 (44.7%)	24 (31.6%)	10 (13.1%)	
Ki67 score				0.408
<30%	40 (52.6%)	27 (35.5%)	13 (17.1%)	
≥30%	36 (47.4%)	21 (27.6%)	15 (19.7%)	
Subtype				0.128
Triple-negative	32 (42.1%)	16 (21.0%)	16 (21.1%)	
Luminal A	29 (38.2%)	21 (27.6%)	8 (10.6%)	
Luminal B	15 (19.7%)	11 (14.5%)	4 (5.2%)	
TILs (%)		12.98±6.22	10.82±6.44	0.154

Notes: *$P < 0.05$.

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Discussion

In recent years, NAC has been widely used. However, the usefulness of NAC has been increasingly questioned. A multicenter study involving several countries in the United States, Australia, and Europe showed that patients who had received NAC tended to opt for more conservative surgical treatments, leading to higher rates of local recurrence.[5] Another study showed that NAC did not provide a survival benefit to patients with BC when compared with adjuvant chemotherapy.[17] However, it has also been shown that BC patients who achieve pathological complete response after NAC can have significantly prolonged survival.[18] Moreover, NAC may facilitate breast conservation in patients who are unwilling to undergo mastectomy. Therefore, it has been suggested that NAC was only suitable for those who were likely to be sensitive to it.[5] Consequently, it is necessary to identify clinicopathological features that can predict the efficacy of NAC and select patients with BC who are sensitive to NAC.

In this study, we divided 76 patients with BC into NAC-sensitive and NAC-insensitive groups based on MP grades and compared clinicopathological characteristics between the two groups. We found that the two groups significantly differed in age, menstrual status, histological grade, T stage, Ki67, and S100A7 expression.

Subsequently, we performed univariate and multivariate logistic regression analyses to identify predictors of NAC efficacy. Univariate analysis showed that age, menstrual status, histological grade, Ki67, subtype, TILs, and S100A7 expression were significantly associated with NAC efficacy. Multivariate analysis showed that only Ki67, histological grade, TILs, and S100A7 expression were independent predictors of NAC efficacy. Previous studies have investigated factors that may influence NAC's efficacy. For instance, Jarząb et al[19] found that NAC efficacy was better in patients with histological grade III disease than in those with histological grade I or II disease. Lin He et al[20] found that high levels of TILs were associated with better NAC efficacy. In addition, many studies have shown that the Ki67 can be used to predict the efficacy of chemotherapy.[21] These findings are consistent with those of the present study. However, instead of selecting and analyzing individual predictors, we constructed a model incorporating these four characteristics and visualised the model in a nomogram to predict NAC efficacy. The ROC curve showed that the model had a prediction accuracy of 0.927, indicating that the model had strong predictive accuracy. The calibration curves also indicate that the predicted probabilities of the model were close to the actual probabilities.

Previous studies have shown that S100A7 can activate the NF-κB signaling pathway in BC cells and that activation of this pathway is closely related to resistance to doxorubicin and paclitaxel in BC.[22–24] Our previous study also found that S100A7 expression was strongly associated with chemotherapy resistance in BC cells.[12] The present study further supports the relationship between S100A7 and chemoresistance using clinical data. Moreover, this study demonstrated for the first time that S100A7 can be used as a predictor of NAC efficacy in BC. Furthermore, we analysed the clinicopathological features associated with S100A7 expression and found that high S100A7 expression was associated with an advanced disease stage.

This study has a few limitations that should be acknowledged. First, owing to the involvement of only a single centre, the inclusion of cases may be localized and limited. Second, this study had a retrospective design; therefore, selective bias was inevitable Third and last, the sample size of this study was small therefore the level of evidence for the results we obtained was not high enough. Future studies should include larger sample sizes to validate the role of S100A7 as a predictor of NAC efficacy.

Conclusions

This retrospective study showed that clinicopathological features such as age, menstrual status, histological grade, T stage, Ki67, and S100A7 expression were significantly different between patients with BC in the NAC-sensitive and NAC-insensitive groups. Univariate and multivariate logistic regression analyses showed that Ki67, histological grade, TILs, and S100A7 expression were independent predictors of NAC efficacy. A nomogram incorporating these four factors demonstrated an accuracy of 0.927 in predicting NAC efficacy. S100A7 may serve as a predictor of NAC efficacy in patients with BC. In addition, we found that S100A7 was associated with advanced clinical stages.

Abbreviations

S100A7, S100 calcium-binding protein A7; BC, breast cancer; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; HER-2, human epidermal growth factor receptor-2; ER, estrogen receptor; PR, progesterone receptor;

TILs, tumor infiltrating lymphocytes; MP, Miller–Payne; IHC, immunohistochemical; IOD, integrated optical density; ROC, receiver operating characteristic.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. The informed consent was waived by the Ethics Committee as this was a retrospective study. This study adheres to the Declaration of Helsinki and patient data are confidential.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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