Original Article

The prognostic role of a phospho-Stathmin 1 signature in breast cancer treated with neoadjuvant chemotherapy

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Background: High expression of Stathmin 1 (STMN1) protein is related to a poor prognosis in various tumors, including breast cancer. In our previous study, a phospho-STMN1 signature was conducted to predict outcomes in adjuvantly treated breast cancer patients. This study aimed to explore the relationship of STMN1 expression with our phospho-STMN1 signature and the prognosis of patients treated with neoadjuvant chemotherapy (NACT).

Methods: A retrospective analysis of 116 patients who received NACT in The First Affiliated Hospital of Sun Yat-sen University between December 2008 and March 2016 was conducted. Patients were followed up through telephone once a year until 2022. The levels of STMN1, Ser16, Ser25, Ser38, and Ser63 phosphorylation and GRP78 expression in pre-NACT biopsy specimens from the patients were detected by immunohistochemistry. The recurrence risk score for each patient was calculated using the p-STMN1/GRP78 model. Clinical and pathological parameters, pathological complete response and objective response rates, and survival data were analyzed.

Results: In patients with NACT-treated breast cancer, high levels of STMN1, Ser25 phosphorylation, Ser38 phosphorylation, and GRP78 were related to worse disease-free survival (DFS), as was a high p-STMN1/GRP78 model risk score. In contrast, high Ser16 and Ser63 phosphorylation levels were related to better DFS [p-STMN1/GRP78 model: P=0.002, HR =0.180 (0.061–0.534); STMN1: P=0.001, HR =0.290 (0.147–0.572); Ser16: P=0.036, HR =2.019 (1.049–3.886); Ser25: P=0.013, HR =0.392 (0.188-0.819); Ser38: P=0.001, HR =0.293 (0.153–0.559); Ser63: P=0.006, HR =3.346 (1.407–7.961); GRP78: P=0.010, HR =0.417 (0.214–0.815)]. However, no significant statistical difference was found in the multivariate regression. The relationship between these markers and the therapeutic effect of NACT (pathological complete response and objective response) showed the same tendency with survival. The area under the receiver operating characteristic curve for the p-STMN1/GRP78 model was 0.790 (P=0.001) with sensitivity of 70% and specificity of 74%.

Conclusions: The expression and serine phosphorylation status of STMN1 may be beneficial as biomarkers for predicting the prognosis of breast cancer patients treated with NACT. Our p-STMN1/GRP78 model could become a widely applied signature for assessing the metastatic risk of breast cancer patients, potentially facilitating their individualized management before NACT.

Keywords: Stathmin 1 (STMN1); breast cancer; neoadjuvant chemotherapy; prognosis; therapeutic effect

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Introduction

Breast cancer is the number one threat to women's health, ranking first among female cancers for incidence and second for mortality (1). With the continuous exploration of breast cancer treatment, neoadjuvant chemotherapy (NACT) has become routinely used in clinical practice, achieving satisfactory results (2,3). Compared with adjuvant therapy, NACT offers similar overall survival (OS) and disease-free survival (DFS) while reducing the clinical stage of breast cancer, improving the breast conservation rate, and evaluating the drug sensitivity (4,5). Hormone status, her2 expression, Ki67 and the type of breast cancer usually related with clinical outcomes of patients who received NACT. Patients who have a pathological complete response (pCR) after neoadjuvant therapy are considered to have a better survival benefit than those without a pCR (6,7).

Stathmin 1 (STMN1), also known as oncoprotein 18, is a microtubule-destabilizing phosphorylated protein associated with tumor metastasis (8). High expression of STMN1 protein has been found to be related with a poor prognosis in various solid tumors (9-12). In breast cancer, STMN1 influences cell proliferation, differentiation, and motility (13), and is associated with vascular, immune, and microtubule-targeted drug responses (8,14,15). STMN1 has four serine phosphorylation sites: Ser16, Ser25, Ser38, and Ser63. As demonstrated in our previous studies, STMN1 increases breast cancer cell migration by binding with glucose-regulated protein of molecular mass 78 (GRP78) upon phosphorylation of STMN1 at Ser38/Ser25. Phosphorylation of STMN1 at Ser25 and Ser38 is required to maintain cell migration and is associated with shorter DFS, whereas STMN1 phosphorylation at Ser16 and Ser 63 has the opposite function (14,16). A p-STMN1/GRP78 signature with higher prognostic accuracy than the TNM staging system has been established to select patients with breast cancer who have a high or low risk of metastasis (17,18). Research has confirmed that STMN1 is associated with prognosis in patients who receive adjuvant therapy for breast cancer, but research in patients treated with NACT is lacking.

In this study, the protein levels of STMN1 and its phosphorylated forms in biopsy specimens from patients with NACT-treated breast cancer were analyzed. We aimed to explore whether STMN1 and its phosphorylation-related proteins are related to therapeutic effect and prognosis in patients with NACT-treated breast cancer, and to determine the predictive ability of the p-STMN1/GRP78 signature in these patients. We present the following article in accordance with the REMARK reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-628/rc).

Highlight box

Key findings

- The expression and serine phosphorylation status of STMN1 may be beneficial as biomarkers for predicting the prognosis of breast cancer patients treated with neoadjuvant chemotherapy.

What is known and what is new?

- In our previous study, a phospho-STMN1 signature was conducted to predict outcomes in adjuvant treated breast cancer patients.
- This signature can also predict outcomes in neoadjuvant treated breast cancer patients.

What is the implication, and what should change now?

- Our model may aid oncologists in identifying those who have a higher risk of relapse or metastasis in order to prescribe appropriate treatment.

Methods

Patients

This retrospective analysis included 116 female patients who received NACT for breast cancer according to their doctor's decision in The First Affiliated Hospital of Sun Yat-sen University between December 2008 and March 2016. Patients were followed up through telephone once a year until 2022. All patients had been diagnosed with invasive breast cancer by tumor biopsy and immunohistochemistry (IHC), and then treated with NACT. Patients with inflammatory or metastatic breast cancer and patients who could not tolerate chemotherapy were excluded. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of First Affiliated Hospital of Sun Yat-sen University (No. [2021]825-1), and informed consent was taken from all the patients.

IHC

IHC was performed on biopsy specimens obtained from The First Affiliated Hospital of Sun Yat-sen University before NACT. IHC to detect STMN1 expression, GRP78 expression, and Ser16, Ser25, Ser38, and Ser63 phosphorylation was performed. After fixation, biopsy

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specimens were rehydrated. Phosphate-buffered saline (PBS) and 3% hydrogen peroxide were used for washing and blocking the activity of endogenous peroxidase, respectively. After boiling in citrate buffer (pH 6.0) at 100 ℃ for 5 min (STMN1 and Ser38), 121 ℃ for 10 min (Ser16 and Ser63), 140 ℃ for 25 min (Ser25 and GRP78), retrieved antigens were blocked 1h at room temperature (RT) using 10% normal goat serum. Polyclonal rabbit anti-human STMN1 antibody (Proteintech) was diluted to 1:400 and incubated with samples in a humid chamber at 4 ℃ overnight. Polyclonal rabbit anti-human STMN1 Ser38 antibody (Cell Signaling Technologies) was diluted to 1:100 and incubated with samples in a humid chamber at 4 ℃ overnight. respectively. Polyclonal rabbit anti-human STMN1 Ser16 antibody (Abcam), polyclonal rabbit anti-human STMN1 Ser25 antibody (Novus), polyclonal rabbit anti-human STMN1 Ser63 antibody (Abcam), and polyclonal rabbit anti-human GRP78 antibody (Novus) were diluted to 1:50 and incubated with samples in a humid chamber at 4 ℃ overnight. All samples were incubated with secondary antibody (GTVision^{TM}III Detection System/Mo&Rb) for 30 min at RT after washing by PBS. Gill Hematoxylin was used to counterstained samples. After clearing by xylene, sample can be mounted.

Pathological and clinical response evaluation

Objective response (OR) to NACT was assessed according to RECIST (Response Evaluation Criteria in Solid Tumors) version 1.0. pCR refers to the absence of invasive carcinoma in the primary breast and negative regional lymph nodes or the presence of only components of ductal carcinoma *in situ*. Pathological and clinical response evaluation was carried out by two pathologists at The First Affiliated Hospital of Sun Yat-sen University.

Statistical analyses

Data analysis was conducted using the SPSS 25.0 statistical software. Statistical analysis was performed by using the *t*-test for comparison of continuous variables and the χ^2 test for comparison of count data between groups. DFS—defined as the time from randomization to disease recurrence or patient death from any cause—was plotted using the Kaplan-Meier method and differences in DFS between markers were analyzed using the log-rank test. The area under the receiver operating characteristic curve (AUC) of the model was calculated to determine its accuracy. All P values were two-sided, with P<0.05 considered to be statistically significant.

Results

The expression and serine phosphorylation status of STMN1 are associated with prognosis in NACT-treated breast cancer

Previously, we examined the correlation between phospho-STMN1 status and DFS in 310 patients with early-stage breast cancer (17,18). In the present study, we performed a retrospective analysis of pre-treatment biopsy specimens from 116 patients who received NACT. Patient characteristics of the study population are presented in *Table 1*. Immunohistochemical staining for STMN1, Ser16, Ser25, Ser38, Ser63, and GRP78 was performed, and the patients were subsequently separated into a high expression group and a low expression group (*Figure 1*).

Kaplan-Meier analysis and the log-rank test showed that patients with high STMN1 expression had a higher incidence of recurrence than those with low STMN1 expression [P=0.001, hazard ratio (HR) =0.290 (0.147–0.572); *Figure 1A*]. A high level of Ser16 and Ser63 phosphorylation [P=0.036, HR =2.019 (1.049–3.886) for Ser16; P=0.006, HR =3.346 (1.407–7.961) for Ser63; *Figure 1B,1E*] was correlated with longer DFS, while a high level of Ser25 and Ser38 phosphorylation [P=0.013, HR =0.392 (0.188–0.819) for Ser25, P=0.001, HR =0.293 (0.153–0.559) for Ser38; *Figure 1C,1D*] was strongly correlated with shorter DFS. High expression of GRP78 [P=0.010, HR =0.417 (0.214–0.815); *Figure 1F*] was significantly correlated with shorter DFS. These results are consistent with those of our previous study in patients with early-stage breast cancer who received adjuvant chemotherapy after surgery.

The relationship between STMN1 phosphorylation and the therapeutic effect of NACT

Patients who achieved a pCR had a tendency of longer DFS than did patients without a pCR (Figure S1). The pCR and OR rates were then examined. Neither rate showed a significant association with STMN1 and its phosphorylation status (Table S1). However, the results showed that patients with high levels of STMN, Ser25 phosphorylation, Ser38 phosphorylation, and GRP78 had obviously better pCR and OR rates than patients in the respective low expression groups, while patients with high

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Table 1 Clinicopathological characteristics of breast cancer patients in the study

Characteristics	Cases	%
Median age (range)	58 (38–70)	
Age		
>55 years	66	56.9
≤55 years	50	43.1
Histology		
Ductal	112	96.6
Lobular	2	1.7
Others	2	1.7
TNM stage		
I	1	0.9
II	60	51.7
III	55	47.4
T stage		
T1	8	6.9
T2	68	58.6
T3	31	26.7
T4	9	7.8
N stage		
N0	29	25.0
N1	51	44.0
N2	25	21.6
N3	11	9.5
ER status		
Positive	67	57.8
Negative	48	41.4
NA	1	0.90
PR status		
Positive	62	53.5
Negative	53	45.7
NA	1	0.90
HER2 status		
Positive	53	45.69
Negative	57	55.17
NA	6	5.17
Neoadjuvant therapy		
With anthracycline but no paclitaxel	28	24.1
With paclitaxel but no anthracycline	16	13.8
With anthracycline and paclitaxel	71	61.2
No paclitaxel nor anthracyclines	1	0.90

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; NA, not available.

levels of Ser16 and Ser63 phosphorylation had worse pCR and OR rates than patients in the respective low expression groups (*Figures 2,3*).

The p-STMN1/ GRP78 model can powerfully predict DFS in NACT-treated breast cancer

In our previous research, we built a prognostic classification system incorporating the phosphorylation states of STMN1 phospho-serine sites and GRP78 expression in patients with early-stage breast cancer. This p-STMN1/GRP78 model could powerfully predict DFS in those patients with more prognostic accuracy than TNM stage. For each patient, the metastatic risk score in terms of DFS was calculated as follows: Risk score = −0.680*Ser16+0.722*Ser38−0.636*Ser63+0.899*GRP78 (17). In this model, low GRP78 expression and STMN1 phosphorylation levels at the serine sites are equal to 0, whereas high levels are equal to 1. Patients whose risk score was ≥0 were assigned to the high-risk group, and those whose risk score was <0 were divided into the low-risk group.

In this study, the risk scores of 64 patients could be calculated using the p-STMN1/GRP78 model. Patients in the low-risk group had longer DFS than patients in the high-risk group [P=0.002, HR =0.180 (0.061–0.534); *Figure 4A*]. The AUC of the p-STMN1/GRP78 model was 0.790 (P=0.001; *Figure 4B*) with sensitivity of 70%, specificity of 74% and cut-off of 0.262, which suggested that the model performed well in predicting DFS in patients with breast cancer treated with NACT.

Additionally, we analyzed the relationship between the risk score calculated using the p-STMN1/GRP78 model and the therapeutic effect of NACT, and no significant result was observed in the pCR or rate (Figure S2, Table S2).

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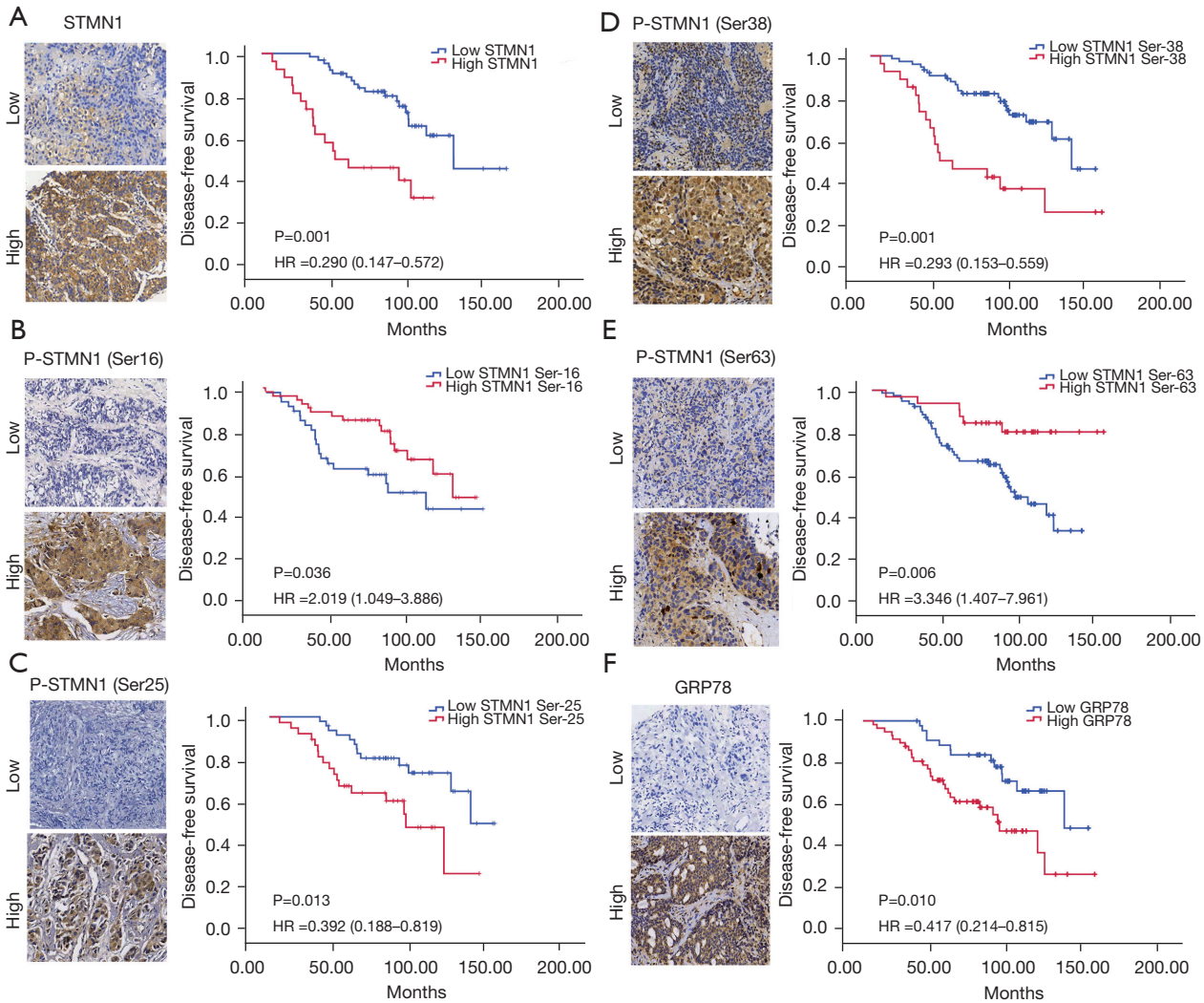

Figure 1 Relationship between STMN1 and its phosphorylation-related proteins and clinical outcomes for breast cancer patients. (A) Relationship between Kaplan-Meier analysis of DFS and STMN1 level by IHC (400×). (B) Relationship between Kaplan-Meier analysis of DFS and STMN1 phosphorylation at Ser16 levelby IHC (400×). (C) Relationship between Kaplan-Meier analysis of DFS and STMN1 phosphorylation at Ser25 levelby IHC (400×). (D) Relationship between Kaplan-Meier analysis of DFS and STMN1 phosphorylation at Ser38 levelby IHC (400×). (E) Relationship between Kaplan-Meier analysis of DFS and STMN1 phosphorylation at Ser63 levelby IHC (400×). (F) Relationship between Kaplan-Meier analysis of DFS and GRP78 level by IHC (400×). DFS, disease-free survival.

Discussion

In various cancers, STMN1 has been reported to be a prognostic marker and is also an independent prognostic factor, along with clinical stage, lymph node status, age, and menopausal status (19,20). In our previous study, we found that the expression of STMN1 and GRP78, and STMN1 phosphorylation sites can be used to predict the prognosis of patients with breast cancer receiving adjuvant therapy, and a prognostic model with a better predictive accuracy than the TNM staging system was proposed (17). In the current study, we further investigated the applicability of these markers and our model in patients with breast cancer treated with NACT. Our results show that this association persisted in these patients. We showed for the first time that among patients with breast cancer receiving NACT, those with high levels of STMN1, Ser25 phosphorylation, Ser38 phosphorylation, and GRP78 showed a worse prognosis than patients with low levels, while patients with high

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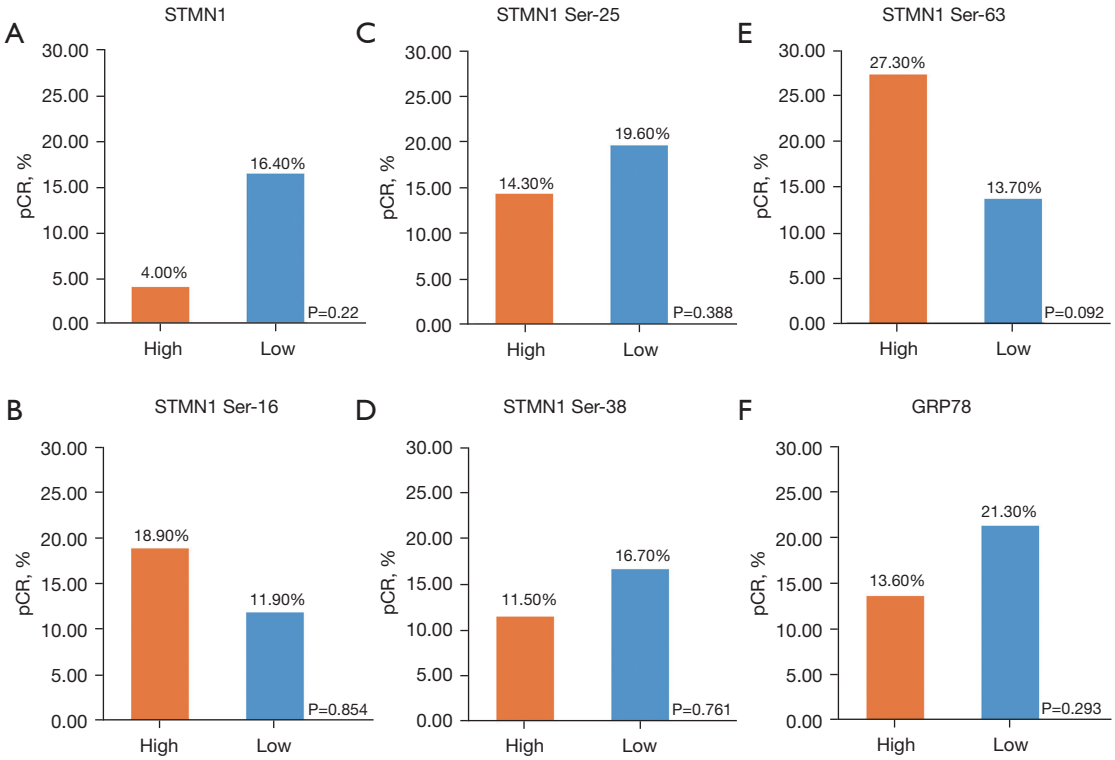

Figure 2 Relationship between STMN1 phosphorylation and pathologic response. (A) Correlation between pathologic response and STMN1 expression. (B) Correlation between pathologic response and STMN1 phosphorylation at Ser-16. (C) Correlation between pathologic response and STMN1 phosphorylation at Ser-25. (D) Correlation between pathologic response and STMN1 phosphorylation at Ser-38. (E) Correlation between pathologic response and STMN1 phosphorylation at Ser-63. (F) Correlation between pathologic response and GRP78. pCR, pathological complete response.

levels of Ser16 and Ser63 phosphorylation showed a better prognosis than patients with low levels. Our p-STMN1/GRP78 model also performed well in predicting prognosis and therapeutic effect of NACT in patients.

Neoadjuvant pCR status and prognosis are closely related, with patients who achieve pCR generally having a better prognosis (21,22). In this study, we analyzed whether the expression of each protein and the p-STMN1/GRP78 model risk score were related to pCR and OR to NACT in patients with breast cancer. Although the results were not statistically significant, patients with high levels of STMN1, Ser25 phosphorylation, Ser38 phosphorylation, and GRP78 exhibited higher pCR and OR rates, while patients with high expression of Ser16 and Ser63 phosphorylation had lower pCR and OR rates. The p-STMN1/GRP78 model did not show the same trend, which is likely because a risk score could only be calculated for 64 patients with effective immunohistochemical expression results of the markers in the model. Since the selected patients received treatment approximately ten years ago, some clinical information was incomplete. This, together with patient loss to follow-up and the ineffective IHC results, may have introduced bias into this study. There were only 52 patients for whom OR rate analysis could be accurately performed, which may have also led to poor OR rate univariate analysis. An important shortcoming of this study was the NACT regimens used to treat the patients were ununiform and inconsistent, which is a direct factor affecting the therapeutic effect of NACT. We look forward to carrying out more rigorous prospective research with a larger sample size to validate and obtain more useful findings.

Conclusions

In conclusion, in our previous study, we proposed that the expression of STMN1, STMN1 phosphorylation sites, and

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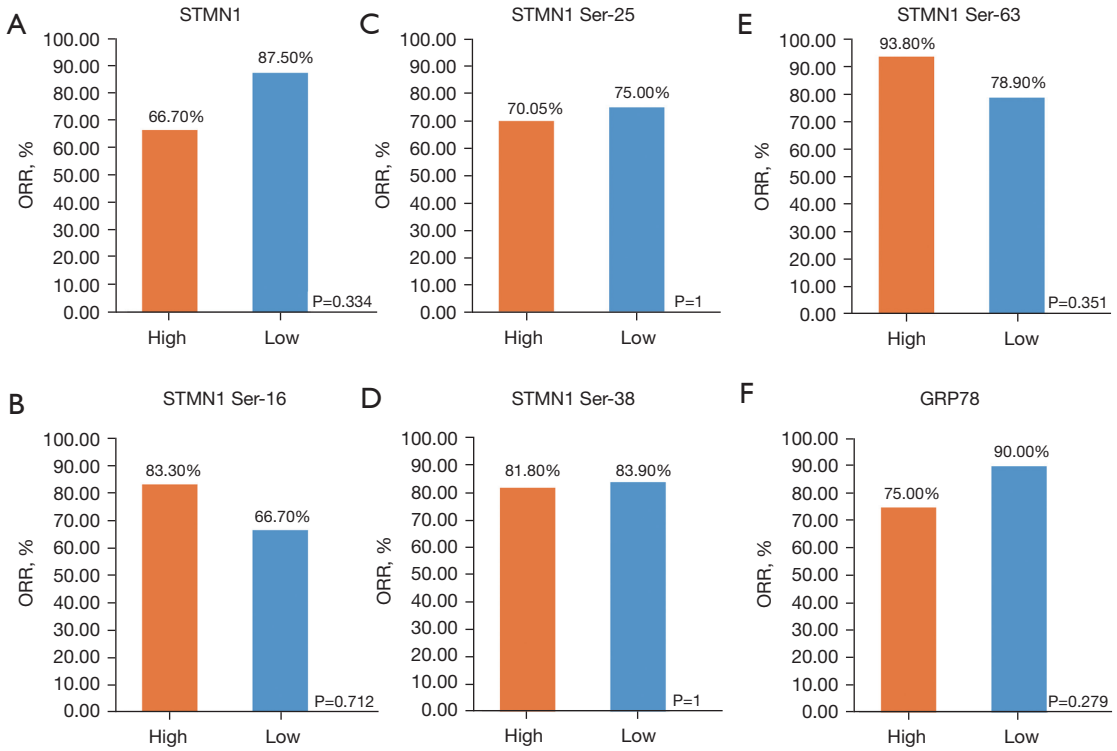

Figure 3 Relationship between STMN1 phosphorylation and objective response rate. (A) Correlation between pathologic response and STMN1 expression. (B) Correlation between objective response rate and STMN1 phosphorylation at Ser-16. (C) Correlation between objective response rate and STMN1 phosphorylation at Ser-25. (D) Correlation between objective response rate and STMN1 phosphorylation at Ser-38. (E) Correlation between objective response rate and STMN1 phosphorylation at Ser-63. (F) Correlation between objective response rate and GRP78. ORR, objective response rate.

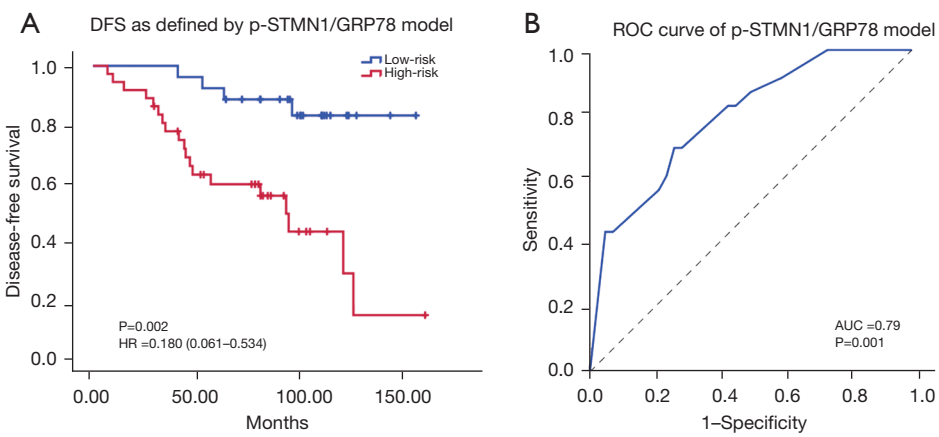

Figure 4 p-STMN1/GRP78 model powerfully predicts DFS for patients treated with NACT. (A) Kaplan-Meier analysis of DFS in breast cancer patients from high and low-risk groups classified by the p-STMN1/GRP78 model. (B) ROC curves to test the prognostic accuracy of the p-STMN1/GRP78 model. DFS, disease-free survival; ROC, receiver operating characteristic; AUC, area under the receiver operating characteristic curve.

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GRP78 can be used to predict the prognosis of patients with breast cancer receiving adjuvant chemotherapy. In this study, we further showed that this association also exists in patients with breast cancer treated with NACT. Our p-STMN1/GRP78 model has excellent prognostic value for patients with early-stage breast cancer regardless of whether they receive adjuvant or neoadjuvant chemotherapy. Our model will aid oncologists in identifying those who have a higher risk of relapse or metastasis in order to prescribe appropriate treatment.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-628/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-628/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-628/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of First Affiliated Hospital of Sun Yat-sen University (No. [2021]825-1), and informed consent was taken from all the patients.

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References

1. Loibl S, Poortmans P, Morrow M, et al. Breast cancer. Lancet 2021;397:1750-69.
2. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. J Clin Oncol 2021;39:1485-505.
3. Tamirisa N, Hunt KK. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. Ann Surg Oncol 2022;29:1489-92.
4. Wolf DM, Yau C, Wulfkuhle J, et al. Redefining breast cancer subtypes to guide treatment prioritization and maximize response: Predictive biomarkers across 10 cancer therapies. Cancer Cell 2022;40:609-23.e6.
5. Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. J Clin Oncol 2022;40:1816-37.
6. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.
7. Haque W, Verma V, Hatch S, et al. Response rates and pathologic complete response by breast cancer molecular subtype following neoadjuvant chemotherapy. Breast Cancer Res Treat 2018;170:559-67.
8. Belletti B, Baldassarre G. Stathmin: a protein with many tasks. New biomarker and potential target in cancer. Expert Opin Ther Targets 2011;15:1249-66.
9. Zhang J, Fu J, Pan Y, et al. Silencing of miR-1247 by DNA methylation promoted non-small-cell lung cancer cell invasion and migration by effects of STMN1. Onco Targets Ther 2016;9:7297-307.
10. Liu YP, Pan LL, Kong CC. Stathmin 1 promotes the progression of liver cancer through interacting with YAP1. Eur Rev Med Pharmacol Sci 2020;24:7335-44.
11. Leiphrakpam PD, Lazenby AJ, Smith LM, et al. Stathmin expression in metastatic colorectal cancer. J Surg Oncol 2021;123:1764-72.

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12. Zarin B, Eshraghi A, Zarifi F, et al. A review on the role of tau and stathmin in gastric cancer metastasis. Eur J Pharmacol 2021;908:174312.
13. Sherbet GV, Cajone F. Stathmin in Cell Proliferation and Cancer Progression. Cancer Genomics Proteomics 2005;2:227-37.
14. Askeland C, Wik E, Finne K, et al. Stathmin expression associates with vascular and immune responses in aggressive breast cancer subgroups. Sci Rep 2020;10:2914.
15. Balasubramani M, Nakao C, Uechi GT, et al. Characterization and detection of cellular and proteomic alterations in stable stathmin-overexpressing, taxol-resistant BT549 breast cancer cells using offgel IEF/PAGE difference gel electrophoresis. Mutat Res 2011;722:154-64.
16. Yoshie M, Ishida A, Ohashi H, et al. Stathmin dynamics modulate the activity of eribulin in breast cancer cells. Pharmacol Res Perspect 2021;9:e00786.
17. Kuang XY, Jiang HS, Li K, et al. The phosphorylation-specific association of STMN1 with GRP78 promotes breast cancer metastasis. Cancer Lett 2016;377:87-96.
18. Kuang XY, Chen L, Zhang ZJ, et al. Stathmin and phospho-stathmin protein signature is associated with survival outcomes of breast cancer patients. Oncotarget 2015;6:22227-38.
19. Ogino S, Nosho K, Baba Y, et al. A cohort study of STMN1 expression in colorectal cancer: body mass index and prognosis. Am J Gastroenterol 2009;104:2047-56.
20. Li J, Kong F, Wu K, et al. miR-193b directly targets STMN1 and uPA genes and suppresses tumor growth and metastasis in pancreatic cancer. Mol Med Rep 2014;10:2613-20.
21. I-SPY2 Trial Consortium; Yee D, DeMichele AM, et al. Association of Event-Free and Distant Recurrence-Free Survival With Individual-Level Pathologic Complete Response in Neoadjuvant Treatment of Stages 2 and 3 Breast Cancer: Three-Year Follow-up Analysis for the I-SPY2 Adaptively Randomized Clinical Trial. JAMA Oncol 2020;6:1355-62.
22. Dey N, Aske J, De P. Targeted Neoadjuvant Therapies in HR+/HER2-Breast Cancers: Challenges for Improving pCR. Cancers (Basel) 2021;13:458.

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Supplementary

Table S1 Relationship between STMN1 Phosphorylation and therapeutic effect of NACT

Proteins	Pathologic response			Objective response rate		
	pCR	Non-pCR	P value	ORR	Non-ORR	P value
STMN1			0.220			0.334
High	1	24		6	3	
Low	11	56		28	4	
GRP78			0.293			0.279
High	8	51		21	7	
Low	10	37		20	2	
Ser38			0.761			≈1
High	3	23		9	2	
Low	12	60		26	5	
Ser25			0.534			≈1
High	5	30		7	3	
Low	9	37		15	5	
Ser63			0.092			0.351
High	9	24		15	1	
Low	10	63		30	8	
Ser16			0.355			0.712
High	10	43		10	2	
Low	5	37		6	3	

NACT, neoadjuvant chemotherapy; pCR, pathological complete response; ORR, objective response rate.

Table S2 Relationship between p-STMN1/GRP78 model risk and therapeutic effect of NACT

Model	Pathologic response			Objective response rate		
	pCR	Non-pCR	P value	ORR	Non-ORR	P value
p-STMN1/GRP78 model risk			0.350			0.812
High	9	28		16	14	
Low	4	23		11	11	

NACT, neoadjuvant chemotherapy; pCR, pathological complete response; ORR, objective response rate.

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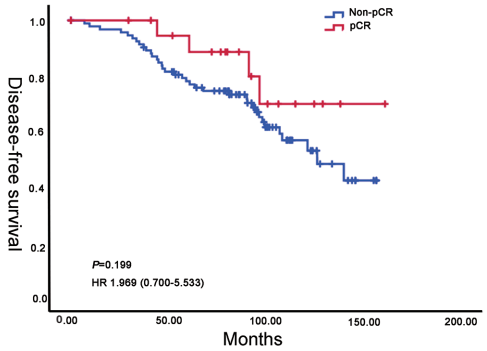

Figure S1 Kaplan-Meier analysis of DFS in breast cancer patients from pCR than non-pCR group. DFS, disease-free survival; HR, hazard ratio; pCR, pathological complete response.

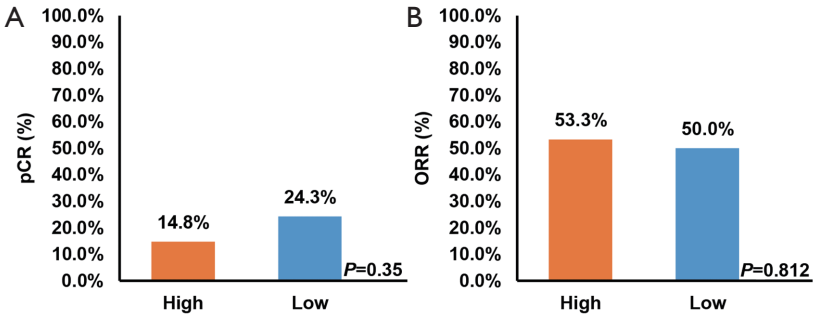

Figure S2 Relationship between p-STMN1GRP78 model risk and therapeutic effect of NACT (A) Correlation between p-STMN1GRP78 model risk and pathologic response. (B) Correlation between p-STMN1GRP78 model risk and objective response rate. NACT, neoadjuvant chemotherapy; pCR, pathological complete response; ORR, objective response rate.

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