BMC Cancer

RESEARCH

Open Access

Prognostic role of STMN1 expression and neoadjuvant therapy efficacy in breast cancer

Li Qian[1,2†], Zhu Cairong[1,2†], Liao Yongdong[1,2†], Li Quan[1,2], Zhong Haihu[1,2], Zhu Xiaofeng[1,2], Ye Xuan[1,2], Chen Yongcheng[5], Chen Kai[3,4], Lu Guanming[5] and Li Jie[1,2*]

Abstract

Purpose breast cancer is common and highly malignant, currently, STMN1 was found to be associated with several human malignancies. The purpose of this study is to investigate STMN1 expression in breast cancer and explore its role in disease progression and its interaction with neoadjuvant therapy efficacy.

Methods we analyzed the tissue STMN1 mRNA expression in BC tissue samples from 105 patients received with neoadjuvant therapy using qPCR between 2019 and 2022.

Results Statistical analysis showed that a high expression of STMN1 before neoadjuvant chemotherapy (NACT) was a trend positively related to non-pCR in the ITT (Intention to Treat) population, while in patients with paclitaxel or docetaxel regimens, before-NACT STMN1 expression was obviously higher in non-pCR (failure to achieve pathologically complete response) patients. Additionally, compared to pCR, high expression of STMN1 after NACT was obviously related to non-pCR. Interestingly, Kaplan-Meier analysis demonstrated that patients with mid-high STMN1 expression before and post-NACT had a poorer PFS to compared to those with low expression.

Conclusions STMN1 is the potential biomarker of NACT and prognosis for breast cancer.

Keywords STMN1, mRNA, Neoadjuvant therapy efficacy, Prognosis, Breast cancer

†Li Qian, Zhu Cairong and Liao Yongdong contributed equally to this work.

*Correspondence:
Li Jie
lijie2958@gwcmc.org
[1]Thyroid and Breast Department, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9# Jinsui Road, Guangzhou 510655, China
[2]Institute of Reproductive Health and Perinatology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China
[3]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Medical Research Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
[4]Breast Tumor Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China
[5]Department of Breast and Thyroid Surgery, Key Laboratory of Molecular Pathology in Tumors of Guangxi, Affiliated Hospital of Youjiang Medical University for Nationalities, Guangxi, China

Introduction

Breast cancer poses the foremost threat to women's health, exhibiting the highest incidence among female cancers and the second-highest mortality rate [1]. As the exploration of breast cancer treatment modalities progresses, neoadjuvant chemotherapy (NACT) has emerged as a standard clinical intervention, yielding satisfactory results. In comparison to adjuvant chemotherapy, NACT provides comparable overall survival (OS) and disease-free survival (DFS) rates, while also facilitating a reduction in the clinical stage of breast cancer, increasing breast conservation rates, and assessing drug sensitivity [2]. Hormone status, Her2 expression, Ki67 levels, and breast cancer subtype are commonly associated with the clinical outcomes of NACT patients [3–5], Patients achieving pathological complete response (pCR) following neoadjuvant treatment are believed to experience enhanced survival benefits compared to those without pCR [6–8]. During the course of NACT, some patients may encounter disease progression, causing them from undergoing surgical intervention. Consequently, with the recent advancements in precision medicine, research into predictive and prognostic factors in breast cancer treatment has become an emerging area of focus [9–13].

STMN1 (Statmin 1), also known as oncoprotein 18, is a microtubule-unstable phosphorylated protein implicated in tumor metastasis [14]. The specific role of STMN1 in the process of breast cancer recurrence after chemotherapy primarily pertains to its influence on microtubule dynamics, cell cycle progression, and resistance to chemotherapeutic drugs [15]. In addition, STMN1 affects cell proliferation, differentiation, and motility, and is related to blood vessel, immune, and microtubule-targeted drug responses [14, 16, 17]. The high expression rate of STMN1 in breast cancer is relatively high, and its high expression levels may serve as a predictor of breast cancer. In addition, the high expression of STMN1 is not confined to breast cancer; it is also observed in various other malignant tumors, such as lung cancer, cervical cancer, ovarian cancer, and pheochromocytoma [18–21]. This suggests that STMN1 may play an important role in the development of multiple cancer types. In breast cancer, STMN1 has four serine phosphorylation sites: Ser16, Ser25, Ser38, and Ser63. The phosphorylation of Ser25 and Ser38 in STMN1 is necessary for cell migration maintenance and is associated with shorter distance-free survival (DFS) [16, 22]. Research has established that phosphorylated STMN1 (p-STMN1) before NACT is related to the prognosis of breast cancer patients receiving NAC [22, 23], but there remains a paucity of research about mRNA STMN1 expression related to therapeutic outcomes in patients before and after receiving NACT.

This study aimed to investigate the prognostic role of STMN1 and its interaction with the efficacy of NACT and prognosis in breast cancer patients.

Methods

mRNA extraction and Quantitative Polymerase Chain Reaction (qPCR) with reverse transcription.

Total RNA was extracted from tumor tissue utilizing TRIzol® Reagent (Life Technologies, USA). RNA was then reverse-transcribed into cDNA using PrimeScript RT Master Mix (RR036A, Takara). Real-time quantitative PCR was performed with TB Green Premix Ex Taq II (RR820A, Takara) following the manufacturer's guidelines. Reactions were conducted in the LightCycler480 system with gene-specific primers. To estimate assay efficiency, standard dilution series were employed. mRNA was quantified relative to the housekeeping gene GAPDH using the $2^{\wedge -\Delta\Delta Ct}$ method.

Patients in roll

The study involved female patients diagnosed with stage II breast cancer who underwent NACT at Guangzhou Women and Children's Medical Center from August 2019 to November 2022. The inclusion criteria included women aged 18 years or older who provided informed consent, non-metastatic breast cancer patients with TNM stage II or higher, no prior chemotherapy, endocrine therapy, surgery, or radiotherapy, normal cardiac function, an ECOG score of ≤ 2, and adequate organ function. Exclusion criteria included patients with other malignancies diagnosed within the past five years or those considered unsuitable for chemotherapy. This retrospective observational clinical study aimed primarily at assessing pathological complete response (pCR) post-NACT, with secondary endpoints of progression-free survival (PFS) and overall survival (OS). Data collection encompassed confirmation of diagnosis, imaging studies, molecular typing, and evaluations of chemotherapy and surgical outcomes, with any discrepancies in case inclusion resolved by the principal investigator.

Treatment protocol

The NACT regimen consisted of adriamycin or epirubicin in conjunction with cyclophosphamide administered every three weeks for four cycles, followed or not by paclitaxel every week or docetaxel every 3 weeks for four cycles, docetaxel combined with cyclophosphamide for four to six cycles, or docetaxel combined with carboplatin for six cycles. HER2-positive breast cancer patients received targeted therapy with trastuzumab, either alone or in combination with pertuzumab. Therapeutic efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST). pCR was defined as the absence of residual invasive carcinoma or ductal carcinoma in

situ (DCIS) in the breast or lymph nodes, as confirmed by microscopic examination [24].

Statistical analysis

A completely randomized, balanced design was used for all experiments. All comparison groups exhibited similar variance. The Mann-Whitney U-test and Chi-square analysis were used to test the significance of differences in various molecular, cellular, and physiological parameters between the means or medians in treatment and control groups. A P value less than 0.05 was considered significant. Error bars in the experiments indicate standard deviation (SD) for a minimum of three independent experiments. A completely randomized, balanced design was employed for all experiments, ensuring similar variances across comparison groups. The significance of differences in various molecular, cellular, and physiological parameters between treatment and control groups was assessed using the Wilcoxon matched-pairs signed rank test or the Mann-Whitney U-test. A P value of less than 0.05 was deemed significant. Error bars in the experiments represent standard deviation (SD) based on a minimum of three independent experiments.

Table 1 Patient characteristics stratified by STMN1 mRNA expression before treatment

	Number of patients (before treatment)			*P* value
	Low STMN1	Medium STMN1	High STMN1	
Age				
Age ≤ 45	17	13	17	0.57
Age>45	18	22	18	
Menopause				
Yes	15	13	13	0.91
No	20	22	20	
Pre-treatment Subtypes				
LuminalA/B	16	25	13	0.04
HER2+	11	4	10	
TNBC	8	6	12	
ER status				
Negative	19	12	25	0.008
Postive	16	23	10	
PR status				
Negative	33	31	31	0.77
Postive	2	4	4	
HER2 status				
Negative	12	14	17	0.51
Positive	23	21	18	
Ki67 Level				
Low(≤30%+)	8	6	3	0.30
High(>30%+)	27	29	32	
Tumor size				
T2	24	23	26	0.80
T3	11	12	9	
Lymphatic stage				
N0	6	8	7	0.95
N1-3	29	27	28	
Grade				
2	9	3	4	0.005
3	4	16	13	
Responder				
p(CR)	11	5	7	0.25
Non-p(CR)	24	30	28	
Progression events				
Yes	1	6	5	0.14
No	34	29	30	
Death events				
Yes	0	4	2	0.16
No	35	31	33	

Abbreviations: ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth receptor 2, Ki67 Level Low:≤30%

Result

Patients in roll

In order to investigate the correlation between STMN1 expression and the efficacy of NACT in breast cancer, we have conducted a prospective study involving patients with newly diagnosed who had not previously received NACT before. A total of 109 patients were recruited from the Thyroid and Breast Department at the Guangzhou Women and Children's Medical Center in China between 2019 and 2022. This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Guangzhou Women and Children's Medical Center. Detailed clinical and pathological information for all patients is presented in Tables 1 and 2. The ages of the enrolled patients ranged from 34 to 66 years, with 62 classified as premenopausal, 41 as postmenopausal, and 2 whose menopausal status could not be determined due to oophorectomy. The median follow-up duration for this study, up to the cut-off date of May 1st, 2024, ranged from 16 to 63 months.

STMN1 before-NACT did not serve as a predictor for the effects of NAC in the ITT population

High STMN1 expression before treatment does not correlate with a poor response to NACT. STMN1 expression levels were quantified using qpCR, revealing a median fold change of mRNA expression/GAPDH before treatment being 0.014. Patients were classified as having a better response pathologic complete response (pCR) or a poor response (non-pCR) to NACT. Results showed a trend of higher STMN1 expression in poor responders compared to good responders ($p = 0.12$) in the ITT population (Fig. 1A). The preoperative tumor grade, expression of ER, PR, HER2, and ki67 were determined by two physicians and we gained all tumor size and lymph

Table 2 Patient characteristics stratified by STMN1 mRNA expression after treatment

	Number of patients (After treatment)			*P* value
	Low STMN1	Medium STMN1	High STMN1	
Age				
Age ≤ 45	13	16	18	0.51
Age>45	22	19	17	
Menopause				
Yes	15	13	13	0.91
No	20	20	22	
After-treatment				
Subtypes				
LuminalA/B	21	20	19	0.63
HER2+	8	5	5	
TNBC	6	10	11	
ER status				
Negative	14	16	17	0.82
Postive	21	19	18	
PR status				
Negative	29	32	31	0.38
Postive	6	2	4	
HER2 status				
Negative	16	22	17	0.32
Positive	19	13	18	
Ki67 Level				
Low(≤30%+)	11	15	12	0.82
High(>30%+)	13	17	19	
Tumor size				
pyTis-0	13	6	7	0.11
pyT1-3	21	29	28	
Lymphatic stage				
pyN0	23	21	17	0.38
pyN1-3	12	14	18	
Grade				
2	8	7	8	0.35
3	11	24	18	
Responder				
p(CR)	13	5	5	0.04
Non-p(CR)	22	30	30	
Progression events				
Yes	0	6	6	0.02
No	35	29	29	
Death events				
Yes	0	3	3	0.24
No	35	32	32	

Abbreviations: ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth receptor 2, Ki67 Level Low:≤30%

nodes messages before treatment through MR or ultrasonography. Consistent with previous reports, STMN1 was higher expression in ER-negative patients. Although pathological grade data were only available for a subset of patients, 33 were evaluated as high grade (3) and 16 people were low grade (1–2). An analysis of the relationship between STMN1 expression and pathological grade revealed a significant association, with higher pathological grades correlating with increased STMN1 expression ($p = 0.023$) (Fig. 1B). In addition, our data also indicated that baseline STMN1 expression did not differ significantly based on tumor stage (T2 VS T3) or nodal status (N0 VS N1-3) (Fig. 1C-D). Furthermore, STMN1 expression was found a trend of higher in high Ki67 samples ($p = 0.09$) (Fig. 1E). Chi-square analysis revealed a greater proportion of STMN1 over-expression

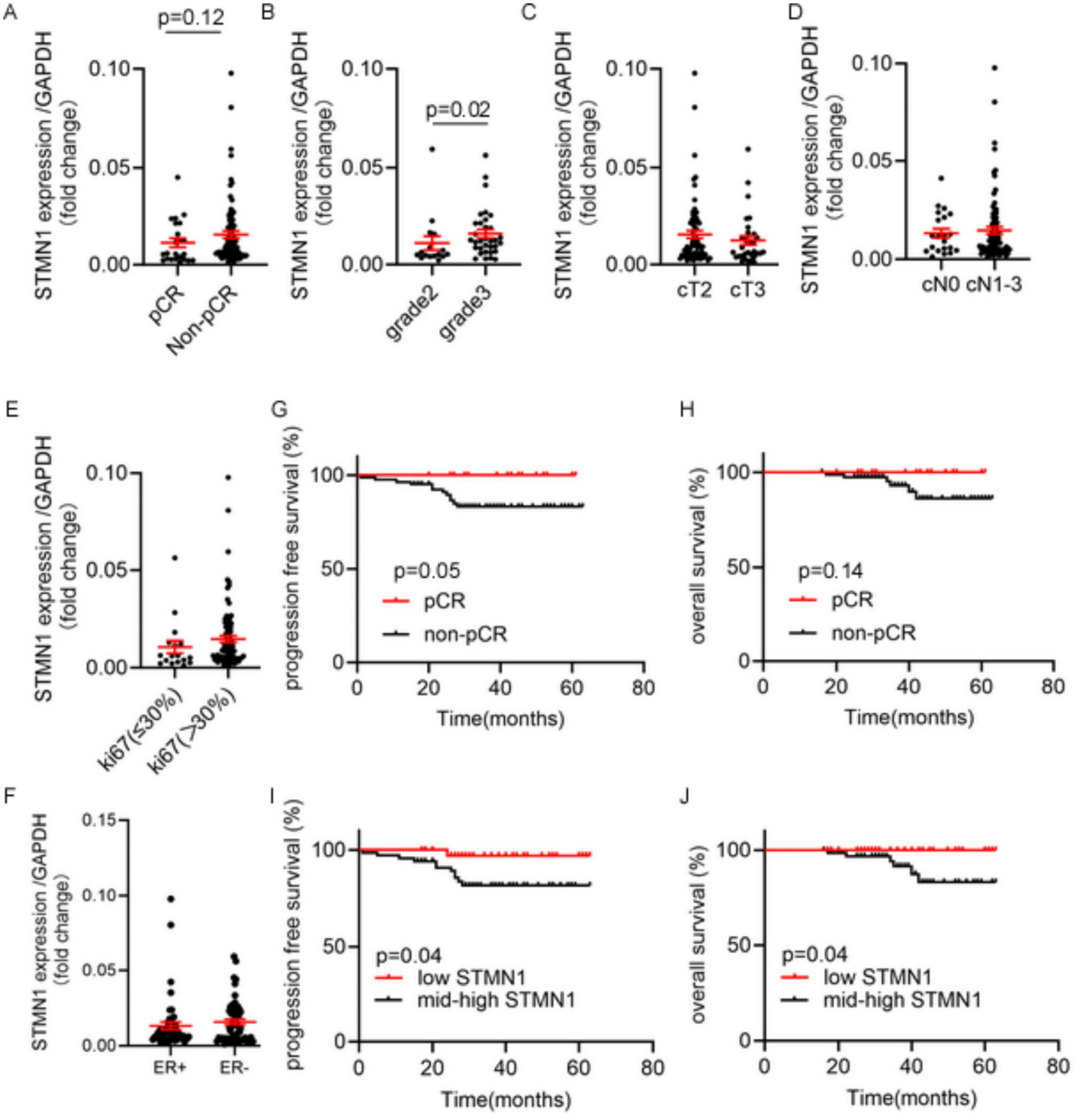

Fig. 1 Baseline STMN1 expression in the pCR and non-pCR groups in ITT population (**A**); High pathological grade and low pathological grade groups(**B**); T2 and T3 groups (**C**); N0 and N1-3 groups (**D**); Ki67 high and low groups (**E**); and ER + and ER- groups (**F**). The Kaplan–Meier curves for PFS (**G**) and OS (**H**) of patients in pCR and non-pCR groups; Kaplan–Meier curves for PFS (**I**) and OS (**J**) of patients in baseline STMN1 high-medium and low groups. Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ by Mann-Whitney U-test

in ER-negative patients. However, the rank sum test indicated that, due to the limited sample size and substantial variability, there was no statistically significant difference in STMN1 expression between ER-negative and ER-positive patients (Fig. 1F). This association warrants further investigation with a larger cohort to yield more robust and conclusive results. Moreover, Kaplan-Meier analysis demonstrated that patients achieving pCR experienced longer PFS ($p = 0.05$) and exhibited a trend towards longer OS ($p = 0.14$) (Fig. 1G-H) compared to those with non-pCR, Interestingly, we divided STMN1 into 3 parts according to high to low, namely low expression, medium expression and high expression, Kaplan-Meier analysis demonstrated that patients with mid-high

STMN1expression post-treatment had an obviously poorer PFS and OS to compared to those with low expression ($p = 0.04$,0.04) (Fig. 1I-J).

STMN1 before-NACT predicted the effect of NAC in patients with Paclitaxel or docetaxel regimens

STMN1 serves as a critical regulator of the cell cycle and mitosis. Existing research indicates that STMN1 may contribute to drug resistance by disrupting microtubule assembly, leading to cell cycle arrest at the G2/M phase. In our study, we focused on a subset of patients who were treated with paclitaxel or docetaxel. Out of 105 patients, 80 received paclitaxel or docetaxel, with 16 of these patients achieving a pCR. Notably, within this subgroup, higher pre-treatment levels of STMN1 expression were associated with poorer outcomes in NACT (Fig. 2A). However, due to the limited sample size, we were unable to establish a definitive correlation between pre-treatment STMN1 expression and PFS or OS (Fig. 2B-C). These findings suggest that STMN1 may serve as a predictor of NACT outcomes in patients undergoing treatment with paclitaxel or docetaxel. Additionally, we examined another subset of patients who received a regimen combining adriamycin or epirubicin in conjunction with cyclophosphamide ($n = 72$ out of 105). Among these patients, 47 subsequently received paclitaxel or docetaxel, with 15 achieving pCR. Furthermore, we analyzed a group of 28 patients who were treated with platinum-based chemotherapy; all of these patients also received paclitaxel or docetaxel, and 7 achieved pCR. However, our analysis indicated that pre-treatment STMN1 expression did not predict the efficacy of NACT and pre-treatment STMN1 levels were not significantly associated with PFS or OS in either of these two cohorts (Fig. 2D-I).

High expression of STMN1 after treatment related to poor response to NAC in the ITT population

To further screen STMN1 expression post-treatment, qpCR was conducted on tumor tissue post-treatment. The median fold change of mRNA expression related to GAPDH post-treatment was 0.005. Firstly, the result suggests that higher expression of STMN1 post-treatment significantly relates to poor response to NACT (Fig. 3A) in the ITT population. Subsequently, we examined the correlation between STMN1 expression and pathological grade after treatment and discovered that a higher pathological grade did not correlate with increased STMN1 expression, likely due to chemotherapy changing the expression of STMN1 (Fig. 3B). And tumor size and lymph node status messages after treatment were evaluated pathologically, different conclusions in some of the clinical data were drawn out, as higher STMN1 expression post-treatment was positively correlated with larger tumor size and more lymph nodes (Fig. 3C-D). However, the relationship between post-treatment STMN1 expression and Ki67 level and pathological grade remains inconclusive (Fig. 3E). Notably, Kaplan-Meier analysis indicated that patients with high STMN1 expression after treatment had a poorer PFS compared to those with low expression ($p = 0.009$) (Fig. 3F). Finally, high post-treatment STMN1 showed a trend towards correlation with OS ($p = 0.09$) (Fig. 3G). The data above indicates that post-NACT STMN1 could be important indicators in predicting the efficacy of NACT and could potentially forecast clinical prognosis.

Separately, in the subgroup of patients treated with paclitaxel or docetaxel, an increase in STMN1 expression after NACT was associated with non-pCR (Fig 4 A). Moreover, this elevation in STMN1 expression was significantly correlated with poorer PFS (Fig. 4B), and there was also a trend toward worse OS (Fig. 4C). A similar result was observed in the subgroup receiving a platinum-based regimen, which can be considered analogous to the paclitaxel or docetaxel subgroup. In these patients, a significant increase in STMN1 expression was noted among those with poor responses to NACT (Fig. 4D), although no clear associations were identified with PFS and OS (Fig. 4E-F). This increase may be attributed to the effects of paclitaxel/docetaxel or the platinum agents. Conversely, no similar findings were observed in the subgroup treated with adriamycin or epirubicin in conjunction with cyclophosphamide. In this subgroup, STMN1 expression did not significantly increase in patients with poor treatment responses (Fig. 4G). Interestingly, a significant correlation was found between high STMN1 expression and poor PFS (Fig. 4H), suggesting a potential role for STMN1 in chemotherapy resistance. Further investigation is warranted to determine whether STMN1 contributes to the resistance observed with platinum and other chemotherapeutic agents.

Neoadjuvant therapy decreased the expression of STMN1

To investigate the potential regulatory effect of NACT on STMN1, a comparative analysis was performed between baseline and post-treatment. Paired t-tests revealed a significant down-regulation of STMN1 by NACT. Respectively, pCR and non-pCR patients were reduced to different degrees, and there was no significant difference between them (Fig. 5A). An effective decrease in STMN1 was defined as a reduction of over 50% as the decrease group, while those with a reduction of less than 50% or an increase were categorized as the non-decrease group. Subsequent analysis revealed that patients with higher Ki67($p = 0.05$)expression were associated with a decrease in STMN1 (Fig. 5B). Conversely, higher tumor grade, earlier stages, and reduced lymphatic metastasis did not correlate with a more pronounced decimation of STMN1

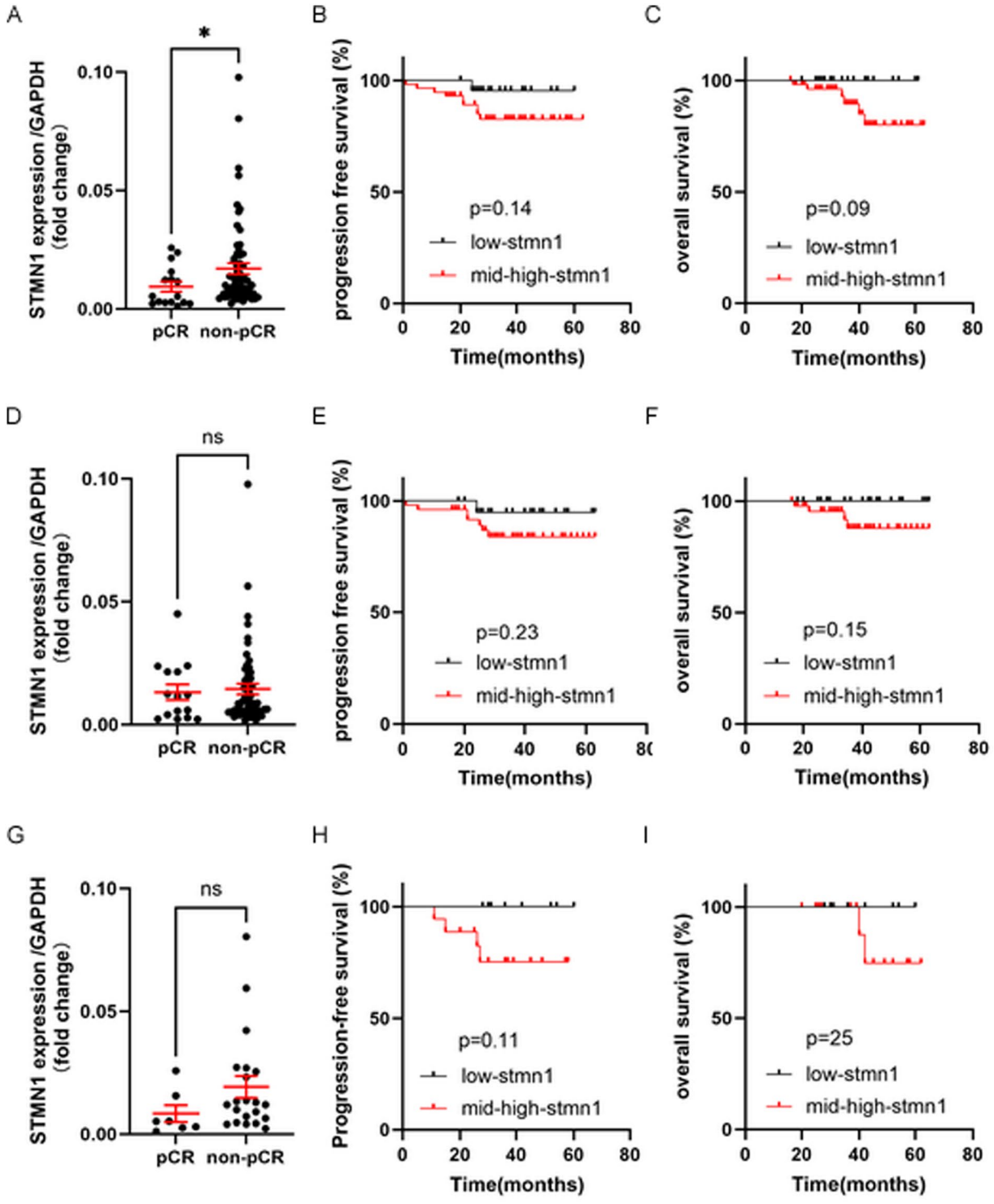

Fig. 2 Baseline STMN1 expression in the pCR and non-pCR groups in patients with paclitaxel or docetaxel regimens (**A**); Kaplan–Meier curves for PFS (**B**) and OS (**C**) of patients in baseline STMN1 high-medium and low groups in patients with paclitaxel or docetaxel regimens. Baseline STMN1 expression in the pCR and non-pCR groups in patients with adriamycin or epirubicin in conjunction with cyclophosphamide regimens (**D**); Kaplan–Meier curves for PFS (**E**) and OS (**F**) of patients in baseline STMN1 high-medium and low groups in patients with adriamycin or epirubicin in conjunction with cyclophosphamide regimens. Baseline STMN1 expression in the pCR and non-pCR groups in patients with carboplatin regimens (**G**); Kaplan–Meier curves for PFS (**H**) and OS (**I**) of patients in baseline STMN1 high-medium and low groups in patients with carboplatin regimens. Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ by Mann-Whitney U-test

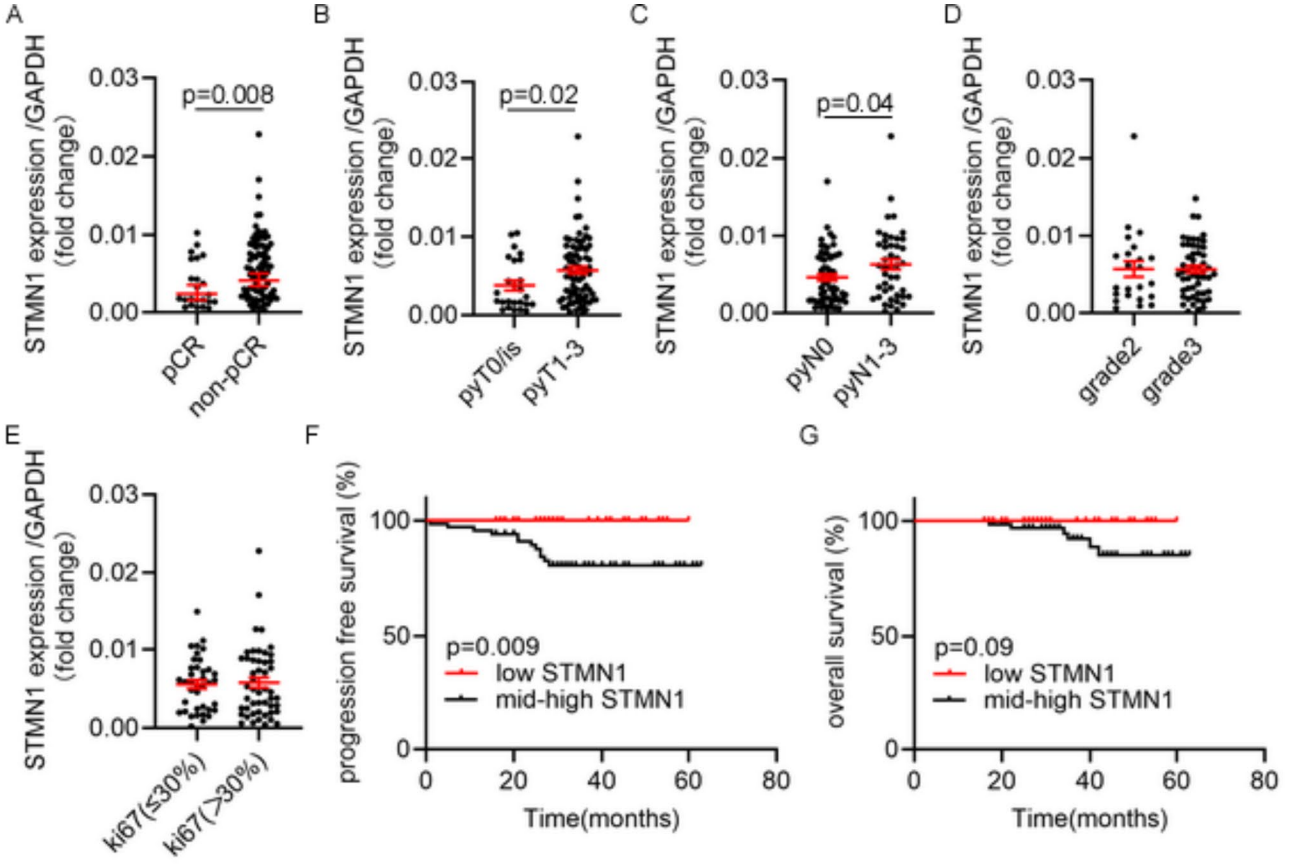

Fig. 3 Post-treatment STMN1 expression in the pCR and non-pCR groups in ITT population (**A**); T0-1 and T2-3 groups (**B**); N0 and N1-3 groups (**C**); high pathological grade and low pathological grade groups(**D**); and Ki67 high and low groups (**E**). The Kaplan–Meier curves for PFS (**F**) and OS (**G**) of patients in post-treatment STMN1 high-medium and low groups. Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ by Mann-Whitney U-test

(Fig. 5C-E). Unfortunately, the data did not show a significant difference in Kaplan-Meier analysis between the decrease group and the non-decrease group, indicating that patients with a significant reduction in STMN1 did not have improved PFS or OS (Fig. 5F-G).

High expression of STMN1 related to poor prognosis in Curtis database

In database analysis, to determine the relationship between STMN1 expression and clinical data including clinical features and prognosis, we utilized medical records from the Curtis database. Our analysis revealed that STMN1 expression was significantly increased in the high-grade (3) subgroup compared to the low-grade (1–2) subgroup. In addition, in patients with high STMN1 expression, it was found to be significantly correlated with tumor size and lymph node metastasis. The subgroups within the Curtis database were further categorized according to CLAUDIN_SUBTYPE, including luminal A, luminal B, HER2+, and TNBC. Notably, increased STMN1 expression was particularly evident in TNBC (basal, normal, or claudin-low), in addition, STMN1 expression was higher in HER2-positive, ER-negative, and PR-negative patients (Fig. 6A-G). STMN1 levels were classified into 3 categories according to high to low expression, namely low expression, medium expression, and high expression. The survival duration of patients with high/medium expression of STMN1 was significantly reduced, underscoring the potential prognostic value of STMN1 expression (Fig. 6H).

Discussion

STMN1 has been recognized as a significant prognostic marker across various cancer types. Previous studies have demonstrated that the expression of STMN1 and its phosphorylation site can serve as a predictor of prognosis in breast cancer patients undergoing NACT [23]. However, investigations on N-phosphorylated modified proteins have revealed that the unique P-N bond structure of N-phosphorylated modification, its chemical stability is poor and easily lost under acidic conditions [25, 26]. Consequently, the use of phosphorylated antibodies in clinical detection is relatively infrequent. Instead, we utilize mRNA detection method, which yields more stable

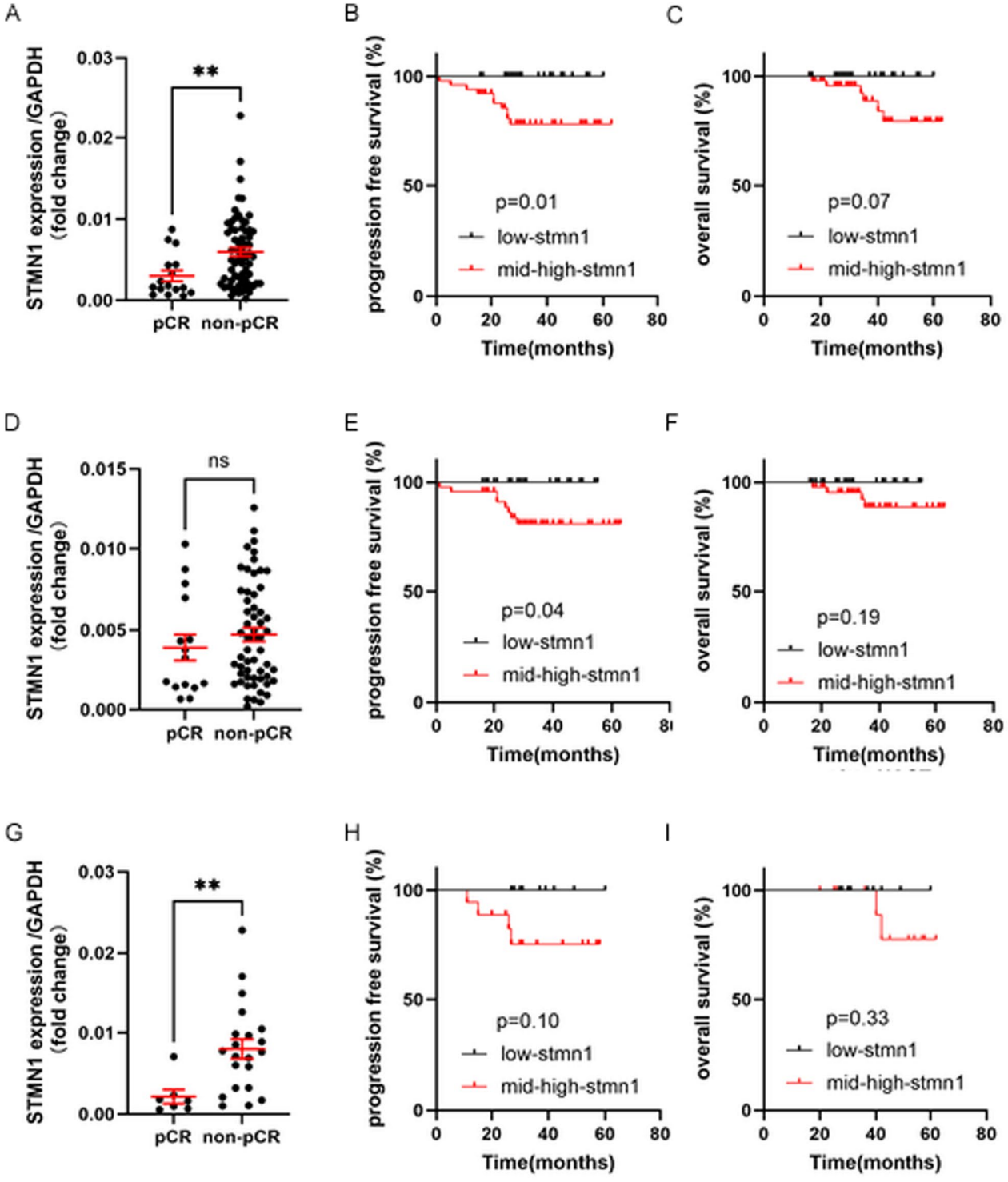

Fig. 4 Post-treatment STMN1 expression in the pCR and non-pCR groups in patients with paclitaxel or docetaxel regimens (**A**); Kaplan–Meier curves for PFS (**B**) and OS (**C**) of patients in post-treatment STMN1 high-medium and low groups in patients with paclitaxel or docetaxel regimens. Post-treatment STMN1 expression in the pCR and non-pCR groups in patients with adriamycin or epirubicin in conjunction with cyclophosphamide regimens (**D**); Kaplan–Meier curves for PFS (**E**) and OS (**F**) of patients in post-treatment STMN1 high-medium and low groups in patients with adriamycin or epirubicin in conjunction with cyclophosphamide regimens. Post-treatment STMN1 expression in the pCR and non-pCR groups in patients with carboplatin regimens (**G**); Kaplan–Meier curves for PFS (**H**) and OS (**I**) of patients in post-treatment STMN1 high-medium and low groups in patients with carboplatin regimens. Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ by Mann-Whitney U-test

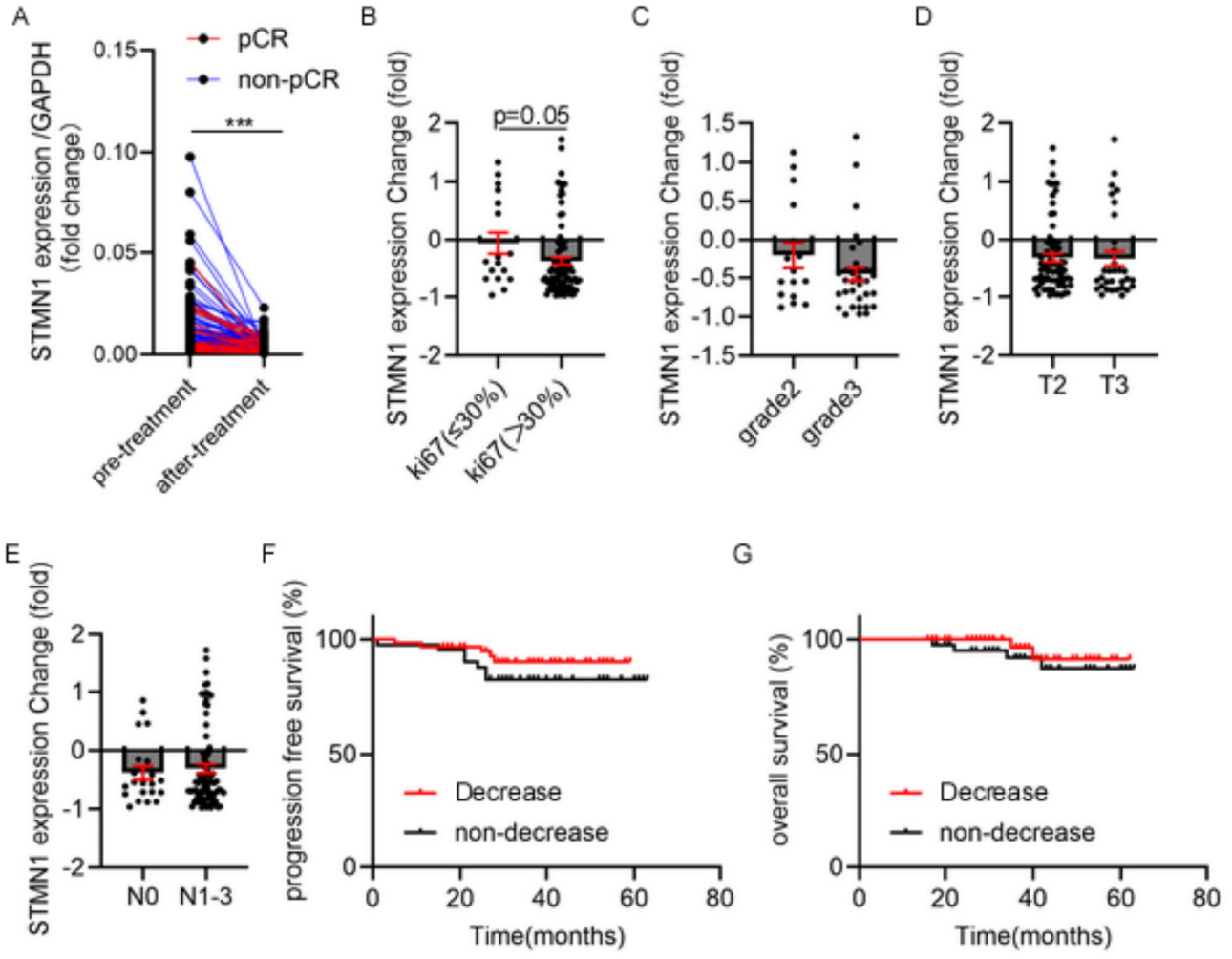

Fig. 5 STMN1 expression changes before and after treatment in ITT patients (**A**); STMN1 expression changes in Ki67 high and low groups (**B**); High pathological grade and low pathological grade groups (**C**); T2 and T3 (**D**); N0 and N1-3 groups (**E**). The Kaplan–Meier curves for PFS (**E**) and OS (**F**) of patients in STMN1 decrease and non-decrease groups. Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ by Mann-Whitney U-test

results and facilitates a convenient and rapid experimental process.

Our study has indicated that the expression of STMN1 prior to chemotherapy does not correlate with the efficacy of NACT in the ITT population. Nevertheless, within chemotherapy regimens that include paclitaxel or docetaxel, elevated levels of STMN1 are significantly associated with non-pCR. This association may be attributed to the role of STMN1 in microtubule regulation. It should be noted that over-expression of STMN1 is also linked to activation of the PI3K signaling pathway. Reports indicate a negative correlation between STMN1 and PTEN; this relationship may be mediated by MAPK signal transduction pathways [27]. Additionally, the interaction between STMN1 and HMGA1, a non-histone protein, may influence STMN1 by phosphorylation, thereby promoting the metastasis of non-small cell lung cancer (NSCLC). Furthermore, STMN1 has been shown to enhance cell migration by activating the p38-MAPK/STAT1 signaling pathway, leading to shorter DFS and OS in patients exhibiting high STMN1 expression within the general population, with statistically significant differences observed [28]. Such mechanisms, which extend beyond microtubule regulation, may elucidate the relationship between STMN1 expression after NACT and the efficacy of the treatment, as well as its implications for clinical prognosis.

In conclusion, our findings demonstrate that chemotherapy agents significantly reduce STMN1 expression. And the mRNA STMN1 expression Assay serves as a highly effective tool to predict the response of NACT, facilitating the identification of patients with breast cancer who may benefit from NACT (with regimens containing paclitaxel or docetaxel). Importantly, patients with elevated post-NACT levels of STMN1 exhibit poorer long-term prognosis with statistical significance.

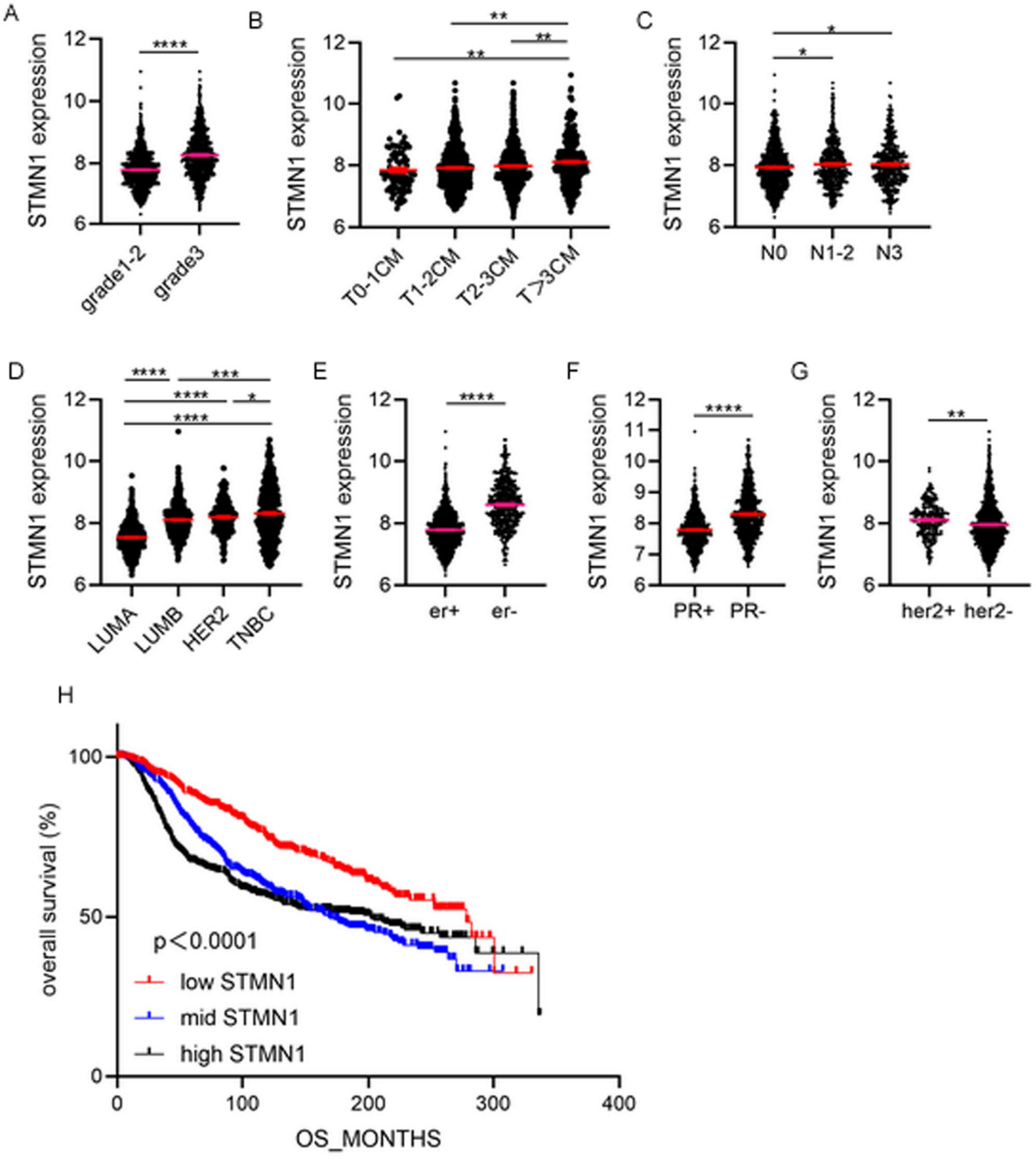

Fig. 6 The Curtis database STMN1 expression in high pathological grade and low pathological grade groups (**A**); in different tumor size groups (**B**); N0, N1-2 and N3 groups (**C**); Subtype of luminal A, luminal B, HER2 + and TNBC groups (**D**); ER- and ER + groups (**E**); PR- and PR + groups (**F**); HER2- and HER2 + groups (**G**). The Kaplan–Meier curves for OS (**H**) of patients in post-treatment STMN1 high, medium and low groups. Data are presented as means ± SEM. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$, ****, $P < 0.0001$ by Mann-Whitney U-test

Subsequent investigations will prioritize the validation of STMN1 as a therapeutic target and exploration of its involvement in tumor heterogeneity, aiming to offer more efficacious treatment alternatives for patients diagnosed with breast cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13798-6.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
LJ and CK conceived of the study and participated in the design of article. LQ、ZCR and LYD conducted the experiment, data analysis and drafted the article. ZCR, LYD, LQ, ZHH, ZXF and YX collected the Tumor samples. LQ LGM, CYC and CK performed the correction of the language and revision. All authors read and approved the final manuscript.

Funding
This work is supported by grants from the National Natural Science Foundation of China (82203122, 82201522, 82271650, 82172917), the Foundation of Guangzhou Women and Children's Medical Center (2023BS036). Guangzhou Science and Technology, Basic and Applied Basic Research Topic (Young Doctor "Sailing" Project) (2024A04J4987).

Data availability
The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Declarations

Ethical approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki and approval was granted by the Ethics Committee of Guangzhou Women and Children's Medical Center. Written informed consent was obtained from individual or guardian participants

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 12 September 2024 / Accepted: 24 February 2025
Published online: 13 March 2025

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49.
2. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, Ruddy K, Tsang J, Cardoso F. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66.
3. Loibl S. Neoadjuvant treatment of breast cancer: maximizing pathologic complete response rates to improve prognosis. Curr Opin Obstet Gynecol. 2015;27(1):85–91.
4. Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, Margolese RG, Hoehn JL, Vogel VG, Dakhil SR, et al. Preoperative chemotherapy: updates of National surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778–85.
5. Conforti F, Pala L, Sala I, Oriecuia C, De Pas T, Specchia C, Graffeo R, Pagan E, Queirolo P, Pennacchioli E, et al. Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer: systematic review and meta-analysis. BMJ. 2021;375:e066381.
6. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164–72.
7. Consortium IST, Yee D, DeMichele AM, Yau C, Isaacs C, Symmans WF, Albain KS, Chen YY, Krings G, Wei S, 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(9):1355–62.
8. Dey N, Aske J, De P. Targeted neoadjuvant therapies in HR+/HER2-Breast cancers: challenges for improving pCR. Cancers (Basel) 2021;13(3).
9. Rizzo A, Cusmai A, Acquafredda S, Giovannelli F, Rinaldi L, Misino A, Palmiotti G. KEYNOTE-522, IMpassion031 and GeparNUEVO: changing the paradigm of neoadjuvant immune checkpoint inhibitors in early triple-negative breast cancer. Future Oncol. 2022;18(18):2301–9.
10. Rizzo A, Santoni M, Mollica V, Logullo F, Rosellini M, Marchetti A, Faloppi L, Battelli N, Massari F. Peripheral neuropathy and headache in cancer patients treated with immunotherapy and immuno-oncology combinations: the MOUSEION-02 study. Expert Opin Drug Metab Toxicol. 2021;17(12):1455–66.
11. Sahin TK, Rizzo A, Aksoy S, Guven DC. Prognostic significance of the Royal marsden hospital (RMH) score in patients with cancer: A systematic review and Meta-Analysis. Cancers (Basel) 2024;16(10).
12. Guven DC, Erul E, Kaygusuz Y, Akagunduz B, Kilickap S, De Luca R, Rizzo A. Immune checkpoint inhibitor-related hearing loss: a systematic review and analysis of individual patient data. Support Care Cancer. 2023;31(12):624.
13. Rizzo A, Schipilliti FM, Di Costanzo F, Acquafredda S, Arpino G, Puglisi F, Del Mastro L, Montemurro F, De Laurentiis M, Giuliano M. Discontinuation rate and serious adverse events of chemoimmunotherapy as neoadjuvant treatment for triple-negative breast cancer: a systematic review and meta-analysis. ESMO Open. 2023;8(6):102198.
14. Belletti B, Baldassarre G. Stathmin: a protein with many tasks. New biomarker and potential target in cancer. Expert Opin Ther Targets. 2011;15(11):1249–66.
15. Sherbet GV, Cajone F. Stathmin in cell proliferation and Cancer progression. Cancer Genomics Proteom. 2005;2(4):227–37.
16. Askeland C, Wik E, Finne K, Birkeland E, Arnes JB, Collett K, Knutsvik G, Kruger K, Davidsen B, Aas T, et al. Stathmin expression associates with vascular and immune responses in aggressive breast cancer subgroups. Sci Rep. 2020;10(1):2914.
17. Balasubramani M, Nakao C, Uechi GT, Cardamone J, Kamath K, Leslie KL, Balachandran R, Wilson L, Day BW, Jordan MA. 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(2):154–64.
18. Zhang J, Fu J, Pan Y, Zhang X, Shen L. 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.
19. 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(13):7335–44.
20. Leiphrakpam PD, Lazenby AJ, Smith LM, Brattain MG, Are C. Stathmin expression in metastatic colorectal cancer. J Surg Oncol. 2021;123(8):1764–72.
21. Zarin B, Eshraghi A, Zarifi F, Javanmard SH, Laher I, Amin B, Vaseghi G. A review on the role of Tau and stathmin in gastric cancer metastasis. Eur J Pharmacol. 2021;908:174312.
22. Yoshie M, Ishida A, Ohashi H, Nakachi N, Azumi M, Tamura K. Stathmin dynamics modulate the activity of eribulin in breast cancer cells. Pharmacol Res Perspect. 2021;9(4):e00786.
23. Xie Z, Zhen T, Lin Y, Shao N, Kuang X. The prognostic role of a phospho-Stathmin 1 signature in breast cancer treated with neoadjuvant chemotherapy. Gland Surg. 2022;11(11):1808–16.
24. Fayanju OM, Ren Y, Thomas SM, Greenup RA, Plichta JK, Rosenberger LH, Tamirisa N, Force J, Boughey JC, Hyslop T, et al. The clinical significance of breast-only and Node-only pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT): A review of 20,000 breast Cancer patients in the National Cancer data base (NCDB). Ann Surg. 2018;268(4):591–601.
25. Kee JM, Muir TW. Chasing phosphohistidine, an elusive sibling in the phosphoamino acid family. ACS Chem Biol. 2012;7(1):44–51.
26. Fuhs SR, Hunter T. pHisphorylation: the emergence of histidine phosphorylation as a reversible regulatory modification. Curr Opin Cell Biol. 2017;45:8–16.

27. Jiang W, Huang S, Song L, Wang Z. STMN1, a prognostic predictor of esophageal squamous cell carcinoma, is a marker of the activation of the PI3K pathway. Oncol Rep. 2018;39(2):834–42.
28. Zeng L, Lyu X, Yuan J, Chen Y, Wen H, Zhang L, Shi J, Liu B, Li W, Yang S. STMN1 promotes tumor metastasis in Non-small cell lung Cancer through Microtubule-dependent and Nonmicrotubule-dependent pathways. Int J Biol Sci. 2024;20(4):1509–27.

Publisher's note