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*Original Article*

# Comparison of the effectiveness of neoadjuvant chemotherapy and adjuvant chemotherapy for improving prognosis in triple-negative breast cancer patients

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**Abstract:** Objective: To compare the effectiveness of surgery combined with neoadjuvant chemotherapy and radiotherapy (SNCR) versus surgery combined with adjuvant chemotherapy and radiotherapy (SACR) in improving the prognosis of triple-negative breast cancer (TNBC) patients. Methods: Clinical data from 112 TNBC patients treated between January 2014 and February 2019 were retrospectively collected. Data included clinical characteristics and 5-year disease-free survival (DFS). Kaplan-Meier (K-M) survival curves were used to analyze the associations of various factors with DFS. Lasso-Cox regression was used to screen significant variables identified by K-M survival analysis. Multivariate Cox regression was used to determine independent prognostic factors affecting DFS. Results: K-M survival analysis showed that treatment regimen (P=0.012), TNM (tumor, node, metastasis) staging (P=0.049), N staging (P=0.015), P53 (P=0.015), KI-67 (P=0.002), neutrophil-to-lymphocyte ratio (NLR) (P<0.001), platelet-to-lymphocyte ratio (PLR) (P<0.001), and cancer antigen 153 (CA153) (P<0.001) were associated with DFS in TNBC patients. Lasso-Cox regression analysis identified treatment regimen, TNM stage, P53, KI-67, NLR, PLR, and CA153 as features related to DFS when λ=0.053741 (1se). Multivariate Cox regression analysis revealed that treatment regimen (P<0.001, 95% CI: 2.309-14.396, HR=5.765), P53 (P=0.010, 95% CI: 1.315-7.864, HR=3.216), and NLR (P=0.001, 95% CI: 2.098-14.553, HR=5.525) were independent prognostic factors affecting DFS. A nomogram model was constructed, and time-dependent receiver operating characteristic (ROC) curve analysis showed that the model's areas under the curve (AUC) for predicting 1-, 3-, and 5-year DFS were 0.928, 0.816, and 0.665, respectively. Conclusion: The SNCR regimen significantly improves DFS in patients with stage IIb to IIIa TNBC compared to the traditional SACR regimen.

**Keywords:** Neoadjuvant chemotherapy, adjuvant chemotherapy, triple-negative breast cancer, prognosis

## Introduction

Breast cancer has become the most common cancer worldwide, with approximately 2.26 million new cases worldwide in 2020, surpassing lung cancer as the most commonly diagnosed cancer [1]. In China [2], there are over 1.6 million new cases each year, with approximately 1.2 million deaths. With advances in tumor biology and bioinformatics, breast cancer treatment strategies have shifted from traditional one-size-fits-all approaches to more individualized methods [3]. By analyzing the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki-67 antigen (KI-67), breast cancer can be classified into four molecular subtypes: Luminal A, Luminal B, triple negative, and HER-2 positive [4]. These subtypes show significant differences in clinical presentation, recurrence and metastasis patterns, and prognosis.

Unlike other types of breast cancer, triple-negative breast cancer (TNBC) typically affects younger women and is characterized by larger tumor size, higher histologic grade, and greater proliferative and invasive potential, resulting in poorer clinical outcomes [5]. The most common sites of invasive TNBC are lymph node metasta-

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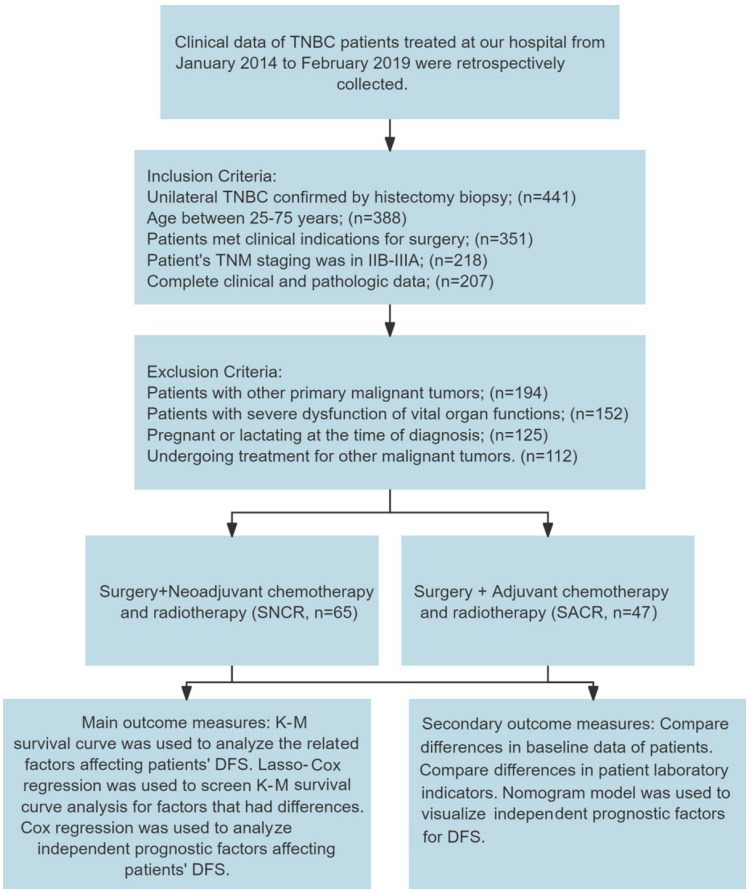


**Figure 1.** Study flow chart.

sis and chest wall recurrence, followed by lung, bone, liver, and brain [6]. The peak period for disease progression is 2 to 3 years after diagnosis. Studies have shown that up to 25% of TNBC patients experience recurrence after surgery, and approximately 46% develop distant metastases within three years of diagnosis [7]. For TNBC patients with brain metastases, median survival is only 6 months, with a 75% mortality rate within 3 months of recurrence [8]. In addition, the 5-year survival rate for TNBC patients is 77%, significantly lower than the 93% for other subtypes [9].

Neoadjuvant chemotherapy (NACT) is a systemic cytotoxic drug treatment strategy administered prior to local therapy, primarily for patients with locally advanced breast cancer [10]. The widespread use of NACT is partly due to the high demand for breast conservation among women [11]. This treatment approach has several clinical advantages, including reducing clinical tumor stage, increasing the likelihood of breast-conserving surgery, assessing the response of cancer cells to chemotherapeutic drugs, improving surgical options, and maintaining acceptable side effects [12]. Most breast cancer patients respond well to NACT, improving treatment outcome and prognosis. However, the impact of NACT on disease-free survival (DFS) and overall survival (OS) in operable TNBC patients remains inconsistent. A study of 319 patients with early-stage TNBC found no significant association between NACT and DFS or OS among the participants [13]. Conversely, another study based on the National Cancer Database showed that among patients with stage II-III (locally advanced) TNBC, those who received NACT had a worse OS compared to those who received adjuvant chemotherapy (ACT) (73.4% vs. 76.8%) [14]. Therefore, it remains unclear whether there is a significant difference between NACT and ACT for the treatment of operable TNBC patients, and the factors influencing pathologic complete response (PCR) after NACT are still undetermined.

This study aims to clarify the impact of NACT versus ACT on DFS in operable TNBC patients. By identifying key prognostic factors and constructing a DFS prediction nomogram, this research aims to improve patient outcome and reduce recurrence rates. Understanding the efficacy of NACT and ACT will help clinicians optimize treatment protocols, leading to better management of this aggressive cancer subtype.

## Methods and materials

### *Sample collection*

Clinical data were retrospectively collected from TNBC patients treated at Yulin Hospital between January 2014 and February 2019. This study was conducted with the approval of the Yulin Hospital Medical Ethics Committee (**Figure 1**).

*Inclusion and exclusion criteria*

Inclusion Criteria: Pathologically confirmed unilateral TNBC through excisional biopsy or core needle biopsy; Age between 25 and 75 years; Patients met clinical surgical indications; Tumor Node Metastasis (TNM) staging between IIB and IIIA; Complete clinical and pathological data.

Exclusion Criteria: Patients with other primary malignant tumors; Patients with severe dysfunction of vital organs such as acute cerebral infarction, acute myocardial infarction, or heart failure; Patients who were pregnant or breastfeeding at the time of diagnosis; Patients receiving treatment for other malignant tumors.

*Treatment regimens*

*Chemotherapy:* TAC regimen: Cyclophosphamide 500 mg/m$^2$ (Product specification: 0.2 g/vial, Manufacturer: Jiangsu Hengrui Medicine Co., Ltd., National Drug Code: H32020857), Epirubicin 75 mg/m$^2$ (Product specification: 10 mg/vial, Manufacturer: Hanhui Pharmaceutical Group Co., Ltd., National Drug Code: H19990280), and Docetaxel 75 mg/m$^2$ (Product specification: 20 mg/vial, Manufacturer: Jiangsu Hengrui Medicine Co., Ltd., National Drug Code: H20020543). These medications are administered intravenously on the first day of each cycle, followed by a 20-day rest period, every 21 days, for a total of six cycles. AC-T regimen: 4 cycles of Cyclophospha-mide 600 mg/m$^2$ and Epirubicin 90-100 mg/m$^2$ were administered intravenously, with dosing on the first day of each cycle, followed by 20 days of rest and one cycle every 21 days; followed by 4 cycles of intravenous chemotherapy with Docetaxel (80-100 mg/m$^2$), still with dosing on the first day of each cycle, followed by 20 days of rest and one cycle every 21 days.

*Radiotherapy regimen:* The radiotherapy plan for breast cancer patients was formulated based on clinical staging, tumor size, and lymph node involvement.

Radiotherapy target area: Affected chest wall, supraclavicular, axilla. Radiation type: 6MV-X ray from Varian IX linear accelerator (Varian, USA). Radiotherapy techniques: Three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), or volumetric modulated arc therapy (VMAT), administered once daily, five times a week. Radiotherapy dosage: For post-mastectomy patients, the total dose was 50 Gy, administered in 25 fractions of 2 Gy each. For breast-conserving surgery patients, the tumor bed received a concurrent boost to 60 Gy in 25 fractions of 2.4 Gy each. Radiotherapy techniques: 3DCRT is quick, requires minimal equipment, and is technically simple, making it suitable for patients with limited financial resources. IMRT allows precise adjustment of the intensity of radiation beam, better protecting surrounding normal tissues. VMAT provides a more uniform dose distribution. The treatment team selected the most appropriate radiotherapy technique based on the patient's specific condition and treatment response to achieve the best therapeutic effect with minimal side effects.

*Sample grouping*

Based on the inclusion and exclusion criteria, a total of 112 eligible samples were obtained. Patients were then divided into two groups according to their treatment regimens: the SNCR (surgery + NACT and radiotherapy) group (n=65) and the SACR (surgery + adjuvant chemotherapy and radiotherapy) group (n=47).

*Clinical data collection*

Clinical data at the first diagnosis included age, body mass index (BMI), TNM staging, T stage, N stage, G stage, tumor diameter, lymph node metastasis, P53 and KI-67 levels, and surgical methods. Laboratory indicators, P53 and KI-67, were detected using immunohistochemistry kits from Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd. Peripheral blood indicators were measured using a Sysmex XT-1800i automated hematology analyzer (Sysmex, Japan). CA125 and CA153 levels were detected using an AUTO LumoA2000Plus chemiluminescence analyzer with corresponding reagent kits. Note: Immunohistochemical indexes were tested before receiving treatment, and the ratio of tumor markers to peripheral blood indexes were tested after patients received treatment.

*Observational indicators*

*Primary observational indicators:* K-M survival curves were used to analyze the association between factors and DFS [15]. Lasso-Cox

regression was used to screen significant variables identified by K-M survival analysis. Cox regression analysis was used to determine independent prognostic factors affecting DFS [16].

*Secondary observational indicators:* The baseline data and laboratory indicators were compared between patients; and a nomogram model was constructed to visualize independent prognostic factors for DFS [17].

*Statistical analysis*

Data were analyzed using SPSS 26.0, and Prism 9 was used for data visualization. The K-S test was used to analyze the distribution of data. Normally distributed data were analyzed using t-tests, with independent sample t-tests used for group comparisons, represented by t values. Non-normally distributed data were analyzed using rank-sum tests, represented by Z values. Clinical data were analyzed using chi-square tests, represented by $\chi^2$ values. Lasso-Cox regression was used to screen characteristic factors of 5-year DFS in TNBC patients. Time-dependent receiver operating characteristic (ROC) curves were used to analyze the value of risk scores generated by a nomogram model in predicting 1-, 3-, and 5-year survival of TNBC patients. Cox regression analysis was used to determine independent prognostic factors affecting DFS. The rms package in R software was used to construct the nomogram. $P<0.05$ was considered significant.

## Results

*Comparison of baseline data*

Comparison of baseline data between the two groups of patients showed no significant differences in age, body mass index (BMI), TNM stage, T stage, N stage, G stage, tumor diameter, lymph node metastasis, P53, KI-67, P53 combined with KI-67, or surgical method ($P>0.05$, **Table 1**).

*Comparison of tumor markers and peripheral blood inflammation indices*

Comparison of tumor markers and peripheral blood inflammation indices between the two groups showed no significant differences in NLR, PLR, CA125 or CA153 (all $P>0.05$, **Figure 2**).

*Factors influencing DFS in TNBC patients*

To analyze the influencing factors, we plotted K-M survival curves for all indicators in relation to the DFS of patients. The results showed that treatment regimen ($P=0.012$), TNM stage ($P=0.049$), N stage ($P=0.015$), P53 ($P=0.015$), KI-67 ($P=0.002$), NLR ($P<0.001$), PLR ($P<0.001$), and CA153 ($P<0.001$) were associated with DFS in TNBC patients (**Figure 3**).

*Lasso-Cox regression screening for DFS prognostic factors*

We used Lasso-Cox regression to screen for factors affecting DFS in TNBC patients. When $\lambda=0.053741$ (1se), we identified 7 characteristics (treatment regimen, TNM stage, P53, KI-67, NLR, PLR, and CA153) to be associated with DFS (**Figure 4**).

*Cox regression analysis of independent prognostic factors for DFS*

Univariate Cox regression analysis identified treatment regimen ($P=0.015$, 95% CI: 1.215-6.353, HR=2.778), P53 ($P=0.019$, 95% CI: 1.170-5.800, HR=2.605), KI-67 ($P=0.004$, 95% CI: 1.578-11.331, HR=4.229), NLR ($P<0.001$, 95% CI: 2.413-14.105, HR=5.834), PLR ($P=0.001$, 95% CI: 0.112-0.567, HR=0.251), and CA153 ($P<0.001$, 95% CI: 3.085-16.351, HR=7.103) as factors associated with DFS (**Table 2**). Multivariate Cox regression analysis revealed that treatment regimen ($P<0.001$, 95% CI: 2.309-14.396, HR=5.765), P53 ($P=0.010$, 95% CI: 1.315-7.864, HR=3.216), and NLR ($P=0.001$, 95% CI: 2.098-14.553, HR=5.525) were independent prognostic factors affecting DFS (**Table 3**).

*Construction of the DFS nomogram*

To determine independent prognostic factors for DFS applicable to clinical practice, we visualized the three prognostic factors and constructed a nomogram model. Time-dependent ROC curve analysis showed that the area under the curve (AUC) of the model for predicting 1-, 3-, and 5-year DFS was 0.928, 0.816, and 0.665, respectively (**Figure 5**).

## Discussion

In recent decades, significant advances in breast cancer treatment have led to a 40%

**Table 1.** Baseline data

| Factor | SNCR (n=65) | SACR (n=47) | $X^2$ Value | *P* Value |
|---|---|---|---|---|
| Age | | | | |
| ≥50 years | 33 | 20 | 0.739 | 0.390 |
| <50 years | 32 | 27 | | |
| BMI | | | | |
| ≥25 kg/m$^2$ | 52 | 33 | 1.428 | 0.232 |
| <25 kg/m$^2$ | 13 | 14 | | |
| TNM Staging | | | | |
| IIB | 31 | 22 | 0.009 | 0.926 |
| IIIA | 34 | 25 | | |
| T Staging | | | | |
| T2 | 24 | 21 | 0.683 | 0.409 |
| T3 | 41 | 26 | | |
| N Staging | | | | |
| N0 | 18 | 8 | 2.847 | 0.241 |
| N1 | 35 | 25 | | |
| N2 | 12 | 14 | | |
| G Staging | | | | |
| G1 | 17 | 11 | 2.213 | 0.330 |
| G2 | 34 | 20 | | |
| G3 | 14 | 16 | | |
| Tumor Diameter | | | | |
| ≥5 cm | 41 | 26 | 0.683 | 0.409 |
| <5 cm | 24 | 21 | | |
| Lymph Node Metastasis | | | | |
| Yes | 18 | 8 | 1.742 | 0.187 |
| No | 47 | 39 | | |
| P53 | | | | |
| Positive | 21 | 13 | 0.597 | 0.278 |
| Negative | 44 | 34 | | |
| KI-67 | | | | |
| High Expression | 32 | 25 | 0.171 | 0.679 |
| Low Expression | 33 | 22 | | |
| P53 Combined with KI-67 | | | | |
| Positive + High Expression | 11 | 10 | 0.339 | 0.560 |
| Others | 54 | 37 | | |
| Surgical Methods | | | | |
| Unilateral Modified Radical Mastectomy | 51 | 39 | 0.353 | 0.553 |
| Others | 14 | 8 | | |

Note: BMI: Body Mass Index, TNM: Tumor Node Metastasis Staging, P53: Tumor Protein P53, KI-67: Ki-67 Antigen.

reduction in mortality, preventing an estimated 300,000 deaths [18]. Although breast cancer remains the leading cause of cancer-related death in women worldwide, the high rate of early detection has improved the rate of cure [19]. Currently, surgery, chemotherapy and radiotherapy are the mainstay treatments for TNBC.

However, there is an ongoing debate within the medical community regarding the choice of treatment methods. For example, some studies have reported that radiotherapy significantly reduces the local recurrence rate (from 17% to 3%) and distant metastasis rate (from 42% to 12%) in breast cancer patients [20]. Another study showed that among 416 breast cancer

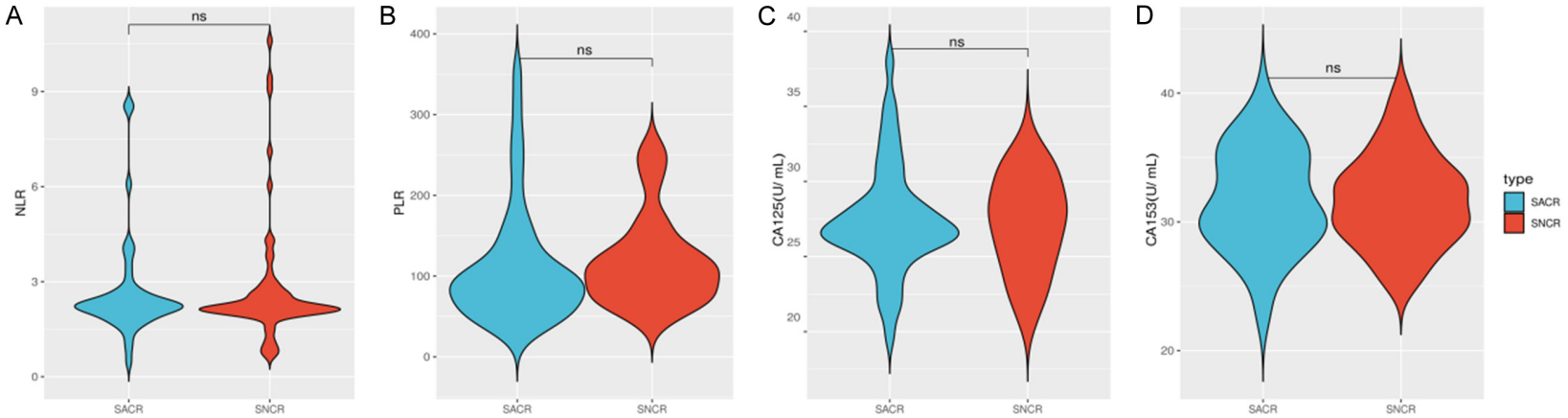


**Figure 2.** Levels of tumor markers and peripheral blood inflammatory indices in patients according to the two treatment regimens. A. NLR levels; B. PLR levels; C. CA125 levels; D. CA153 levels. Note: NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, CA125: Cancer Antigen 125, CA153: Cancer Antigen 153; nsP>0.05.

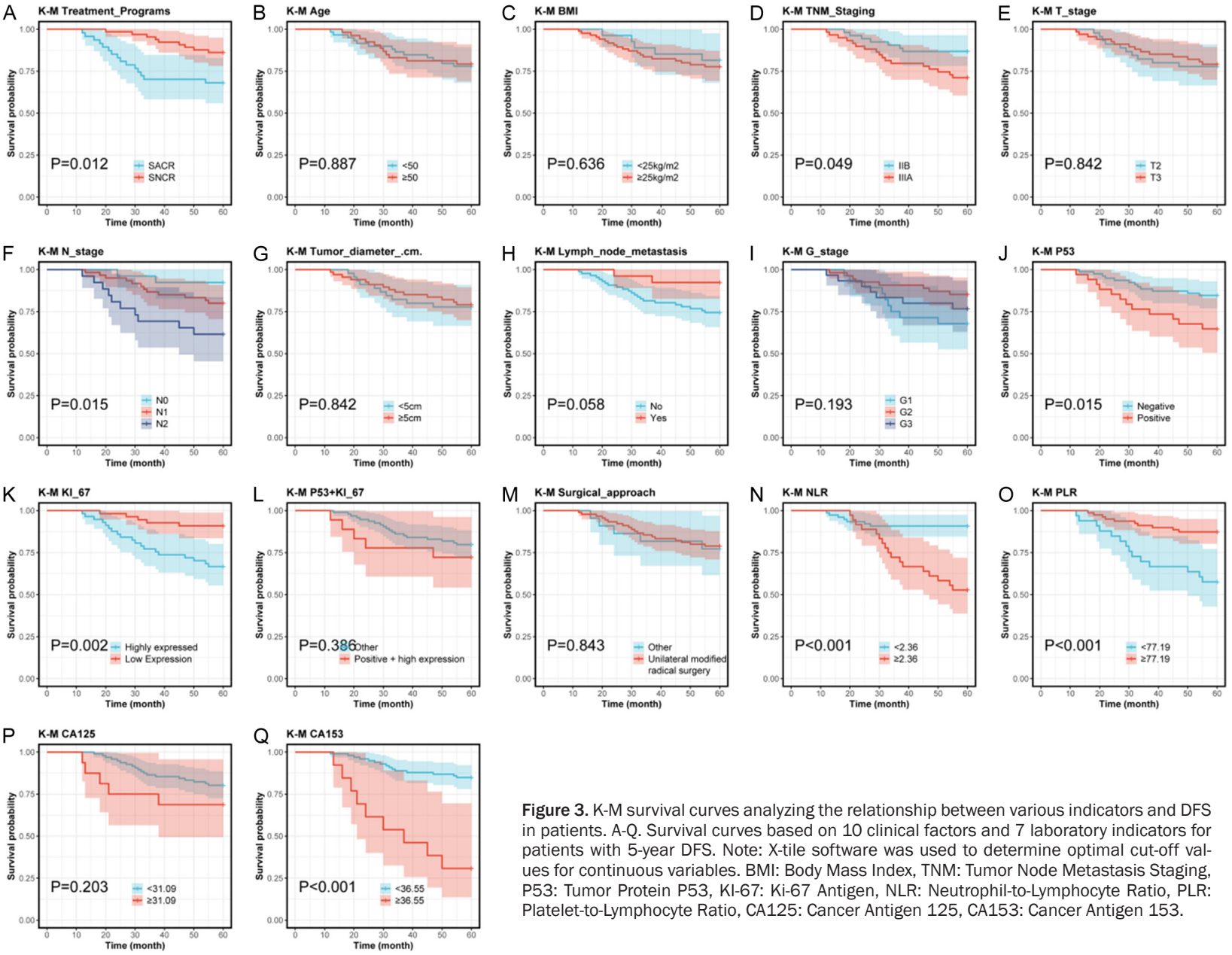


**Figure 3.** K-M survival curves analyzing the relationship between various indicators and DFS in patients. A-Q. Survival curves based on 10 clinical factors and 7 laboratory indicators for patients with 5-year DFS. Note: X-tile software was used to determine optimal cut-off values for continuous variables. BMI: Body Mass Index, TNM: Tumor Node Metastasis Staging, P53: Tumor Protein P53, KI-67: Ki-67 Antigen, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, CA125: Cancer Antigen 125, CA153: Cancer Antigen 153.

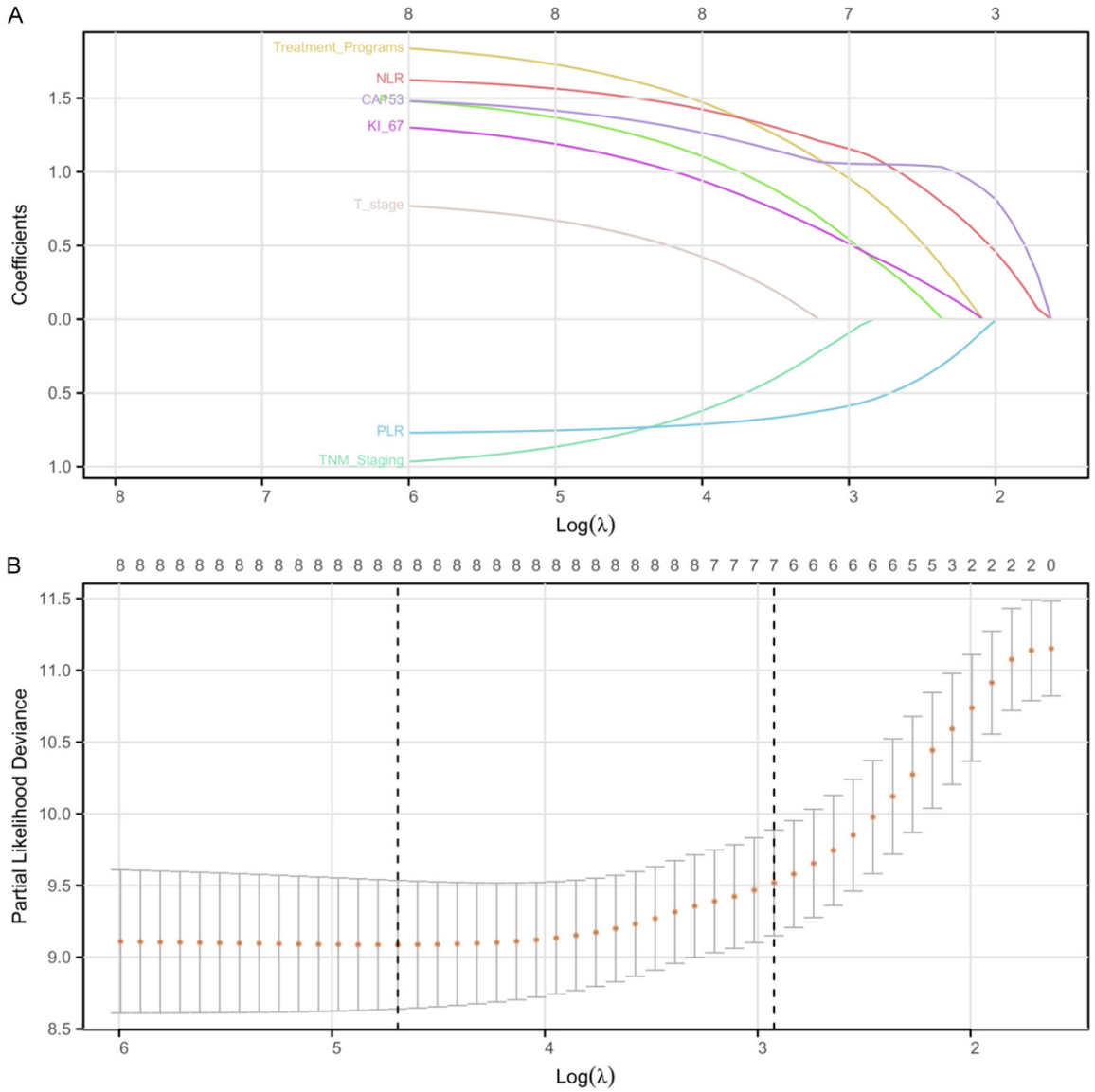


**Figure 4.** Lasso-Cox regression screening for 7 DFS-related features. A, B. Coefficient distribution of Lasso regression analysis and calculation of adjusted values (lambda) based on 10-fold cross-validation. Note: TNM: Tumor Node Metastasis Staging, P53: Tumor Protein P53, KI-67: Ki-67 Antigen, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, CA153: Cancer Antigen 153.

**Table 2.** Univariate Cox regression analysis

| Factor | β Value | SE | *P* Value | HR | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|
| Treatment Regimen | 1.022 | 0.422 | 0.015 | 2.778 | 1.215 | 6.353 |
| TNM Staging | -0.859 | 0.449 | 0.056 | 0.424 | 0.176 | 1.022 |
| T Stage | 0.083 | 0.414 | 0.842 | 1.086 | 0.482 | 2.446 |
| P53 | 0.957 | 0.409 | 0.019 | 2.605 | 1.170 | 5.800 |
| KI-67 | 1.442 | 0.503 | 0.004 | 4.229 | 1.578 | 11.331 |
| NLR | 1.764 | 0.45 | <0.001 | 5.834 | 2.413 | 14.105 |
| PLR | -1.381 | 0.415 | 0.001 | 0.251 | 0.112 | 0.567 |
| CA153 | 1.96 | 0.425 | <0.001 | 7.103 | 3.085 | 16.351 |

Note: TNM: Tumor Node Metastasis Staging, P53: Tumor Protein P53, KI-67: Ki-67 Antigen, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, CA153: Cancer Antigen 153.

**Table 3.** Multivariate Cox regression analysis

| Factor | β Value | SE | *P* Value | HR | 95% CI Lower | 95% CI Upper |
|---|---|---|---|---|---|---|
| Treatment Regimen | 1.752 | 0.467 | <0.001 | 5.765 | 2.309 | 14.396 |
| P53 | 1.168 | 0.456 | 0.01 | 3.216 | 1.315 | 7.864 |
| KI-67 | 1.057 | 0.544 | 0.052 | 2.877 | 0.990 | 8.357 |
| NLR | 1.709 | 0.494 | 0.001 | 5.525 | 2.098 | 14.553 |
| PLR | -0.828 | 0.512 | 0.106 | 0.437 | 0.160 | 1.193 |
| CA153 | 1.036 | 0.539 | 0.055 | 2.817 | 0.979 | 8.100 |

Note: P53: Tumor Protein P53, KI-67: Ki-67 Antigen, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, CA153: Cancer Antigen 153.

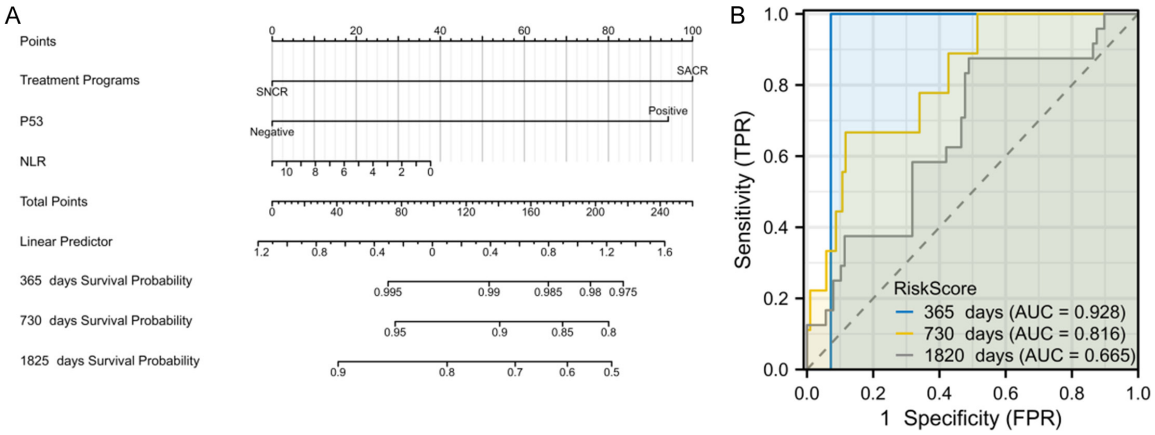


**Figure 5.** Construction of DFS-related nomogram prediction model. A. DFS-related nomogram prediction model. B. Time-dependent ROC curve analysis of the nomogram model for predicting 1-, 3-, and 5-year DFS. Note: P53: Tumor Protein P53, NLR: Neutrophil-to-Lymphocyte Ratio, DFS: Disease-free survival.

patients treated with SNCR, the 5-year local recurrence rate was only 6.4% [21]. In addition, a 15-year follow-up study showed that the local recurrence rate of NACT was higher than that of ACT (21.4% vs. 15.9%) [22]. In this study, univariate analysis identified treatment regimen, TNM stage, N stage, P53, KI-67, NLR, PLR, and CA153 as factors associated with DFS in TNBC patients. These results suggest that a comprehensive consideration of pathologic and biological markers is crucial for the treatment and prognostic assessment of TNBC. These markers not only help clinicians formulate more individualized treatment plans, but also serve as key indicators for predicting treatment outcome and disease progression.

To further identify the independent prognostic factors affecting DFS in TNBC patients, we used a two-step statistical analysis. First, we used the Lasso-Cox regression model to screen several predictive indicators that showed significance in the Kaplan-Meier survival analysis. Lasso-Cox regression introduces a penalty term to compress the coefficients of non-essential variables to zero, thereby achieving automatic variable selection and model simplification, effectively avoiding overfitting and improving the explanatory power and stability of the model [23]. After identifying the key predictive factors, we applied the traditional Cox regression model to analyze the independent effects of these factors on DFS. This method allowed us to quantify the effect of each variable on patient survival, adjusted for other variables, providing a clearer understanding of the variable's influence and guiding clinical decision-making. Our results identified treatment regimen, P53, and NLR as independent prognostic factors for DFS in TNBC patients.

NLR is an indicator that reflects the inflammatory state of the body. Kusama et al. [24] suggested NLR as an independent predictor and pointed out that it could serve as a useful surrogate marker for tumor-infiltrating lympho-

cytes in predicting pCR in TNBC. Wang et al. [25] found that NLR could predict the efficacy and prognosis of NACT with taxanes and anthracyclines in TNBC patients. Patients with lower NLR who received lobaplatin had higher tpCR rates and better long-term prognosis. A higher NLR typically indicates a higher level of systemic inflammation. The inflammatory environment promotes tumor cell proliferation, invasion, and metastasis, which negatively affect DFS [26]. A higher NLR usually indicates higher neutrophil and lower lymphocyte counts. Neutrophils contribute to the formation of a tumor-friendly microenvironment and to tumor cell survival and dissemination, while lymphocytes, especially T cells, are key to the body's anti-tumor immune response [27]. Lower lymphocyte counts may indicate weaker anti-tumor immune surveillance, which may also negatively impact DFS.

A previous study analyzing 319 patients with stage I and II TNBC found no significant difference in DFS or OS between NACT and ACT, regardless of BRCA status [13]. Another study based on the National Cancer Database showed that in stage II-III TNBC patients, OS was worse in the NACT group compared to the ACT group (73.4% vs. 76.8%) [14]. These studies suggest that the treatment regimen has a limited impact on the prognosis of TNBC patients. However, our study found that the SNCR regimen significantly improved DFS compared to the SACR regimen. We attribute this to the systemic treatment intervention of the SNCR regimen prior to surgery, which helps to control micrometastases and effectively assess tumor response to chemotherapy to guide subsequent treatment. This regimen significantly reduces tumor size, facilitating more thorough surgical resection and reducing the likelihood of residual cancer cells during surgery. Postoperative radiation therapy further enhances local control by ensuring thorough elimination of tumor cells, which significantly reduces the risk of local recurrence. This comprehensive treatment approach enhances the overall therapeutic effect and significantly improves DFS for patients.

However, our study has some limitations, including small sample size, retrospective design, lack of long-term follow-up data, and single-center study. The small sample size may result in insufficient statistical power, which limits the generalizability and reproducibility of the results. As a retrospective study, there is a potential for selection bias and information bias, which limits the ability to establish causal relationships. In addition, the lack of long-term follow-up data prevents the capture of late recurrence events in breast cancer patients, which affects the long-term evaluation of treatment efficacy. Finally, data from a single medical center may limit the broader applicability of the results, affecting generalizability to other regions or populations. Future studies should include larger sample size, prospective and multicenter designs, and long-term follow-up to improve the validity and reliability of the research.

In conclusion, the SNCR regimen significantly improves DFS in patients with stage IIb to IIIa TNBC compared to the traditional SACR regimen.

## Disclosure of conflict of interest

None.

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