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ORIGINAL RESEARCH

Pretreatment Systemic Inflammation Response Index in Patients with Breast Cancer Treated with Neoadjuvant Chemotherapy as a Useful Prognostic Indicator

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Background and Objective: Systemic inflammation response index (SIRI=N×M/L), based on neutrophil (N), monocyte (M), and lymphocyte (L) counts, is used to predict the survival of patients with malignant tumors and can fully evaluate the balance between host immune and inflammatory condition. The present study is aimed to evaluate the potential prognostic significance of SIRI in patients with breast cancer undergoing neoadjuvant chemotherapy.

Subjects and Methods: A total of 262 breast cancer patients treated with neoadjuvant chemotherapy were enrolled in this retrospective study. The optimal cutoff value of SIRI by receiver operating characteristic curve stratified patients into low SIRI ($<0.85\times10^9$/L) group and high SIRI ($\geq0.85\times10^9$/L) group. The associations between breast cancer and clinicopathological variables by SIRI were determined by chi-square test or Fisher's exact test. Kaplan–Meier plots and log-rank test were used to evaluate the clinical outcomes of disease-free survival (DFS) and overall survival (OS). Univariate and multivariate Cox proportional hazards regression models were used to analyze the prognostic value of SIRI. The toxicity of neoadjuvant chemotherapy was evaluated by the National Cancer Institute Common Toxicity Criteria (NCICTC).

Results: The results were shown that SIRI had prognostic significance by optimal cutoff value of 0.85×10^9/L on DFS and OS in univariate and multivariate Cox regression survival analyses. Compared with patients who had high SIRI, patients with low SIRI had longer DFS and OS (41.27 vs 30.45 months, HR: 1.694, 95% CI: 1.128–2.543, P=0.011; 52.86 vs 45.75 months, HR: 1.288, 95% CI: 0.781–3.124, P=0.002, respectively). The patients with low SIRI had better 3-, 5-, and 10-year rates of DFS and OS than those with high SIRI. The common toxicities after neoadjuvant chemotherapy were hematologic and gastrointestinal reaction, and the SIRI had no significance on toxicities of all enrolled patients, excepted diarrhea. In patients without neural invasion, those with low SIRI had better prognosis and lower recurrence rates than those with high SIRI.

Conclusion: Pretreatment SIRI with the advantage of repeatable, convenient, and non-invasive is a useful prognostic indicator for breast cancer patients who received neoadjuvant chemotherapy and is a promising biomarker for breast cancer on treatment strategy decisions.

Keywords: systemic inflammation response index, SIRI, breast cancer, neoadjuvant chemotherapy, survival, prognosis

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Introduction

Breast cancer is the most frequent neoplasm and is leading major cause of cancer-related morbidity and mortality worldwide among women.[1] In China, breast cancer

has the highest incidence for females, and the incidence of breast cancer is increasing year after year.[2] The postmenopausal women with breast cancer in China will reach 100/100,000 in the future, and the incidence of breast cancer is increasing rapidly in coastal developed cities of China.[3] Although many patients with breast cancer are successfully treated by the early diagnoses and improved treatment strategies, approximately 20–25% patients are diagnosed with locally advanced breast cancer.[4] Lots of studies have indicated that surgery combined with adjuvant chemoradiotherapy can effectively improve the survival rate of patients with breast cancer.[5–7]

Neoadjuvant chemotherapy (NACT) is the gold standard of care for locally advanced cancer and has been widely used to the treatment for locally advanced breast cancer.[8] According to the NACT for breast cancer, the breast-conserving surgery rate is increasing, and the tumor stage is decreasing.[9] Many NACT regimens have been applied to the treatment for breast cancer; however, there are no internationally generally accepted NACT regimens for patients with advanced breast carcinoma.[10] Therefore, it is necessary to look for accurate and sensitive tumor indicators of breast cancer to improve the survival outcome and provide the better prognosis factor for breast cancer.

Some histologic and immunologic biomarkers have been used to evaluate the prognosis of breast cancer. However, these biomarkers largely depend on the primary tumor sample, and are often expensive, time-consuming and arduous, and are usually limited their use in clinical practice.[11] The molecular subtypes, which include ER, PR, Ki-67, and HER2 expression condition, are very important for the prognosis of breast cancer. Hence, it is very important to search easily accessible and reliable markers for the prognosis of patients with breast cancer.

Cancer-related inflammation is a fundamental component of the tumor microenvironment and can influence the mechanism in the pathogenesis of patients with carcinoma. The inflammatory cells in peripheral venous blood might influence tumor carcinogenesis, progression, and metastasis.[12] A great deal of studies have indicated that the inflammatory markers, such as white blood cell (W), neutrophil (N), monocyte (M), platelet (P), lymphocyte (L), as well as neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), are present and detectable in the systemic circulation, and have been widely proposed as prognostic factors for many malignancies.[13–16]

A novel and integrated indicator that named Systemic Inflammation Response Index (SIRI), which is based on neutrophil (N), monocyte (M), and lymphocyte (L) counts, is reported to be associated with clinical outcomes and predict the survival of patients with gastric cancer.[17] This integrated indicator may comprehensively reflect the balance of host immune and inflammatory status compared with NLR, LMR, and PLR. Nevertheless, the SIRI has been studied rarely in breast cancer patients with treated NACT. Therefore, our study aims to evaluate the prognostic significance of SIRI in patients with breast cancer receiving NACT.

Materials and Methods

Study Population

We enrolled 262 patients with breast cancer undergoing NACT to this study in Cancer Hospital Chinese Academy of Medical Sciences from January 1999 to 2014 December. This research was a retrospective study. The detailed treatment information, clinical and demographic data for all enrolled patients were extracted from the medical record. This study was approved by the ethics committee of Cancer Hospital Chinese Academy of Medical Sciences. It complied with the standards of the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients before the study.

The inclusion criteria for the patients were as follows: 1) all patients with breast cancer were confirmed by core needle biopsy before NACT treatment; 2) all patients received surgery treatment; 3) Karnofsky Performance Scores (KPS) ≥80 and Performance Status (Zubrod-ECOG-WHO, ZPS) ranged from 0 to 2 scores; 4) all patients had complete clinical records and follow-up information; 5) Patients could survive for more than 3 months; 6) the blood samples were obtained within 1 week before NACT treatment.

The exclusion criteria for the patients were as follows: 1) patients had received chemotherapy, radiotherapy, endocrine therapy, and targeted therapy before NACT treatment; 2) patients with malignant disease or distant metastases; 3) patients with serious complications, or any form of acute and chronic inflammatory disease; 4) patients who had blood product transfusion within 1 month before NACT treatment.

Chemotherapy Protocols

We used anthracyclines-based and/or taxanes-based NACT regimens, and one cycle of these regimens was repeated every 3 weeks. Anthracyclines (Zhejiang Hisun Pharmaceutical Co., Ltd, Taizhou, China); Cyclophosphamide (Baxter Oncology GmbH, Halle, Germany); 5-Fluorouracil (Tianjin Jinyao Pharmaceutical Co., Ltd, China); Taxol (Jiangsu Hengrui Medicine Co., Ltd, Lianyungang, China); Platinum compounds (Bristol-Myers Squibb biopharmaceutical company, S.r.l., Italy).

AC regimen (A: 90 mg/m^2, C: 600 mg/m^2). ACF regimen (A: 90 mg/m^2, C: 600 mg/m^2, F: 500 mg/m^2). CT regimen (C: 600 mg/m^2, T: 175 mg/m^2). ACT regimen (A: 90 mg/m^2, C: 600 mg/m^2, T: 175 mg/m^2). AT regimen (A: 90 mg/m^2, T: 175 mg/m^2). TP regimen (T: 175 mg/m^2, P: AUC 4–6).

Classification Standard and Response Evaluation

We used the eighth edition of American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) TNM stage classification to evaluate the tumor pathology stage of all enrolled patients.[18,19] Breast cancer molecular subtypes were classified as Luminal A, Luminal B HER2-positive, Luminal B HER2-negative, HER2-enriched, and triple negative.[20] The Miller and Payne grade (MPG) was used to determine the histological response.[21] Response rates were defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[22] The hematoxylin and eosin (HE) stain was used to diagnose lymph vessel invasion and neural invasion of tumor. The National Cancer Institute Common Toxicity Criteria (NCICTC) was used to evaluate the toxicity of NACT.

Peripheral Venous Blood Parameters

Peripheral venous blood samples were obtained within 1 week before NACT. The samples were collected by a sterile EDTA tube and obtained with empty stomach. Hematologic parameters were analyzed by XE-2100 hematology analyzer (Sysmex, Kobe, Japan).

Follow-Up

All patients were followed up by inpatients and outpatients every 3 months for the first to second year after surgery, every 6 months for the third to fifth year after surgery, then annually every year and until death.[23] Follow-up assessments included laboratory tests (routine blood test, blood biochemical), breast ultrasonography, mammography and some other examinations as it fits. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of local recurrence or distant metastases, death from any cause or last follow-up. Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause or last follow-up.

Statistical Analysis

The optimal cutoff value was accessed by the receiver operating characteristic curve (ROC) analyses, and the area under the curve was determined by the predictive value. The ratio closest to the point with maximum sensitivity and specificity was defined as the optimal cutoff value. The clinicopathologic categorical variables were presented as frequencies and percentages (%), and the associations between breast cancer and clinicopathological variables were evaluated using the chi-square test or Fisher's exact test. The association between breast cancer and survival was analyzed by the Kaplan–Meier plots and log-rank test. The independent prognostic factors were accessed by the univariate and multivariate Cox proportional hazards regression model, and the hazard ratios (HRs) and 95% confidence interval (CI) were obtained by the Cox proportional hazards regression model. All statistical analyses were performed using the SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA) and GraphPad prism software (version 5.0; GraphPad Inc., La Jolla, CA, USA). Alpha was set at 0.05, and a two-tailed $P<0.05$ was considered statistically significant.

Results

Demographic and Clinicopathologic Characteristics of All Breast Cancer Patients

We enrolled 262 cases with breast cancer in this retrospective study. The optimal cutoff value of SIRI by ROC analysis was 0.85×10^9/L, and the optimal cutoff value was used for all analyses. The patients with breast cancer were categorized into two groups by SIRI: low SIRI group ($<0.85\times10^9$/L) and high SIRI group ($\geq0.85\times10^9$/L). The clinicopathological characteristics of patients with breast cancer were shown in Table 1. All enrolled patients were females. The age was ranged from 27 to 73 years, and the median age was 48 years. In low SIRI group, there were 155 patients (59.2%), and in high SIRI group, there were 107 patients (40.8%). The median body mass index (BMI) of all patients was ranged from 18.03 to 39.06, and the

Table 1 Demographic and Clinicopathologic Characteristics of All Breast Cancer Patients

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
Cases (n)	262	155 (59.2%)	107 (40.8%)		
Age (years)				0.840	0.359
<48	138 (52.7%)	78	60		
≥48	124 (47.3%)	77	47		
Marital status				0.915	0.922
Married	243 (92.7%)	145	98		
Unmarried	9 (3.4%)	5	4		
Divorce	7 (2.7%)	4	3		
Widowhood	3 (1.2%)	1	2		
Occupation				0.826	0.662
Mental worker	165 (63.0%)	101	64		
Manual worker	35 (13.4%)	20	15		
Others	62 (23.6%)	34	28		
BMI				0.020	0.888
<24.50	148 (56.5%)	87	61		
≥24.50	114 (43.5%)	68	46		
Menopause				3.895	0.048
No	160 (61.1%)	87	73		
Yes	102 (38.9%)	68	34		
ABO blood type				2.486	0.647
A	84 (32.1%)	52	32		
B	78 (29.7%)	44	34		
O	73 (27.9%)	40	33		
AB	27 (20.3%)	19	8		
Tumor site				0.382	0.536
Right	126 (48.1%)	77	49		
Left	136 (51.9%)	78	58		
Primary tumor site				2.002	0.735
Upper outer quadrant	166 (63.4%)	95	71		
Lower outer quadrant	21 (8.0%)	14	7		
Lower inner quadrant	12 (4.6%)	8	4		
Upper inner quadrant	38 (14.5%)	25	13		
Central	25 (9.5%)	13	12		
US-Tumor size				0.344	0.842
≤2cm	95 (36.3%)	58	37		
>2 and <5cm	138 (52.6%)	81	57		
≥5cm	29 (11.1%)	16	13		
US-LNM				4.975	0.026
No	156 (59.5%)	101	55		
Yes	106 (40.5%)	54	52		
US-BIRADS classification				1.360	0.506
4	36 (13.8%)	19	17		
5	103 (39.3%)	59	44		
6	123 (46.9%)	77	46		

(*Continued*)

Table 1 (Continued).

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
Clinical stage					
Clinical T stage				2.695	0.610
T1	47 (17.9%)	28	19		
T2	117 (44.7%)	75	42		
T3	66 (25.2%)	35	31		
T4	32 (12.2%)	17	15		
Clinical N stage				1.443	0.837
N0	48 (18.3%)	31	17		
N1	89 (34.0%)	49	40		
N2	77 (29.4%)	45	32		
N3	48 (18.3%)	30	18		
Clinical TNM stage				0.189	0.664
II	107 (40.8%)	65	42		
III	155 (59.2%)	90	65		
Type of surgery				0.008	0.930
Mastectomy	221 (84.4%)	131	90		
Breast-conserving surgery	41 (15.6%)	24	17		
Tumor size				3.544	0.170
≤2cm	117 (44.7%)	62	55		
>2 and <5cm	120 (45.8%)	78	42		
≥5cm	25 (9.5%)	15	10		
Histologic type				2.372	0.305
Ductal	251 (95.8%)	149	102		
Lobular	4 (1.5%)	1	3		
Others	7 (2.7%)	5	2		
Histologic grade				3.626	0.163
I	74 (28.2%)	37	37		
II	136 (51.9%)	86	50		
III	52 (19.9%)	32	20		
Pathological TNM classification					
Pathological T stage				1.912	0.752
Tis/T0	42 (16.0%)	22	20		
T1	101 (38.6%)	59	42		
T2	82 (31.3%)	51	31		
T3	25 (9.5%)	17	8		
T4	12 (4.6%)	6	6		
Pathological N stage				0.361	0.986
N0	98 (37.4%)	57	41		
N1	51 (19.5%)	31	20		
N2	40 (15.3%)	25	15		
N3	73 (27.8%)	42	31		
Pathological TNM stage				1.662	0.798
Tis/T0	34 (13.0%)	19	15		
I	47 (17.9%)	26	21		

(*Continued*)

Table 1 (Continued).

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
II	59 (22.5%)	39	20		
III	122 (46.6%)	71	51		
Total lymph nodes				4.065	0.044
<21	120 (45.8%)	63	57		
≥21	142 (54.2%)	92	50		
Positive lymph nodes				0.150	0.928
0	97 (37.0%)	57	40		
<6	71 (27.1%)	41	30		
≥6	94 (35.9%)	57	37		
Total axillary lymph nodes				0.926	0.336
<20	118 (45.0%)	66	52		
≥20	144 (55.0%)	89	55		
Positive axillary lymph nodes				0.048	0.976
0	99 (37.8%)	58	41		
<5	63 (24.1%)	37	26		
≥5	100 (38.1%)	60	40		
Postoperative complications				0.217	0.641
No	253 (96.6%)	149	104		
Yes	9 (3.4%)	6	3		
Postoperative radiotherapy				0.323	0.570
No	61 (23.3%)	38	23		
Yes	201 (76.7%)	117	84		
Postoperative endocrine therapy				0.052	0.819
No	130 (49.6%)	76	54		
Yes	132 (50.4%)	79	53		
Postoperative targeted therapy				1.378	0.240
No	189 (72.1%)	116	73		
Yes	73 (27.9%)	39	34		

median BMI was 24.50. In this study, a low SIRI was significantly associated with menopause (χ^2=3.895, P=0.048), US-LNM (χ^2=4.975, P=0.026), total lymph nodes (χ^2=4.065, P=0.044).

Relationships Between SIRI and Hematologic Parameters

In this study, the maximum (sensitivity + specificity) point of the ROC curve was regarded as the optimal cutoff value of SIRI. The cutoff value of ALT, AST, LDH, IgA, IgG, IgM, ALB, CRP, CA125, CA153, CEA, D-D, FDP, W, R, Hb, N, M, P, L, NLR, MLR, PLR by median value were 23 U/L, 23 U/L, 190 U/L, 2.30 g/L, 11.67 g/L, 1.27 g/L, 44.00 g/L, 1.10 mg/dl, 27.73 U/mL, 21.86 U/mL, 3.52 ng/mL, 0.83 mg/L FEU, 2.01 ug/mL, 6.00×10^9/L, 4.34×10^9/L, 128.00×10^9/L, 3.83×10^9/L, 1.67×10^9/L, 0.34×10^9/L, 244.00×10^9/L, 2.50, 0.22, 160.00, respectively. The hematologic parameters of patients with breast cancer are shown in Table 2. A low SIRI was significantly related to W (P<0.001), Hb (P=0.010), N (P<0.001), L (P=0.030), M (P<0.001), NLR (P<0.001), MLR (P<0.001), PLR (P=0.003) (Table 2).

Association of SIRI and NACT or Postoperative Chemotherapy

All enrolled patients received anthracyclines-based and taxanes-based NACT regimens. All cases were treated with NACT, and 27 patients received the AC/ACF regimen, 29 patients received the CT/ACT regimen, 121 patients received the AT regimen, 75 patients received

Table 2 Relationships Between SIRI and Hematologic Parameters

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
Cases (n)	262	155 (59.2%)	107 (40.8%)		
ALT				0.005	0.943
<23	183 (69.9%)	108	75		
≥23	79 (30.1%)	47	32		
AST				0.531	0.466
<23	182 (69.5%)	105	77		
≥23	80 (30.5%)	50	30		
LDH				0.080	0.778
<190	174 (66.4%)	104	70		
≥190	88 (33.6%)	51	37		
IgA				0.019	0.892
<2.30	136 (51.9%)	81	55		
≥2.30	126 (48.1%)	74	52		
IgG				0.816	0.366
<11.67	141 (53.8%)	87	54		
≥11.67	121 (46.2%)	68	53		
IgM				0.743	0.389
<1.27	160 (61.1%)	98	62		
≥1.27	102 (38.9%)	57	45		
ALB				0.071	0.790
<44.00	98 (37.4%)	59	39		
≥44.00	164 (62.6%)	96	68		
CRP				0.973	0.323
<1.10	226 (86.3%)	131	95		
≥1.10	36 (13.7%)	24	12		
CA125				0.784	0.376
<27.73	224 (85.5%)	135	89		
≥27.73	38 (14.5%)	20	18		
CA153				0.542	0.461
<21.86	209 (79.8%)	126	83		
≥21.86	53 (20.2%)	29	24		
CEA				0.475	0.491
<3.52	211 (80.5%)	127	84		
≥3.52	51 (19.5%)	28	23		
D-D				0.106	0.744
<0.83	218 (83.2%)	128	90		
≥0.83	44 (16.8%)	27	17		
FDP				0.005	0.941
<2.01	156 (59.5%)	92	64		
≥2.01	106 (40.5%)	63	43		
White blood cell (W)				28.720	<0.001
<6.00	133 (50.8%)	100	33		
≥6.00	129 (49.2%)	55	74		

(*Continued*)

Table 2 (Continued).

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
Red blood cell (R)				1.225	0.268
<4.34	116 (44.3%)	73	43		
≥4.34	146 (55.7%)	82	64		
Hemoglobin (Hb)				6.660	0.010
<128.00	108 (41.2%)	74	34		
≥128.00	154 (58.8%)	81	73		
Neutrophil (N)				67.708	<0.001
<3.83	134 (51.2%)	112	22		
≥3.83	128 (48.8%)	43	85		
Lymphocyte (L)				4.712	0.030
<1.67	143 (54.6%)	76	67		
≥1.67	119 (45.4%)	79	40		
Monocyte (M)				58.091	<0.001
<0.34	133 (50.8%)	109	24		
≥0.34	129 (49.2%)	46	83		
Platelet (P)				0.409	0.523
<244.00	136 (51.9%)	83	53		
≥244.00	126 (48.1%)	72	54		
NLR				92.661	<0.001
<2.50	160 (61.1%)	132	28		
≥2.50	102 (38.9%)	23	79		
MLR				99.033	<0.001
<0.22	152 (58.0%)	129	23		
≥0.22	110 (42.0%)	26	84		
PLR				8.768	0.003
<160.00	158 (60.3%)	105	53		
≥160.00	104 (39.7%)	50	54		

TP regimen, and 10 patients received other regimens, such as FP, T, F, TF, EV regimen. However, 116 patients were received postoperative chemotherapy, and 18 patients were treated with AC/ACF regimen, 17 patients were treated with CT/ACT regimen, 27 patients were treated with AT regimen, 21 patients were treated with TP regimen, and 33 patients were treated with other regimens, such as C, CTF, CTP, A, AF, AMF, AP, F, FP, T, TF, V, VP regimen. The clinical objective response rate (CR+PR) was 61.4%, and the clinical benefit rate (CR+PR+SD) was 97.3%, and non-clinical response rate (SD+PD) was 38.6%. The pathological response was accessed by MPG system, and the grade 1 rate was 5.0%, the grade 2 rate was 29.8%, the grade 3 rate was 39.3%, the grade 4 rate was 10.3%, and the grade 5 rate was 15.6%. Moreover, the pathological response of pCR rate was 20.6%. The NACT or postoperative chemotherapy of patients with breast cancer is shown in Table 3. A low SIRI was significantly related to NACT (P=0.004).

Correlation Between SIRI and Breast Cancer Molecular Subtypes

All enrolled cases were diagnosed and confirmed by core needle biopsy prior to NACT. Before NACT, 8 cases were Luminal A subtype, 27 cases were Luminal B HER2-positive subtype, 98 cases were Luminal B HER2-negative subtype, 62 cases were HER2-enriched subtype, and 67 cases were triple-negative subtype, respectively. After NACT and surgery, 9 patients were Luminal A subtype, 25 patients were Luminal B HER2-positive subtype, 94 patients were Luminal B HER2-negative subtype, 66 patients were HER2-enriched subtype, and 68 patients

Table 3 Association of SIRI and Neoadjuvant Chemotherapy or Postoperative Chemotherapy

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
Cases (n)	262	155 (59.2%)	107 (40.8%)		
Neoadjuvant chemotherapy regimen				15.269	0.004
AC/ACF	27 (10.3%)	17	10		
CT/ACT	29 (11.1%)	22	7		
AT	121 (46.2%)	78	43		
TP	75 (28.6%)	31	44		
Others	10 (3.8%)	7	3		
Chemotherapy times				0.531	0.466
<6	85 (32.4%)	53	32		
≥6	177 (67.6%)	102	75		
Response				2.105	0.716
CR	5 (1.9%)	3	2		
PR	156 (59.5%)	91	65		
SD	94 (35.9%)	55	39		
PD	7 (2.7%)	6	1		
Miller and Payne grade				4.252	0.373
1	13 (5.0%)	7	6		
2	78 (29.8%)	50	28		
3	103 (39.3%)	64	39		
4	27 (10.3%)	12	15		
5	41 (15.6%)	22	19		
Pathological response				0.366	0.545
pCR	54 (20.6%)	30	24		
Non-pCR	208 (79.4%)	125	83		
Postoperative chemtherapy regimen				1.618	0.899
0	146 (55.7%)	85	61		
AC/ACF	18 (6.9%)	9	9		
CT/ACT	17 (6.5%)	10	7		
AT	27 (10.3%)	18	9		
TP	21 (8.0%)	12	9		
Others	33 (12.6%)	21	12		
Postoperative chemotherapy times				1.294	0.523
0	146 (55.7%)	85	61		
<4	41 (15.7%)	22	19		
≥4	75 (28.6%)	48	27		

were triple-negative subtype, respectively. There was no significant association between tumor molecular subtypes and SIRI (Table 4).

Correlation Between SIRI and Side Effects of Chemotherapy

In this study, the common toxicities after NACT were hematologic and gastrointestinal reaction. And we used the NCICTC to evaluate and analyze the side effects of NACT. There were no chemotherapy-related deaths in our study. Moreover, we used the SIRI to access the side effects of NACT, and the result indicated that the SIRI before NACT had no significance on toxicities of all enrolled patients, excepted diarrhea (χ^2=4.199, P=0.040) (Table 5).

Univariate and Multivariate Cox Regression Survival Analyses

We used the univariate and multivariate Cox proportional-hazards models to determine the independent prognostic factors. According to univariate and multivariate analysis,

Table 4 Correlation Between SIRI and Breast Cancer Molecular Subtypes

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
Cases (n)	262	155 (59.2%)	105 (40.8%)		
Core needle biopsy					
Molecular subtype				2.811	0.590
Luminal A	8 (3.1%)	5	3		
Luminal B HER2+	27 (10.3%)	14	13		
Luminal B HER2-	98 (37.4%)	64	34		
HER2 enriched	62 (23.7%)	34	28		
Triple negative	67 (25.5%)	38	29		
ER status				0.988	0.320
Negative	108 (41.2%)	60	48		
Positive	154 (58.8%)	95	59		
PR status				0.857	0.354
Negative	129 (49.2%)	80	49		
Positive	133 (50.8%)	75	58		
HER2 status				0.468	0.494
Negative (0–++)	168 (64.1%)	102	66		
Positive (+++)	94 (35.9%)	53	41		
Ki-67 status				0.022	0.882
Negative (≤14%)	60 (22.9%)	35	25		
Positive (>14%)	202 (77.1%)	120	82		
Postoperative pathology (IHC)					
Molecular subtype				1.882	0.758
Luminal A	9 (3.4%)	6	3		
Luminal B HER2+	25 (9.5%)	14	11		
Luminal B HER2-	94 (35.9%)	59	35		
HER2 enriched	66 (25.2%)	35	31		
Triple negative	68 (26.0%)	41	27		
ER status				0.088	0.767
Negative	122 (46.6%)	71	51		
Positive	140 (53.4%)	84	56		
PR status				0.016	0.900
Negative	131 (50.0%)	78	53		
Positive	131 (50.0%)	77	54		
HER2 status				0.940	0.332
Negative (0–++)	173 (66.0%)	106	67		
Positive (+++)	89 (34.0%)	49	40		
Ki-67 status				0.409	0.523
Negative (≤14%)	92 (35.1%)	52	40		
Positive (>14%)	170 (64.9%)	103	67		
AR status				0.071	0.790
Negative	164 (62.6%)	96	68		
Positive	98 (37.4%)	59	39		

(*Continued*)

Table 4 (Continued).

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
CK5/6 status				1.357	0.244
Negative	228 (87.0%)	138	90		
Positive	34 (13.0%)	17	17		
E-cad status				0.411	0.521
Negative	109 (41.6%)	67	42		
Positive	153 (58.4%)	88	65		
EGFR status				0.111	0.739
Negative	198 (75.6%)	116	82		
Positive	64 (24.4%)	39	25		
P53 status				0.075	0.784
Negative	132 (50.4%)	77	55		
Positive	130 (49.6%)	78	52		
TOP2A status				1.838	0.175
Negative	107 (40.8%)	58	49		
Positive	155 (59.2%)	97	58		
Lymph vessel invasion				0.227	0.634
Negative	162 (61.8%)	94	68		
Positive	100 (38.2%)	61	39		
Neural invasion				2.605	0.107
Negative	197 (75.2%)	111	86		
Positive	65 (24.8%)	44	21		

the clinical T stage, Miller and Payne grade, pathological T stage, pathological TNM stage, core needle biopsy (molecular subtype, ER status, Ki-67 status), postoperative pathology IHC (Ki-67 status), neural invasion, PLR, SIRI, postoperative chemotherapy, postoperative radiotherapy for DFS and OS were the significant prognostic factors (Table 6). The median DFS and OS of all enrolled patients were 36.85 months (range from 4.00 to 197.97 months) and 49.95 months (range from 5.93 to 250.97 months), respectively (Figure 1A and B).

The result was indicated that SIRI was the significant prognostic factor. And patients with low SIRI had significantly lower risks of disease progression compared with patients with high SIRI. Moreover, low SIRI was associated with prolonged DFS and OS by univariate analysis (P=0.018, hazard ratio [HR]: 1.817, 95% confidence interval [CI]: 0.389–8.485 and P=0.007, HR: 1.321, 95% CI: 1.049–4.109, respectively). And low SIRI was also associated with prolonged DFS and OS (P=0.011, HR: 1.694, 95% CI: 1.128–2.543 and P=0.002, HR: 1.288, 95% CI: 0.781–3.124, respectively; Table 6).

In low SIRI group, the mean DFS and OS for all enrolled patients were 41.27 months (range from 4.00 to 197.97 months) and 52.86 months (range from 5.93 to 250.97 months), respectively. In high SIRI group, the mean DFS and OS for all enrolled patients were 30.45 months (range from 4.93 to 194.90 months) and 45.75 months (range from 8.13 to 238.27 months), respectively. We also found that the mean DFS and OS time for patients with low SIRI were longer than for those with high SIRI by using log-rank methods (χ^2=4.766, P=0.029 and χ^2=4.181, P=0.041, respectively; Figure 1C and D).

Survival and Evaluation of the Prognostic Significance of SIRI

Among the 262 patients with breast cancer, the DFS rates at 3-, 5-, and 10-year were 31.7% (83/262), 17.2% (45/262), 4.6% (12/262); the OS rates at 3-, 5-, and 10-year were 42.7% (112/262), 28.2% (74/262), 7.6% (20/262), respectively. In low SIRI group, the DFS rates at 3-, 5-, and 10-year were 36.1% (56/155), 20.6% (32/155), 5.8% (9/155); and the OS rates at 3-, 5-, and 10-year in low SIRI were 46.5% (72/155), 31.0% (48/155), 8.4% (13/155), respectively. In high SIRI group, the DFS rates at 3-, 5-, and 10-year were 25.2% (27/107), 12.1% (13/107), 2.8% (3/107), respectively. The results were indicated

Table 5 Main Toxicities According to NCICTC Scale of the Patients with Breast Cancer Undergoing Neoadjuvant Chemotherapy

Parameters		Low SIRI < 0.85	High SIRI≥0.85	χ^2	P value
Cases (n)	262	155 (59.2%)	107 (40.8%)		
Decreased appetite				0.155	0.694
No	20 (7.6%)	11	9		
Yes	242 (92.4%)	144	98		
Nausea				0.161	0.688
No	14 (5.3%)	9	5		
Yes	248 (94.7%)	146	102		
Vomiting				0.598	0.439
No	98 (37.4%)	55	43		
Yes	164 (62.6%)	100	64		
Diarrhea				4.199	0.040
No	237 (90.5%)	145	92		
Yes	25 (9.5%)	10	15		
Mouth ulcers				3.113	0.078
No	252 (96.2%)	147	105		
Yes	10 (3.8%)	8	2		
Alopecia				0.115	0.735
No	111 (42.4%)	67	44		
Yes	151 (57.6%)	88	63		
Peripheral neurotoxicity				0.383	0.536
No	239 (91.2%)	140	99		
Yes	23 (8.8%)	15	8		
Anemia				0.661	0.718
Grade 0	98 (37.4%)	61	37		
Grade 1–2	162 (61.8%)	93	69		
Grade 3–4	2 (0.8%)	1	1		
Leukopenia				0.230	0.891
Grade 0	77 (29.4%)	47	30		
Grade 1–2	106 (40.5%)	61	45		
Grade 3–4	79 (30.1%)	47	32		
Neutropenia				1.365	0.505
Grade 0	72 (27.5%)	45	27		
Grade 1–2	104 (39.7%)	57	47		
Grade 3–4	86 (32.8%)	53	33		
Thrombocytopenia				1.089	0.580
Grade 0	178 (67.9%)	104	74		
Grade 1–2	81 (30.9%)	50	31		
Grade 3–4	3 (1.2%)	1	2		
Gastrointestinal reaction				0.119	0.942
Grade 0	9 (3.4%)	5	4		
Grade 1–2	250 (95.4%)	148	102		
Grade 3–4	3 (1.2%)	2	1		
Myelosuppression				0.290	0.865
Grade 0	55 (21.0%)	34	21		
Grade 1–2	101 (38.5%)	58	43		
Grade 3–4	106 (40.5%)	63	43		

Table 6 Univariate and Multivariate Cox Regression Survival Analyses of the SIRI for the Prediction of DFS and OS in Breast Cancer Patients

Parameters	DFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Age (years)		0.058				0.093		
<48	1 (Reference)				1 (Reference)			
≥48	4.013 (0.955–16.870)				3.857 (0.800–18.597)			
BMI		0.47				0.237		
<24.50	1 (Reference)				1 (Reference)			
≥24.50	2.352 (1.012–5.463)				1.564 (0.218–3.457)			
Menopause		0.737				0.278		
No	1 (Reference)				1 (Reference)			
Yes	0.765 (0.159–3.670)				0.394 (0.073–2.123)			
ABO blood type		0.054				0.029		0.033
A	1 (Reference)				1 (Reference)		1 (Reference)	
B	1.772 (0.463–6.787)				2.936 (0.860–10.021)		1.913 (1.008–3.632)	
O	4.277 (1.317–13.890)				7.667 (2.024–29.049)		2.666 (1.323–5.370)	
AB	1.109 (0.182–6.754)				4.403 (0.621–31.223)		2.402 (1.018–5.665)	
Primary tumor site		0.132				0.595		
Upper outer quadrant	1 (Reference)				1 (Reference)			
Lower outer quadrant	0.539 (0.093–3.122)				1.285 (0.208–7.944)			
Lower inner quadrant	1.389 (0.576–3.566)				0.241 (0.004–12.903)			
Upper inner quadrant	0.483 (0.131–1.777)				0.300 (0.055–1.620)			
Central	1.606 (0.326–7.924)				1.051 (0.191–5.769)			
US-LNM		0.34				0.131		
No	1 (Reference)				1 (Reference)			
Yes	1.786 (0.542–5.884)				2.254 (0.786–6.467)			
US-BIRADS classification		0.724				0.24		
4	1 (Reference)				1 (Reference)			
5	2.710 (0.227–32.330)				0.325 (0.027–3.866)			
6	0.979 (0.372–2.572)				0.156 (0.012–2.103)			

(*Continued*)

Table 6 (Continued).

Parameters	DFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Clinical stage								
Clinical T stage		<0.001		0.007		0.005		0.003
T1	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
T2	1.767 (0.346–5.032)		1.975 (0.496–5.916)		3.142 (0.580–17.024)		2.251 (0.643–7.433)	
T3	1.432 (0.268–7.640)		1.548 (0.231–6.300)		1.946 (0.172–5.192)		1.706 (0.300–4.660)	
T4	1.724 (0.106–4.904)		1.363 (0.128–4.028)		1.669 (0.090–4.993)		1.630 (0.209–4.898)	
Clinical N stage		0.233				0.88		
N0	1 (Reference)				1 (Reference)			
N1	0.835 (0.124–5.623)				0.914 (0.163–5.125)			
N2	1.071 (0.199–5.764)				1.626 (0.250–10.576)			
N3	1.197 (0.178–8.061)				1.541 (0.173–13.766)			
Clinical TNM stage		0.061				0.814		
II	1 (Reference)				1 (Reference)			
III	2.385 (1.070–8.390)				2.206 (1.008–7.296)			
Neoadjuvant chemotherapy regimen		0.033		0.757		0.754		
AC/ACF	1 (Reference)		1 (Reference)		1 (Reference)			
CT/ACT	1.004 (0.595–4.115)		1.791 (0.304–5.060)		1.642 (0.183–14.717)			
AT	1.691 (0.356–8.033)		1.627 (0.288–8.527)		1.493 (0.270–8.239)			
TP	1.786 (0.953–4.026)		1.617 (0.250–4.527)		2.944 (0.564–15.376)			
Others	1.193 (0.750–8.450)		1.571 (0.160–5.037)		1.054 (0.070–15.943)			
Neoadjuvant chemotherapy times		0.324				0.246		
<6	1 (Reference)				1 (Reference)			
≥6	1.706 (0.590–4.937)				2.180 (0.584–8.141)			
Response		0.067				0.631		
CR	1 (Reference)				1 (Reference)			
PR	1.553 (0.766–7.458)				4.021 (0.193–83.616)			
SD	1.775 (1.048–6.516)				3.767 (0.140–101.307)			
PD	1.681 (1.046–7.183)				0.781 (0.007–90.182)			
Tumor size		0.054				0.001		0.019
≤2cm	1 (Reference)				1 (Reference)		1 (Reference)	
>2 and <5cm	1.564 (0.565–4.478)				1.072 (0.118–3.296)		1.400 (0.187–3.855)	
≥5cm	1.540 (0.109–3.679)				1.094 (0.111–3.787)		1.261 (0.190–3.757)	

Type of surgery Mastectomy	1 (Reference)	0.935			1 (Reference)	0.217		
Breast-conserving surgery	1.054 (0.302–3.680)				2.321 (0.609–8.844)			
Miller and Payne grade 1 2 3 4 5	 1 (Reference) 0.104 (0.017–0.645) 0.080 (0.010–0.610) 0.000 (0.000–0.008) 0.012 (0.000–0.396)	<0.001	 1 (Reference) 0.823 (0.305–2.221) 0.674 (0.248–1.830) 0.283 (0.074–1.083) 0.825 (0.166–4.109)	<0.001	 1 (Reference) 0.197 (0.023–1.687) 0.503 (0.062–4.082) 0.001 (0.000–0.046) 2.807 (0.076–104.171)	<0.001	 1 (Reference) 0.855 (0.284–2.574) 0.706 (0.239–2.090) 0.097 (0.024–0.390) 0.609 (0.083–4.458)	<0.001
Histologic type Ductal Lobular Others	 1 (Reference) 0.063 (0.002–2.122) 0.367 (0.009–14.164)	0.281			 1 (Reference) 3.017 (0.061–149.412) 0.015 (0.000–1.446)	0.152		
Histologic grade I II III	 1 (Reference) 1.237 (0.574–3.263) 1.748 (0.275–5.030)	0.153			 1 (Reference) 0.387 (0.043–3.492) 0.744 (0.077–7.202)	0.382		
Pathological TNM classification								
Pathological T stage Tis/T0 T1 T2 T3 T4	 1 (Reference) 1.072 (0.738–4.645) 1.040 (0.130–3.025) 1.338 (0.188–4.071) 1.230 (0.211–5.113)	0.003	 1 (Reference) 1.069 (0.693–3.609) 1.671 (0.377–3.608) 1.578 (0.371–5.072) 1.536 (0.611–4.383)	<0.001	 1 (Reference) 1.797 (1.039–7.626) 1.074 (0.382–4.624) 1.435 (0.634–6.288) 1.067 (0.913–4.864)	<0.001	 1 (Reference) 1.790 (0.935–6.917) 1.988 (0.518–5.806) 1.036 (0.867–3.487) 1.357 (0.780–4.279)	<0.001
Pathological N stage N0 N1 N2 N3	 1 (Reference) 1.123 (0.115–3.265) 1.921 (0.295–5.052) 2.254 (0.645–7.540)	0.065			 1 (Reference) 1.633 (0.282–3.794) 1.161 (0.872–3.325) 1.705 (0.446–3.243)	0.169		
Pathological TNM stage Tis/T0 I II III	 1 (Reference) 1.568 (0.949–3.986) 1.180 (0.760–3.431) 1.889 (0.930–4.383)	<0.001	 1 (Reference) 1.789 (0.751–4.261) 1.128 (0.482–2.642) 1.871 (0.868–4.031)	<0.001	 1 (Reference) 3.189 (1.275–7.973) 1.121 (0.441–2.849) 1.034 (0.385–2.776)	<0.001	 1 (Reference) 2.829 (1.105–7.245) 1.294 (0.491–3.407) 1.475 (0.536–4.059)	<0.001

(*Continued*)

Table 6 (Continued).

Parameters	DFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Total lymph nodes		0.995				0.939		
<21	1 (Reference)				1 (Reference)			
≥21	1.007 (0.108–9.349)				1.044 (0.345–3.164)			
Positive lymph nodes		0.005		0.009		0.811		
0	1 (Reference)		1 (Reference)		1 (Reference)			
<6	1.700 (0.000–3.539)		3.789 (1.471–9.763)		1.722 (0.049–60.858)			
≥6	1.752 (0.000–4.224)		6.037 (1.808–20.161)		2.522 (0.115–55.522)			
Core needle biopsy								
Molecular subtype		0.011		0.016		0.012		0.01
Luminal A	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Luminal B HER2+	1.023 (0.110–2.542)		1.064 (0.117–2.595)		1.826 (0.447–6.980)		1.598 (0.610–5.907)	
Luminal B HER2-	0.109 (0.006–1.964)		0.435 (0.143–1.323)		0.225 (0.005–10.031)		0.657 (0.212–2.037)	
HER2 enriched	1.384 (0.804–5.178)		1.127 (0.714–3.172)		1.245 (0.361–6.215)		1.257 (0.126–5.562)	
Triple negative	1.166 (0.676–5.757)		1.638 (0.373–7.190)		2.574 (0.402–9.387)		1.932 (0.441–8.458)	
ER status		<0.001		<0.001		0.002		0.006
Negative	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Positive	1.916 (0.617–4.906)		1.688 (0.373–7.190)		1.571 (0.993–3.167)		1.281 (0.448–3.664)	
PR status		0.352				0.525		
Negative	1 (Reference)				1 (Reference)			
Positive	2.116 (0.437–10.256)				1.879 (0.269–13.140)			
HER2 status		0.542				0.426		
Negative (0–++)	1 (Reference)				1 (Reference)			
Positive (+++)	3.808 (1.052–9.730)				2.396 (0.278–20.618)			
Ki-67 status		0.017		0.001		0.005		<0.001
Negative (≤14%)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Positive (>14%)	5.275 (1.346–20.674)		2.230 (1.391–3.574)		5.885 (1.037–33.391)		2.558 (1.565–4.183)	
Postoperative pathology (IHC)								

Molecular subtype		0.44				0.052		
Luminal A	1 (Reference)				1 (Reference)			
Luminal B HER2+	0.325 (0.007–14.229)				0.001 (0.000–0.134)			
Luminal B HER2-	0.775 (0.023–26.006)				0.033 (0.001–1.878)			
HER2 enriched	0.039 (0.000–6.483)				0.000 (0.000–0.056)			
Triple negative	0.042 (0.001–2.145)				0.006 (0.000–1.097)			
ER status		0.025		0.909		0.036		0.478
Negative	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Positive	0.142 (0.026–0.784)		0.937 (0.306–2.867)		0.131 (0.020–0.875)		1.487 (0.497–4.445)	
PR status		0.025		0.004		0.143		
Negative	1 (Reference)		1 (Reference)		1 (Reference)			
Positive	6.341 (1.259–31.939)		2.569 (1.356–4.870)		4.265 (0.612–29.730)			
HER2 status		0.123				0.001		0.348
Negative (0–++)	1 (Reference)				1 (Reference)		1 (Reference)	
Positive (+++)	1.553 (0.446–6.299)				1.053 (0.761–4.687)		2.006 (0.469–8.583)	
Ki-67 status		0.01		<0.001		0.003		<0.001
Negative (≤14%)	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Positive (>14%)	5.267 (1.476–18.797)		2.843 (1.639–4.932)		4.634 (0.981–11.885)		4.071 (2.252–7.358)	
AR status		0.06				0.483		
Negative	1 (Reference)				1 (Reference)			
Positive	0.294 (0.082–1.052)				0.657 (0.203–2.123)			
CK5/6 status		0.035		0.123		0.804		
Negative	1 (Reference)		1 (Reference)		1 (Reference)			
Positive	0.097 (0.011–0.847)		0.509 (0.216–1.200)		0.770 (0.098–6.076)			
E-cad status		0.313				0.214		
Negative	1 (Reference)				1 (Reference)			
Positive	0.567 (0.189–1.705)				2.327 (0.615–8.812)			
EGFR status		0.149				0.081		
Negative	1 (Reference)				1 (Reference)			
Positive	0.399 (0.115–1.389)				0.202 (0.034–1.218)			

(*Continued*)

Table 6 (Continued).

Parameters	DFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
P53 status		0.771				0.498		
Negative	1 (Reference)				1 (Reference)			
Positive	0.848 (0.280–2.566)				1.521 (0.453–5.105)			
TOP2A status		0.016		0.131		0.002		0.207
Negative	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Positive	0.250 (0.081–0.770)		0.635 (0.352–11.145)		0.094 (0.021–0.422)		0.685 (0.381–1.233)	
Lymph vessel invasion		0.01		0.008		0.064		
Negative	1 (Reference)		1 (Reference)		1 (Reference)			
Positive	4.720 (1.444–15.435)		3.598 (1.783–13.263)		3.474 (0.931–12.958)			
Neural invasion		0.035		0.001		0.017		0.028
Negative	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Positive	4.512 (1.115–18.263)		3.277 (1.127–9.602)		1.481 (0.129–4.800)		1.473 (0.211–4.053)	
CA125		0.187				0.279		
<27.73	1 (Reference)				1 (Reference)			
≥27.73	2.355 (0.659–8.412)				1.701 (0.368–5.334)			
CA153		0.12		0.150		0.835		
<21.86	1 (Reference)		1 (Reference)		1 (Reference)			
≥21.86	2.512 (0.785–8.036)		1.819 (1.124–2.941)		1.121 (0.383–3.283)			
CEA		0.823				0.184		
<3.52	1 (Reference)				1 (Reference)			
≥3.52	1.125 (0.400–3.164)				2.356 (0.666–8.340)			
White blood cell (W)		0.142				0.928		
<6.00	1 (Reference)				1 (Reference)			
≥6.00	2.966 (0.696–12.644)				0.936 (0.221–3.971)			
Red blood cell (R)		0.723				0.914		
<4.34	1 (Reference)				1 (Reference)			
≥4.34	1.185 (0.463–3.035)				1.060 (0.367–3.062)			
Hemoglobin (Hb)		0.082				0.424		
<128.00	1 (Reference)				1 (Reference)			
≥128.00	2.716 (0.881–8.377)				1.678 (0.471–5.970)			

Neutrophil (N) <3.83 ≥3.83	 1 (Reference) 1.246 (0.261–5.947)	0.783			 1 (Reference) 5.384 (0.687–42.223)	0.109		
Lymphocyte (L) <1.67 ≥1.67	 1 (Reference) 1.041 (0.241–4.502)	0.957			 1 (Reference) 2.246 (0.501–10.069)	0.291		
Monocyte (M) <0.34 ≥0.34	 1 (Reference) 1.425 (0.467–4.347)	0.533			 1 (Reference) 0.527 (0.180–1.542)	0.242		
Platelet (P) <244.00 ≥244.00	 1 (Reference) 0.527 (0.207–1.343)	0.179			 1 (Reference) 0.586 (0.179–1.911)	0.375		
NLR <2.50 ≥2.50	 1 (Reference) 2.214 (0.725–6.762)	0.163			 1 (Reference) 1.051 (0.336–3.288)	0.932		
MLR <0.22 ≥0.22	 1 (Reference) 1.395 (0.395–4.929)	0.606			 1 (Reference) 0.755 (0.194–2.934)	0.685		
PLR <160.00 ≥160.00	 1 (Reference) 7.254 (2.297–22.908)	0.001	 1 (Reference) 3.601 (1.930–10.756)	0.009	 1 (Reference) 1.704 (0.921–3.005)	0.001	 1 (Reference) 2.014 (1.154–3.516)	0.004
SIRI <0.85 ≥0.85	 1 (Reference) 1.817 (0.389–8.485)	0.018	 1 (Reference) 1.694 (1.128–2.543)	0.011	 1 (Reference) 1.321 (1.049–4.109)	0.007	 1 (Reference) 1.288 (0.781–3.124)	0.002
Postoperative chemotherapy No Yes	 1 (Reference) 5.903 (1.811–19.236)	0.003	 1 (Reference) 1.836 (1.152–2.928)	0.011	 1 (Reference) 4.503 (1.263–16.059)	0.02	 1 (Reference) 3.001 (1.068–10.764)	0.017
Postoperative radiotherapy No Yes	 1 (Reference) 0.300 (0.045–1.099)	0.003	 1 (Reference) 0.596 (0.304–1.168)	0.002	 1 (Reference) 0.122 (0.036–0.410)	0.001	 1 (Reference) 0.513 (0.252–1.045)	0.003

(*Continued*)

Table 6 (Continued).

Parameters	DFS				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Postoperative endocrine therapy		0.223				0.76		
No	1 (Reference)				1 (Reference)			
Yes	1.942 (0.667–5.651)				1.207 (0.362–4.019)			
Postoperative targeted therapy		0.299				0.967		
No	1 (Reference)				1 (Reference)			
Yes	1.953 (0.552–6.914)				0.966 (0.193–4.832)			

that patients in low SIRI group had better 3-, 5-, and 10-year rates of DFS and OS than those in high SIRI group. However, there were no significant differences between low SIRI group and high SIRI group among 3-, 5-, and 10-year rates (Table 7, Figure 2A–D).

Association of Molecular Subtypes by Core Needle Biopsy and SIRI in Patients with Breast Cancer

By univariate and multivariate analysis, the molecular subtypes by core needle biopsy was the significant prognostic factor in Table 6. In order to further evaluate the prognostic value of SIRI, the SIRI was accessed by the molecular subtypes. The SIRI with different molecular subtypes was analyzed by the log-rank test. And the patients with low SIRI had longer DFS and OS than those with high SIRI. Moreover, the mean DFS and OS time for patients with low SIRI by the log-rank test were longer than in those with high SIRI in HER2-positive subtype (χ^2=5.349, P=0.021 and χ^2=3.277, P=0.070, respectively). However, there were no significant differences between low SIRI group and high SIRI group by other molecular subtypes.

Correlation Between Miller and Payne Grade (MPG) and SIRI in Patients with Breast Cancer

According to univariate and multivariate analyses, the MPG was the significant prognostic factor (Table 6). In order to further evaluate the prognostic efficiency of SIRI, we analyzed the SIRI by MPG. The SIRI with different MPG Grade was analyzed by the log-rank test. The mean DFS and OS time for patients with low SIRI were longer than in those with high SIRI. However, there were no significant differences between low SIRI group and high SIRI group by MPG.

Association of Pathological TNM Stage and SIRI in Patients with Breast Cancer

According to univariate and multivariate analyses, pathological TNM stage was the significant prognostic factor. Hence, in order to further to study the prognostic efficiency of SIRI, the SIRI was analyzed by pathological TNM stage. The SIRI with different pathological TNM stage was analyzed by the log-rank test. The mean DFS and OS time for patients with low SIRI were longer than in those with high SIRI. However, there were no

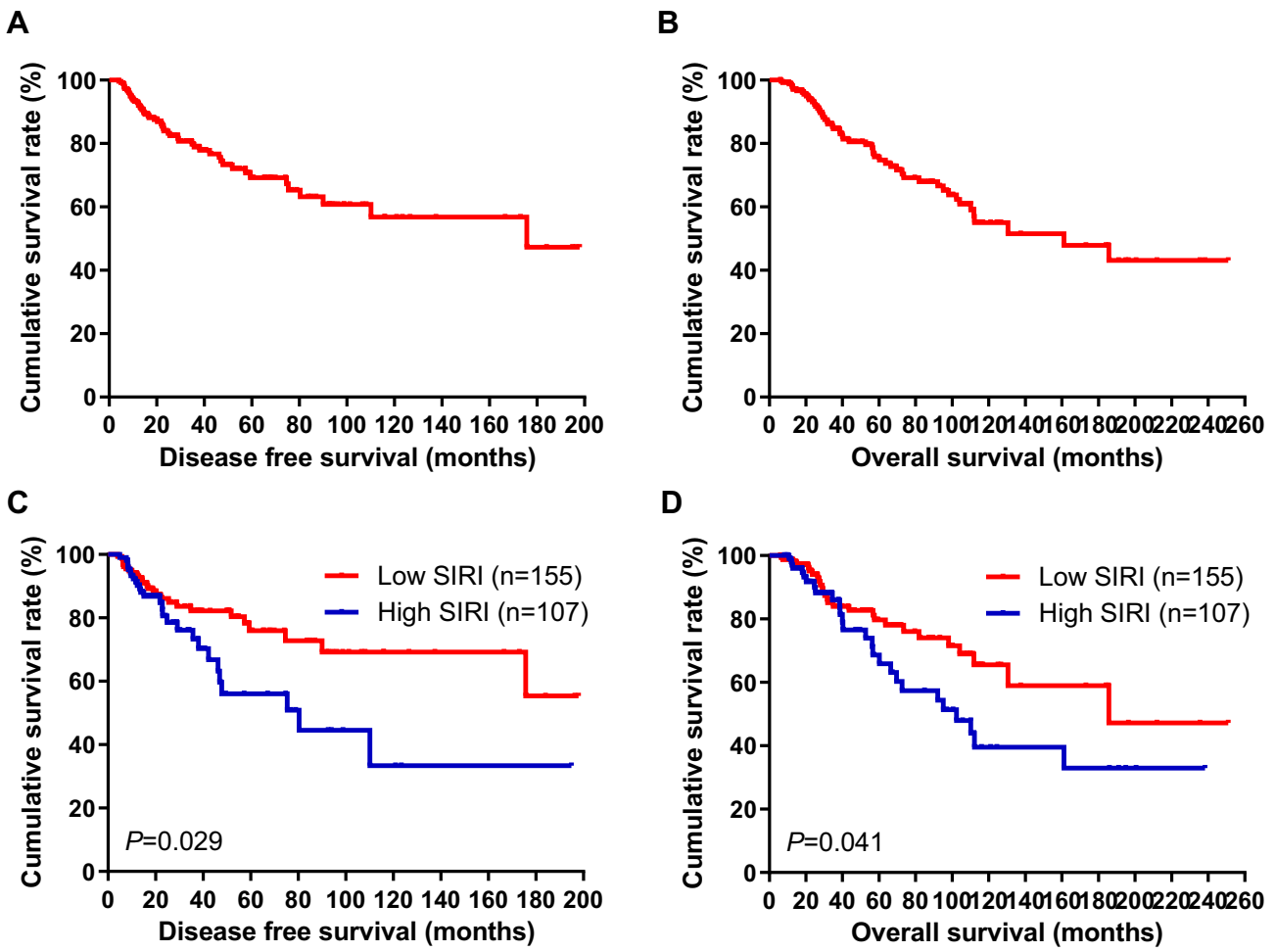

Figure 1 DFS and OS of patients with breast cancer. (**A**) Kaplan–Meier analysis of DFS of all patients with breast cancer. (**B**) Kaplan–Meier analysis of OS of all patients with breast cancer. (**C**) Kaplan–Meier analysis of DFS for the SIRI of all patients with breast cancer. (**D**) Kaplan–Meier analysis of OS for the SIRI of all patients with breast cancer. SIRI is a novel systemic inflammation response index (SIRI=N×M/L), which is based on neutrophil (N), monocyte (M), and lymphocyte (L) counts.

significant differences between low SIRI group and high SIRI group by pathological TNM stage.

Correlation Between Ki-67 Status and SIRI in Patients with Breast Cancer

The results indicated that Ki-67 status in both core needle biopsy and postoperative pathology IHC was the significant prognostic factor. In core needle biopsy, the mean DFS and OS time for patients with low SIRI by the log-rank test were longer than in those with high SIRI in Ki-67 negative (χ^2=3.195, P=0.074 and χ^2=1.393, P=0.238, respectively). Moreover, the mean DFS and OS time for patients with low SIRI by the log-rank test were longer than in those with high SIRI in Ki-67 positive (χ^2=1.730, P=0.189 and χ^2=5.028, P=0.025, respectively). In postoperative pathology IHC, the mean DFS and OS time for

Table 7 3-, 5-, and 10-Year DFS and OS Rates of Breast Cancer Patients

Parameters	Cases (n)	DFS			OS		
		3 Years (%)	5 Years (%)	10 Years (%)	3 Years (%)	5 Years (%)	10 Years (%)
Total	262	83/262 (31.7%)	45/262 (17.2%)	12/262 (4.6%)	112/262 (42.7%)	74/262 (28.2%)	20/262 (7.6%)
Low SIRI	155	56/155 (36.1%)	32/155 (20.6%)	9/155 (5.8%)	72/155 (46.5%)	48/155 (31.0%)	13/155 (8.4%)
High SIRI	107	27/107 (25.2%)	13/107 (12.1%)	3/107 (2.8%)	40/107 (37.2%)	26/107 (24.3%)	7/107 (6.5%)
χ^2		3.472	3.212	1.306	2.127	1.389	0.306
P value		0.062	0.073	0.253	0.144	0.239	0.58

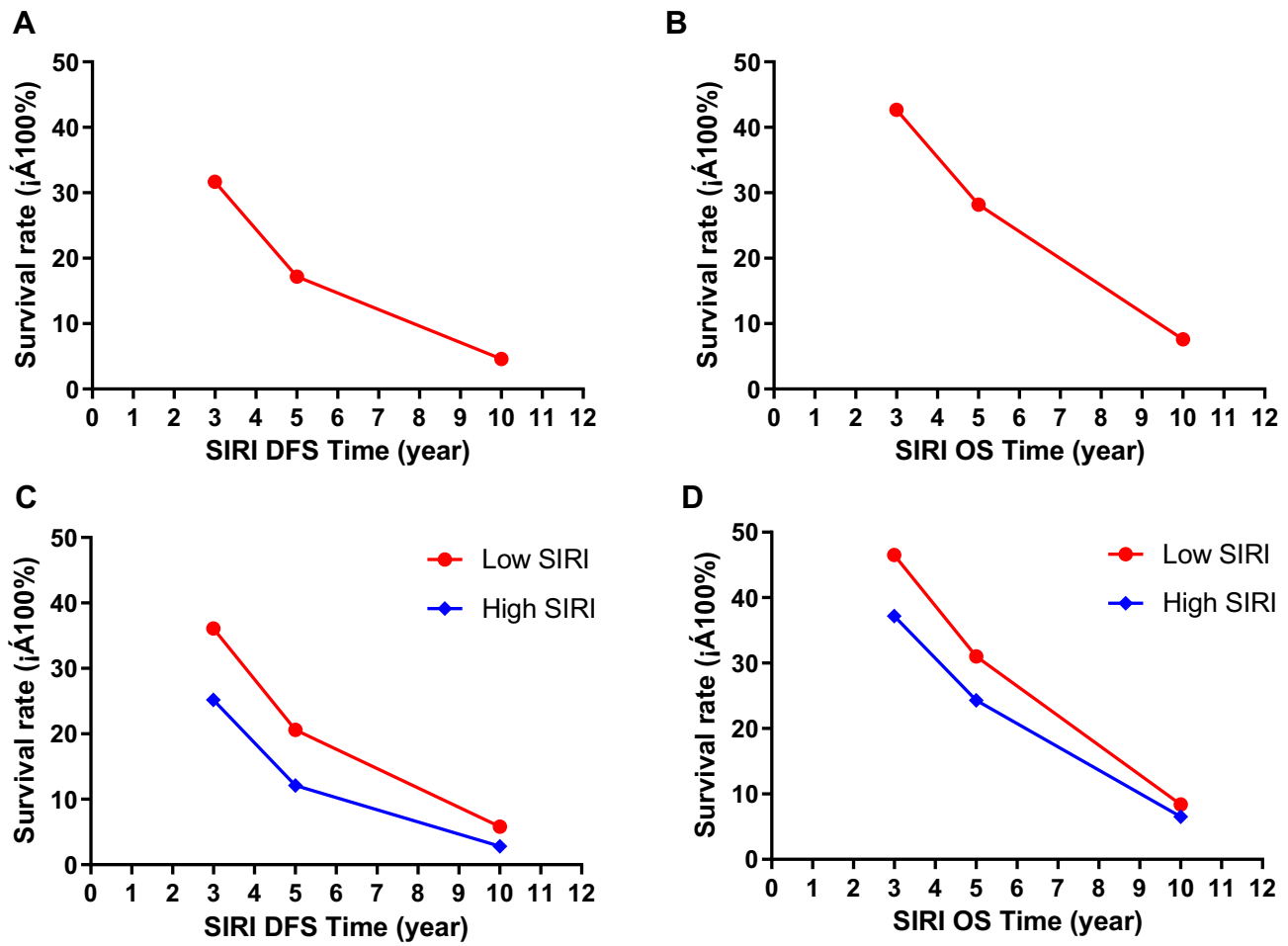

Figure 2 The 3-, 5-, and 10-year rates of DFS and OS in patients with breast cancer. (**A**) The 3-, 5-, and 10-year rates of DFS in all patients with breast cancer. (**B**) The 3-, 5-, and 10-year rates of OS in all patients with breast cancer. (**C**) The 3-, 5-, and 10-year rates of DFS in all patients by SIRI with breast cancer. (**D**) The 3-, 5-, and 10-year rates of OS in all patients by SIRI with breast cancer.

patients with low SIRI by the Log-rank test were longer than in those with high SIRI in Ki-67 negative (χ^2=5.451, P=0.020 and χ^2=3.360, P=0.067, respectively). And the mean DFS and OS time for patients with low SIRI by the log-rank test were longer than in those with high SIRI in Ki-67 positive (χ^2=0.564, P=0.453 and χ^2=2.088, P=0.149, respectively).

Association of Neural Invasion and SIRI in Patients with Breast Cancer

The neural invasion was the significant prognostic factor by univariate and multivariate analyses in Table 6. Consequently, in order to further determine the prognostic efficiency of SIRI, the SIRI was analyzed by neural invasion. The results proved that the mean DFS and OS time for patients with low SIRI by the log-rank test were longer than in those with high SIRI in patients without lymph vessel invasion (χ^2=8.290, P=0.004 and χ^2=7.209, P=0.007, respectively). And the results show that the mean DFS and OS time for patients with low SIRI by the log-rank test were longer than in those with high SIRI in patients with neural invasion (χ^2=0.051, P=0.822 and χ^2=0.016, P=0.901, respectively).

Discussion

Breast cancer is the most common women cancer and is the major leading cause of cancer-related death all over the world.[24] Comprehensive therapies, including operation, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy, have improved survival time and quality of life for these breast cancer patients.[25] The neoadjuvant treatment can turn inoperable tumors into operable tumors or reduce tumor stage for more frequent conservative breast surgery. Moreover, NACT has become the standard treatment for locally advanced breast cancer, and the

quality of life and clinical outcomes for these patients have largely improved.[26] Therefore, it is of importance to search accurate indicator for choosing the optimal treatment regimen and improving clinical outcomes.

Various studies have shown that tumors are associated to systemic inflammation.[27–29] However, the mechanisms between tumors and inflammation reaction are yet ambiguous and poorly understood. Some studies have suggested that systemic inflammatory cells, such as neutrophils, monocytes, platelets, and lymphocytes, are linked to prognosis of many malignancies. Neutrophils restrain inflammatory factors, which include matrix metalloproteinase-9 (MMP-9), nuclear factor-κB (NF-kB) and vascular endothelial growth factor (VEGF), to influence the proliferation, development, progression, and metastasis.[30–32] Monocytes have been proved that it can promote tumor angiogenesis, inflammatory response and metastases, and releases some cytokines and chemokines, such as oncostatin-M and VEGF, to inhibit the immune system.[33,34] Platelets are an indicator of tumor activity and angiogenesis, and are associated with tumor growth, invasion, and metastasis by releasing VEGF-integrin cooperative signaling.[35,36] Moreover, lymphocytes are an important component of anticancer immunity and immune surveillance and are associated to prevent the tumor growth and progression.[37,38]

Some studies have shown that inflammatory markers and immune-based prognostic indexes were used to evaluate the prognosis of breast cancer, such as NLR, d-NLR, MLR/LMR, and PLR.[39–41] However, these inflammatory markers were associated with poor prognosis in breast cancer patients, and the potential mechanisms were not yet clear. The SIRI based on three inflammatory cells, such as neutrophil, monocyte, and lymphocyte, and can fully evaluate the balance between host immune and inflammatory condition. Nevertheless, the prognostic value of the preoperative SIRI in breast cancer patients received NACT is still unclear. In the present study, the SIRI was the significant prognostic factor by univariate and multivariate analyses.

In our study, the clinicopathologic and demographic characteristics of all enrolled patients were analyzed. The optimal cutoff value of the SIRI was 0.85×10^9/L by ROC analysis. The results shown that low SIRI was significantly associated with menopause, US-LNM and total lymph nodes. And the low SIRI was in connection with W, Hb, N, L, M, NLR, MLR, and PLR. Moreover, the low SIRI was also significantly associated with NACT. Meanwhile, the common toxicities after NACT were hematologic and gastrointestinal reaction, and the SIRI had no significance on toxicities of all enrolled patients, excepted diarrhea.

On the basis of univariate and multivariate Cox regression analyses, the clinical T stage, Miller and Payne grade, pathological T stage, pathological TNM stage, core needle biopsy (molecular subtype, ER status, Ki-67 status), postoperative pathology IHC (Ki-67 status), neural invasion, PLR, SIRI, postoperative chemotherapy, postoperative radiotherapy were the independent factors. We also found that patients with low SIRI had better prognosis and survived longer than those with high SIRI. Meanwhile, patients with low SIRI had higher 3-, 5-, and 10-year rates. Moreover, our results indicated that Ki-67 status was the significant prognostic factor, and patients with low SIRI had better prognosis and survived longer than those with high SIRI. The results also indicated that patients with low SIRI had better prognosis than those with high SIRI in patients with neural invasion.

Several limitations are presented in this study. Firstly, this is a retrospective single-center study. And multicenter study and more patients should be enrolled. Secondly, the cases are not more by subgroup analysis, and influence the outcomes. Thirdly, the SIRI value of different studies may be different by different cutoff points or endpoints. Therefore, more and better designed randomized controlled trials should be studied to support our findings, and further to study the SIRI and try to combine with other biomarkers to access the clinical outcome.

Conclusion

SIRI is the significant prognostic factor for breast cancer patients and can effectively predict the survival and prognosis for breast cancer. Taking into consideration the high incidence of breast cancer and the unbalanced distribution of medical conditions in China, the repeatable, convenient and non-invasive biomarkers should be used in the prevention and treatment of breast cancer. A comprehensive understanding of hematological parameters is of great importance for finding new targets for subjective treatment and doctors to implement effective treatment in clinical practice.

Data Sharing Statement

The material supporting the conclusion of this article has been included within the article.

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Disclosure

The authors declare that they have no competing interests.

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