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ORIGINAL RESEARCH

Pretreatment System Inflammation Response Index (SIRI) is a Valuable Marker for Evaluating the Efficacy of Neoadjuvant Therapy in Breast Cancer Patients

Yunuo Zhang[1], Jingna Wu[1], Weiming Chen[2], Xinhong Liang[3]

[1]Department of Medical Oncology, Meizhou People's Hospital, Meizhou, People's Republic of China; [2]Data Center, Meizhou People's Hospital, Meizhou, People's Republic of China; [3]Radiology Department, Meizhou People's Hospital, Meizhou, People's Republic of China

Correspondence: Xinhong Liang, Radiology Department, Meizhou People's Hospital, Meizhou, People's Republic of China, Email xinhong1988liang@163.com

Objective: Immune inflammatory response are involved in the development and progression of cancer. However, there are still inconsistent research results on the value of peripheral blood inflammatory indicators for evaluating the efficacy of neoadjuvant therapy (NAT) in breast cancer. The purpose of this study was to investigate the relationship between pretreatment systemic immune inflammatory response index (SII), systemic inflammatory response index (SIRI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and NAT efficacy in breast cancer.

Methods: A retrospective analysis was performed on 326 patients with breast cancer who underwent NAT at Meizhou People's Hospital from November 2017 to October 2023. Clinicopathological data was collected, including gender, age, body mass index (BMI), hypertension, diabetes mellitus, family history of cancer, TNM stage, and the molecular subtypes of breast cancer. The optimal cutoff values of SII, SIRI, NLR, PLR, and LMR were calculated using receiver operating characteristic (ROC) curve, and the relationship between inflammatory indexes and other clinicopathological features and the efficacy of NAT was analyzed.

Results: In this study, 162 (49.7%) breast cancer patients did not respond to NAT and 164 (50.3%) patients responded to NAT. The levels of SII (p=0.002), SIRI (p<0.001), and NLR (p=0.006) in patients who responded to NAT were significantly higher than those in patients who did not. When the efficacy of NAT was considered as the endpoint of SII, SIRI, and NLR, the critical value of the SII, SIRI, and NLR was 572.53 (under the ROC curve (AUC)=0.598), 0.745 (AUC=0.630), and 2.325 (AUC=0.588), respectively. Logistic regression analysis showed that a high SIRI level (≥0.745/<0.745, OR: 2.447, 95% CI: 1.375–4.357, p=0.002) was an independent factor associated with the efficacy of NAT in breast cancer patients.

Conclusion: High SIRI levels (≥0.745) may be an independent factor associated with the efficacy of NAT in patients with breast cancer.

Keywords: breast cancer, neoadjuvant therapy, systemic immune inflammatory response index, efficacy

Introduction

Breast cancer is a malignant tumor that occurs in the epithelial tissue of the breast, the great majority of which is women.[1] Breast cancer is a common malignant tumor in women, statistics in 2020 show that the global incidence of female breast cancer is 11.7%, with approximately 2.26 million new cases of breast cancer worldwide every year. Breast cancer has the highest incidence of malignant tumors in the world.[2] Breast cancer is classified into four molecular subgroups, luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) enriched (HER2+), and triple negative breast cancer (TNBC), based on the expression of hormone receptors (HR) (including estrogen receptor (ER) and progesterone receptor (PR)), HER2, and Ki67 (a proliferation index marker) in the patient's cancer tissue.[3] Luminal A subtype breast cancer was defined as ER positive (ER+), PR≥20%, HER2 negative (HER2-), Ki67<20%. Luminal

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B-like (HER2-) breast cancer was ER+, HER2-, and Ki67≥20%, PR<20%. Luminal B-like (HER2+) breast cancer was defined as ER+, HER2+, any Ki67 level and PR level. Luminal B-like (HER2-) and Luminal B-like (HER2+) are combined to form the Luminal B type. HER2+ subtype breast cancer was defined as HER2+, ER-, and PR-, and TNBC is defined as ER-, PR-, and HER2-.[4,5]

Neoadjuvant therapy (NAT) is a preoperative systemic treatment for breast cancer patients without distant metastases and includes neoadjuvant endocrine therapy, neoadjuvant chemotherapy, and neoadjuvant targeted therapy.[6,7] The purpose of NAT is to reduce the tumor size, increase the chance of surgical resection, and increase the possibility of breast preservation surgery.[8,9] In addition, information about tumor sensitivity to drugs can be obtained during NAT, so as to guide subsequent therapy, and improve patient prognosis.[10] Assessment of response to NAT is critical for predicting survival and guiding subsequent treatment. The response to NAT of breast cancer patients includes both clinical and pathological responses. Evaluation of clinical response was mainly performed to evaluate the maximum change in tumor diameter before and after NAT.[11] The assessment of pathological response was mainly based on the reduction of tumor cells between the pre-NAT puncture biopsy tissue and the surgical specimen.[12,13] Imaging and pathological methods are of great value in evaluating the efficacy of NAT. However, at the same time, the value of other predictive biomarkers in evaluating the efficacy of NAT needs to be continuously explored.

The inflammatory response in the body is closely associated with the occurrence of tumors.[14] Inflammation plays an important role in the occurrence, progression, metastasis, and drug resistance of cancer, and the changes in tumor-related inflammatory cells reflect the degree of the tumor inflammatory response.[15] Peripheral blood inflammatory parameters are correlated with the prognosis of cancer.[16] The neutrophil-to-lymphocyte ratio (NLR),[17–20] platelet-to-lymphocyte ratio (PLR),[17,19–22] lymphocyte-monocyte ratio (LMR),[23] and systemic immune severity index (SII)[17] were potential markers for predicting pathologic complete response (pCR) in breast cancer patients receiving NAT. However, these studies differ in whether high or low levels of the relevant indicators have a predictive value. In addition, some studies have shown that the NLR and PLR are not predictive markers of the efficacy of NAT in breast cancer.[24–26] Therefore, more researches are needed on peripheral blood inflammatory indicators to evaluate the efficacy of NAT in breast cancer.

Materials and Methods

Subjects

A total of 326 breast cancer patients were collected from November 2017 to October 2023 after receiving NAT and undergoing surgical treatment at Meizhou People's Hospital. All the patients were pathologically diagnosed with breast cancer. The exclusion criteria were as follows: (1) receiving other anti-tumor therapy before NAT; (2) had other malignant tumors in the past; and (3) there were diseases affecting inflammatory indicators such as trauma, surgery, infection, and immune diseases before NAT. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

NAT Regimens and Curative Effect Observation

Patients with luminal A, luminal B-like (HER2-), and TNBC were treated with the TEC regimen (docetaxel (T) 75mg/m^2 or albuminpaclitaxel 260mg/m^2 + epirubicin (E) 80mg/m^2 + cyclophosphamide (C) 500mg/m^2). Patients with luminal B-like (HER2+) and HER2+ subtype breast cancer were treated with the TCbHP/TCbH regimen (docetaxel (T) 75mg/m^2 or albuminpaclitaxel 260mg/m^2 + carboplatin (Cb) [area under curve (AUC) of 6] + trastuzumab (H) (initial dose 8mg/kg, followed by 6mg/kg) + pertuzumab (initial dose 840mg, followed by 420mg)). Twenty-one days is a treatment cycle. Patients were evaluated for NAT efficacy after 6 cycles of treatment, followed by surgery.

The efficacy of all patients was evaluated after NAT, and the size of the lesion, axillary lymph nodes, and distant metastases were observed using imaging. The patients with Miller-Payne grade V and no invasive tumor cells found at the primary tumor site were classified as effective, and those with grade I to IV were classified as non-effective.

Data Collection

Clinicopathological features of the patients were collected, including gender, age, body mass index (BMI), hypertension, diabetes mellitus, family history of cancer, TNM stage, and molecular subtypes of breast cancer. 2mL peripheral blood was collected through venipuncture of an antecubital vein with ethylenediamine tetraacetic acid (EDTA) as an anticoagulant at admission or 2–3 days before treatment, and routine blood test was detected using a Sysmex XE-2100 hematology analyzer (Sysmex Corporation, Japan).

Data Processing and Statistical Analysis

The inflammatory indices SII, SIRI, NLR, PLR and LMR were calculated according to the following formulas:

SII=platelet×neutrophil/lymphocyte

SIRI=monocyte×neutrophil/lymphocyte

NLR=neutrophil/lymphocyte

PLR=platelet/lymphocyte

LMR= lymphocyte/monocyte

Continuous variables conforming to normal distribution were described as mean±standard deviation, and continuous variables not conforming to the normal distribution were described as median (25th percentile, 75th percentile). The count data were expressed as the number of cases (%). Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values of the SII, SIRI, NLR, PLR, and LMR to distinguish the efficacy and inefficacy of NAT. The association between the efficacy of NAT and the clinicopathological features of breast cancer patients was evaluated using *Chi*-square test or Fisher's exact test. The association between the efficacy of NAT and inflammatory markers was evaluated using the nonparametric test. Logistic regression analysis was used to evaluate the relationship between these inflammatory markers, clinicopathological features and efficacy of NAT in breast cancer patients. $p<0.05$ was set as statistically significant. SPSS statistical software version 26.0 (IBM Inc., USA) was used for data analysis.

Results

Clinicopathological Features of Breast Cancer Patients

Of the 326 patients with breast cancer included in this study, all were female. There were 143 cases (43.9%) with aged <55 years old and 183 cases (56.1%) with aged ≥55 years old. There were 14 cases (4.3%) with BMI <18.5 kg/m^2 and 165 cases (50.6%) with BMI≥24.0 kg/m^2. There were 43 (13.2%), 27 (8.3%), and 24 (7.4%) patients had hypertension, diabetes mellitus, and family history of cancer, respectively. There were 60 patients in stage I-II and 266 patients in stage III-IV. The number of luminal A, luminal B, HER2+, and TNBC patients was 15 (4.6%), 180 (55.2%), 75 (23.0%), and 56 (17.2%), respectively. The levels of SII, SIRI, NLR, PLR, and LMR in these breast cancer patients were 609.83 (424.31, 877.56), 0.86 (0.60, 1.27), 2.42 (1.79, 3.32), 154.73 (115.50, 197.17), and 4.34 (3.24, 5.92), respectively (Table 1).

Comparison of Clinicopathological Features Among Breast Cancer Patients with or Without Effective After NAT

In this study, 162 (49.7%) breast cancer patients did not respond to NAT and 164 (50.3%) patients responded to NAT. The proportion of overweight (BMI≥24.0 kg/m^2) in patients who responded to NAT was lower than that of patients who did not respond to NAT (42.1% vs 59.3%, $p=0.008$). The differences between the two groups in the proportion of patients with hypertension, diabetes mellitus, and family history of cancer, and the distribution of disease stages and molecular subtypes were not statistically significant (all $p>0.05$) (Table 2). The levels of SII ($p=0.002$), SIRI ($p<0.001$), and NLR ($p=0.006$) in patients responded to NAT were significantly higher than those in patients who did not. The differences in PLR and LMR levels between the two groups were not statistically significant (all $p>0.05$) (Figure 1).

Table 1 The Clinicopathological Features of Breast Cancer Patients Receiving NAT

Clinicopathological Features	Breast Cancer Patients (n=326)
Gender	
Female, n (%)	326 (100.0%)
Age (Years)	
<50, n (%)	143 (43.9%)
≥50, n (%)	183 (56.1%)
BMI (kg/m^2)	
<18.5, n (%)	14 (4.3%)
18.5–23.9, n (%)	147 (45.1%)
≥24.0, n (%)	165 (50.6%)
Hypertension	
No, n (%)	283 (86.8%)
Yes, n (%)	43 (13.2%)
Diabetes mellitus	
No, n (%)	299 (91.7%)
Yes, n (%)	27 (8.3%)
Family history of cancer	
No, n (%)	302 (92.6%)
Yes, n (%)	24 (7.4%)
T-stage	
T1-T2, n (%)	166 (50.9%)
T3-T4, n (%)	160 (49.1%)
N-stage	
N0-N1, n (%)	137 (42.0%)
N2-N3, n (%)	189 (58.0%)
TNM stage	
I-II, n (%)	60 (18.4%)
III-IV, n (%)	266 (81.6%)
Molecular subtypes	
Luminal A, n (%)	15 (4.6%)
Luminal B, n (%)	180 (55.2%)
HER2+, n (%)	75 (23.0%)
TNBC, n (%)	56 (17.2%)
Inflammation index levels	
SII, median (P25, P75)	609.83 (424.31, 877.56)
SIRI, median (P25, P75)	0.86 (0.60, 1.27)
NLR, median (P25, P75)	2.42 (1.79, 3.32)
PLR, median (P25, P75)	154.73 (115.50, 197.17)
LMR, median (P25, P75)	4.34 (3.24, 5.92)

Abbreviations: HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; p25, 25th percentile; p75, 75th percentile.

Logistic Regression Analysis of Factors Associated with the Efficacy of NAT in Breast Cancer Patients

When the efficacy of NAT was considered as the endpoint of SII, SIRI, and NLR, the critical value of SII was 572.53 (sensitivity 64.6%, specificity 55.6%, area under the ROC curve (AUC)=0.598), the SIRI cutoff value was 0.745 (sensitivity 73.8%, specificity 50.0%, AUC=0.630), and the NLR cutoff value was 2.325 (sensitivity 64.0%, specificity 53.1%, AUC=0.588) by receiver operating characteristic (ROC) curve analysis (Figure 2).

Table 2 Comparison of Clinicopathological Features Among Breast Cancer Patients with or Without Effective After NAT

Clinicopathological Features	Neoadjuvant Therapy (NAT)		*p* Values
	Non-Effective (n=162)	Effective (n=164)	
Age (Years)			
<50, n (%)	66(40.7%)	77(47.0%)	0.267
≥50, n (%)	96(59.3%)	87(53.0%)	
BMI (kg/m^2)			
<18.5, n (%)	6(3.7%)	8(4.9%)	0.008
18.5–23.9, n (%)	60(37.0%)	87(53.0%)	
≥24.0, n (%)	96(59.3%)	69(42.1%)	
Hypertension			
No, n (%)	139(85.8%)	144(87.8%)	0.626
Yes, n (%)	23(14.2%)	20(12.2%)	
Diabetes mellitus			
No, n (%)	146(90.1%)	153(93.3%)	0.322
Yes, n (%)	16(9.9%)	11(6.7%)	
Family history of cancer			
No, n (%)	150(92.6%)	152(92.7%)	1.000
Yes, n (%)	12(7.4%)	12(7.3%)	
T-stage			
T1-T2, n (%)	82(50.6%)	84(51.2%)	1.000
T3-T4, n (%)	80(49.4%)	80(48.8%)	
N-stage			
N0-N1, n (%)	69(42.6%)	68(41.5%)	0.911
N2-N3, n (%)	93(57.4%)	96(58.5%)	
TNM stage			
I–II, n (%)	34(21.0%)	26(15.9%)	0.255
III–IV, n (%)	128(79.0%)	138(84.1%)	
Molecular subtypes			
Luminal A, n (%)	8(4.9%)	7(4.3%)	0.852
Luminal B, n (%)	92(56.8%)	88(53.7%)	
HER2+, n (%)	37(22.8%)	38(23.2%)	
TNBC, n (%)	25(15.4%)	31(18.9%)	
Inflammation index levels			
SII, median (P25, P75)	538.46 (366.29, 833.19)	694.29 (466.17, 915.95)	0.002
SIRI, median (P25, P75)	0.76 (0.46, 1.17)	0.98 (0.72, 1.41)	<0.001
NLR, median (P25, P75)	2.27 (1.71, 3.19)	2.51 (2.06, 3.53)	0.006
PLR, median (P25, P75)	152.61 (117.80, 185.01)	155.34 (115.10, 205.72)	0.339
LMR, median (P25, P75)	4.64 (3.25, 6.26)	4.20 (3.18, 5.58)	0.111

Abbreviations: HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; p25, 25th percentile; p75, 75th percentile.

Univariate logistic regression analysis showed that a high SII level (≥572.53/<572.53, odds ratio (OR): 2.284, 95% confidence interval (CI): 1.463–3.567, $p<0.001$), high SIRI level (≥0.745/<0.745, OR: 2.814, 95% CI: 1.768–4.478, $p<0.001$), and high NLR level (≥2.325/<2.325, OR: 2.014, 95% CI: 1.292–3.139, $p=0.002$) were significantly associated with NAT efficacy. Multivariate logistic regression analysis showed that a high SIRI level (≥0.745/<0.745, OR: 2.447, 95% CI: 1.375–4.357, $p=0.002$) was an independent factor associated with the efficacy of NAT in breast cancer (Table 3).

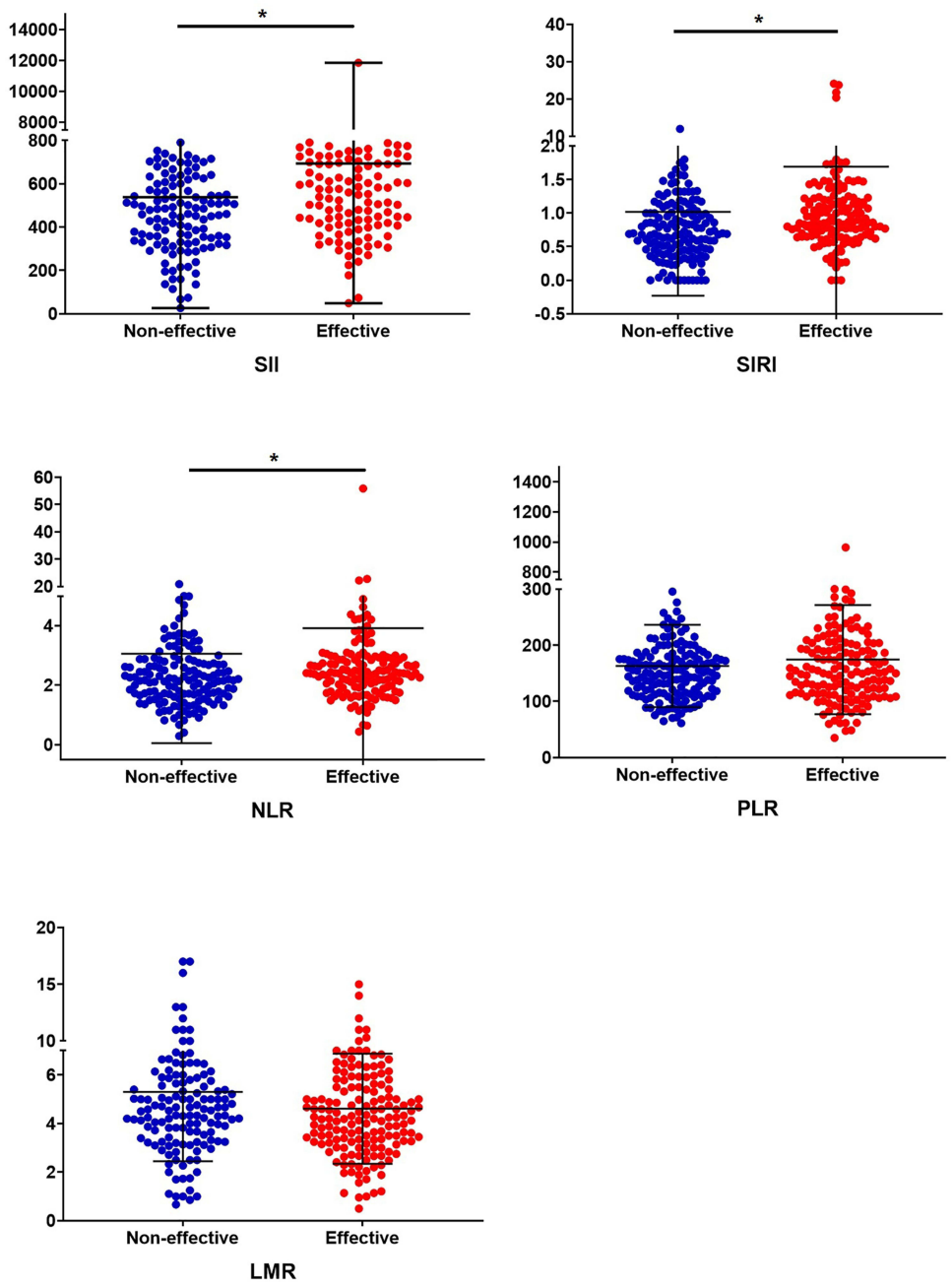

Figure 1 The levels of SII, SIRI, NLR, PLR, and LMR in patients with or without response to NAT. *, $p<0.05$.

Discussion

In this study, we determined the predictive value of the SII, SIRI, NLR, PLR, and LMR after NAT for breast cancer. We retrospectively collected the clinical medical records of 326 patients before NAT and determined the optimal cut-off value based on ROC curve analysis. We found that the SIRI was an independent correlation factor in predicting the effectiveness of NAT for breast cancer, specifically that patients with a high SIRI had a higher response rate.

Inflammation plays an important role in the occurrence, progression, metastasis, and drug resistance of cancer, and the changes in tumor-related inflammatory cells reflect the degree of the tumor inflammatory response.[15] Lymphocytes play an important role in host tumor immunity, especially in cytotoxicity, cell death, and inhibition of tumor cell growth and proliferation.[14] Lymphocytes in the peripheral blood can be recruited by chemokines released by the tumor

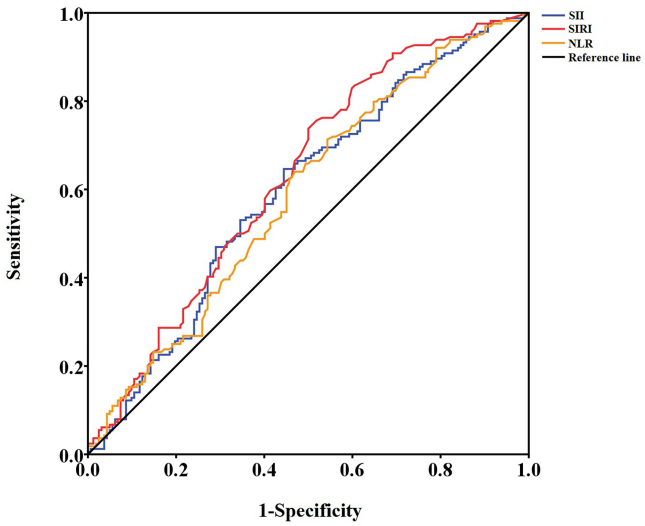

Figure 2 The ROC curve of SII, SIRI, and NLR based on the efficacy of NAT.

microenvironment (TME) to clear cancer cells by binding to ligands on the surface of the tumor cells.[27] A decrease in the number of lymphocytes is believed to be the cause of the body's low immune response to tumors, which leads to the proliferation and progression of tumors.[28] Tumor-associated macrophages (TAMs) are derived from monocytes in the peripheral blood. Chemokine ligand 2(CCL2) secreted by the TME, binds to chemokine receptor 2(CCR2) expressed on monocytes in the peripheral blood and recruits it to the TME.[29–31] Tumor-associated neutrophils (TANs) are derived from peripheral neutrophils that are recruited into tumor tissues by CXCR2 ligands such as CXCL1, 2, and 5 and play an important inflammatory role.[32] TANs and TAMs have been shown to accelerate tumor progression by generating growth factors and cytokines that promote tumor angiogenesis and generate anti-immune responses.[33–36] Thus, the immune response to cancer is derived from lymphocytes, and high levels of TAMs and TANs from monocytes and neutrophils are significantly associated with tumor aggressiveness and prognosis. Combined with these parameters, the SIRI can effectively reflect the immune state of the human body.

Kim et al found that the baseline SIRI and SIRI changes after NAT could serve as potential biomarkers for predicting breast cancer survival outcomes.[37] Jiang et al found that pre-treatment SIRI is a valuable prognostic indicator for patients

Table 3 Logistic Regression Analysis of Factors Associated with the Efficacy of NAT in Breast Cancer Patients

Variables	Univariate		Multivariate	
	OR (95% CI)	*p* Values	OR (95% CI)	*p* Values
Age (<50/≥50, years old)	1.287 (0.830–1.996)	0.259	0.925 (0.564–1.515)	0.755
BMI (kg/m^2)				
18.5–23.9	1.000 (reference)	–	1.000 (reference)	–
<18.5	0.920 (0.304–2.786)	0.882	0.928 (0.287–3.004)	0.901
≥24.0	0.496 (0.316–0.779)	0.002	0.436 (0.264–0.720)	0.001
Hypertension (No/Yes)	1.191 (0.626–2.266)	0.594	1.011 (0.490–2.084)	0.977
Diabetes mellitus (No/Yes)	1.524 (0.685–3.394)	0.302	1.137 (0.467–2.768)	0.777
Family history of cancer (No/Yes)	1.013 (0.441–2.327)	0.975	0.866 (0.351–2.135)	0.754
TNM stage (I-II/III-IV)	0.709 (0.403–1.247)	0.233	0.695 (0.380–1.272)	0.238
SII (≥572.53/<572.53)	2.284 (1.463–3.567)	<0.001	1.472 (0.803–2.699)	0.211
SIRI (≥0.745/<0.745)	2.814 (1.768–4.478)	<0.001	2.447 (1.375–4.357)	0.002
NLR (≥2.325/<2.325)	2.014 (1.292–3.139)	0.002	1.125 (0.613–2.062)	0.704

Abbreviations: OR, odds ratio; CI, confidence interval.

with breast malignancies treated with NAT.[38] Hiroki Kusama et al found that low NLR (<2.6) and low PLR (<180) were associated with pathologic complete response (pCR) of NAT response in TNBC.[21] Yang et al found that a low NLR (<2.46), low PLR (<118.78), and low SII (<403.20) were associated with pCR of the NAT response in breast cancer.[17] LMR (>6.2) was related to the pCR rates of breast cancer patients receiving NAT.[23] Low PLR (<181.7) and NLR (<2.35) before NAT are biomarkers for predicting pCR to NAT in patients with breast cancer.[18] TNBC patients with a low PLR (<145.71) and NLR (<2.74) values had a high pCR rate.[19] Cuello-López J suggested that breast cancer patients with a low PLR (<150) achieved a higher pCR after NAT.[39] However, other studies have reported contradictory results. Patients with high NLR (>2.464) and PLR (>106.3) achieved a significantly higher rate of pCR than those with low NLR (≤2.464) and PLR (≤106.3) levels.[22] A low LMR (<6.1) was considered a valuable predictor of the efficacy of NAC in breast cancer patients.[40] In addition, Wataru Goto et al found that there was no significant correlation between the LMR and pCR.[41] These studies differ in whether high or low levels of the relevant indicators have a predictive value. It may be related to the different sample sizes and chemotherapy regimens included in different studies. Secondly, some factors will affect the level of peripheral blood inflammatory indicators, such as acute inflammation, chronic infection, psychological changes, and lifestyle changes. Thirdly, the involvement of inflammatory cells in tumor progression is a dynamic process, and the level of peripheral inflammation in the above studies was mostly at a certain point before NAT, which could not fully reflect the level of inflammatory cells in the whole process. Thus, multicenter studies with larger sample sizes are required to elucidate this relationship.

SIRI has the advantages of high accessibility, an almost noninvasive, low cost, and good repeatability. Similar to classical tumor markers, SIRI can change with the changes in the tumor load and immune-inflammatory response status of patients, and this dynamic change can accurately reflect the trend of tumor progression and treatment effect. Therefore, SIRI is likely to be a good indicator and tool for monitoring systemic immune inflammatory response and predicting changes in cancer patients' characteristics. Huang et al found that SIRI can be used as a potential biomarker to predict survival outcomes after NAT therapy (AC/EC→TH (doxorubicin/epirubicin and cyclophosphamide, followed by docetaxel), AC/EC (doxorubicin/epirubicin and cyclophosphamide), TAC/TEC (docetaxel, doxorubicin/epirubicin and cyclophosphamide) chemotherapy regimens) for breast cancer.[37] In this study, TEC regimen was used for patients with luminal A, luminal B-like (HER2-) and TNBC, and TCbHP/TCbH regimen was used for HER2+ subtype breast cancer patients. It illustrates the potential value of SIRI in evaluating the efficacy of multiple chemotherapy regimens in NAT for breast cancer patients.

This study is one of the few to examine the relationship between levels of peripheral blood immunoinflammatory marker levels and NAT effectiveness in patients with breast cancer. This study still has the following limitations: (1) it was a single-center retrospective study, and the study design may have lead to bias and incompleteness in data interpretation. (2) It did not examine the relationship between the changes in peripheral blood inflammatory markers before and after NAT and the effectiveness of NAT in breast cancer patients. (3) The number of patients included in this study was small; therefore, the number of different molecular subgroups was small, and the expression differences of inflammatory indicators among different molecular subtypes were not studied.

Conclusions

In conclusion, the results of this study indicate that a high SIRI level (≥0.745) may be an independent factor associated with NAT efficacy in breast cancer patients. A study on the relationship between peripheral blood biomarkers and the efficacy of NAT can predict the effectiveness of NAT and provide a valuable reference for the formulation of treatment plans for breast cancer patients.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital. All participants signed informed consent in accordance with the Declaration of Helsinki.

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Author Contributions

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

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Disclosure

The authors declare that they have no competing interests.

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