Original Article

Association between the systemic immune-inflammation index and the efficacy of neoadjuvant chemotherapy, prognosis in HER2 positive breast cancer—a retrospective cohort study

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Background: The prognosis of patients who can achieve a complete response after neoadjuvant chemotherapy could be significantly improved. Thus, accurately predicting the efficacy of neoadjuvant chemotherapy is of great clinical significance. Currently, previous indicators such as neutrophil to lymphocyte ratio was poor in predicting the efficacy and prognosis of neoadjuvant chemotherapy in human epidermal growth factor receptor 2 (HER2) positive breast cancer patients.

Methods: The data of 172 HER2 positive breast cancer patients admitted to the Nuclear 215 Hospital of Shaanxi Province from January 2015 to January 2017 were retrospectively collected. After neoadjuvant chemotherapy, the patients were divided into the complete response group (n=70) and the non-complete response group (n=102). The clinical characteristics and systemic immune-inflammation index (SII) levels of the two groups were compared. The patients were followed-up for 5 years post-surgery to observe whether recurrence or metastasis occurred after the operation by clinic visit combined with telephone calls.

Results: The SII of the complete response group was significantly lower than that of the non-complete response group (587.43±175.97 *vs.* 821.82±231.58; P=0.000). The SII was valuable in predicting which HER2 positive breast cancer patients would fail to achieve a pathological complete response, and the area under the curve (AUC) was 0.773 [95% confidence interval (CI): 0.705–0.804; P=0.000]. A SII >755.10 was an adverse factor for HER2 positive breast cancer patients achieving a pathological complete response after neoadjuvant chemotherapy [P=0.000; relative risk (RR): 0.172 (95% CI: 0.082–0.358)]. The SII level was valuable in predicting recurrence within 5 years of surgery, and had an AUC of 0.828 (95% CI: 0.757–0.900; P=0.000). A SII >755.10 was a risk factor for recurrence within 5 years of surgery [P=0.001; RR: 4.945 (95% CI: 1.949–12.544)]. The SII level was valuable in predicting metastasis within 5 years of surgery, and had an AUC of 0.837 (95% CI: 0.756–0.917; P=0.000). A SII >755.10 was a risk factor for metastasis within 5 years of surgery [P=0.014, RR: 4.553 (95% CI: 1.362–15.220)].

Conclusions: The SII was associated with the prognosis and efficacy of neoadjuvant chemotherapy in HER2 positive breast cancer patients.

Keywords: Systemic immune-inflammation index (SII); breast cancer; human epidermal growth factor receptor 2 (HER2); neoadjuvant chemotherapy

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Introduction

Breast cancer is one of the most common malignant tumors in women, and its incidence is increasing year by year (1). According to recent cancer statistics, breast cancer has surpassed lung cancer as the most commonly diagnosed malignant tumor (1). Thus, the prevention of breast cancer needs to be prioritized. A medical and health system with an early detection and early diagnosis mode needs to be established so patients can receive early treatment.

Many studies have explored the factors related to the treatment and prognosis of breast cancer patients (2-5), and the prognosis of such patients needs to be improved. Scientists found that the overexpression of human epidermal growth factor receptor 2 (HER2) was directly related to the growth, invasion and prognosis of tumors (6). About 10–34% of invasive breast cancer patients have HER2 overexpression or HER2 gene amplification (6). HER2 molecules activate mitogen-activated protein kinase and other pathways by forming heterodimers with other receptors of the epidermal growth factor family and thus promote the occurrence and progression of tumors (7).

Neoadjuvant therapy has been widely used in clinical practice to treat breast cancer. Before the emergence of neoadjuvant targeted therapy and neoadjuvant endocrine therapy, neoadjuvant therapy mainly referred to neoadjuvant chemotherapy. Neoadjuvant chemotherapy has indeed benefited some patients. Notably, it has enabled some patients who could not receive breast-conserving therapy to undergo conservative treatment and enabled some patients once thought to be inoperable to undergo surgery. The concept of neoadjuvant therapy now extends to neoadjuvant chemotherapy, neoadjuvant targeted therapy, and neoadjuvant endocrine therapy.

The prognosis of patients who achieve a pathological complete response after neoadjuvant chemotherapy is significantly improved, while the prognosis of those who do not achieve a pathological complete response or even have progressive disease is relatively poor (8). Thus, accurate predictions of the efficacy of neoadjuvant chemotherapy before neoadjuvant chemotherapy could provide a theoretical basis for improving the prognosis of patients in the next step. At present, researchers have found that the expression level of related genes and positron emission tomography/computed tomography can be used to predict the efficacy of neoadjuvant chemotherapy in HER2 positive blast cancer patients, but there are some disadvantages such as high price (9-11).

In recent years, the systemic immune-inflammation index (SII) has become a popular indicator in research. An increased SII level indicates an increased level of inflammation and a decreased level of immune function in patients (12). Thus, an increase in the SII level is related to the poor prognosis of patients with malignant tumors. Moreover, one study showed that the SII was related to the long-term prognosis of triple-negative breast cancer patients (13). Studies on other types of breast cancer patients have also confirmed that an increase in the SII level was related to the poor prognosis of breast cancer patients (14-17). In patients receiving neoadjuvant chemotherapy, studies have also found that the SII was related to the overall survival rate and disease-free survival rate (18,19). In triple-negative breast cancer patients receiving neoadjuvant chemotherapy, Chinese scholars have reported that the SII level was related to the efficacy of neoadjuvant chemotherapy (20). Among HER2 positive breast cancer

Highlight box

Key findings

- The systemic immune-inflammation index (SII) was associated with the prognosis and efficacy of neoadjuvant chemotherapy in human epidermal growth factor receptor 2 (HER2) positive breast cancer patients.

What is known and what is new?

- An increased SII level is associated with a poor prognosis in patients with malignant tumors.
- This study sought to explore the relationship between the SII and neoadjuvant chemotherapy efficacy in HER2 positive breast cancer patients.

What is the implication, and what should change now?

- The SII could be used to predict the prognosis and efficacy of neoadjuvant chemotherapy in HER2 positive breast cancer patients. For patients with an increased SII before neoadjuvant chemotherapy, intensive treatment should be adopted, which may improve the prognosis of patients.

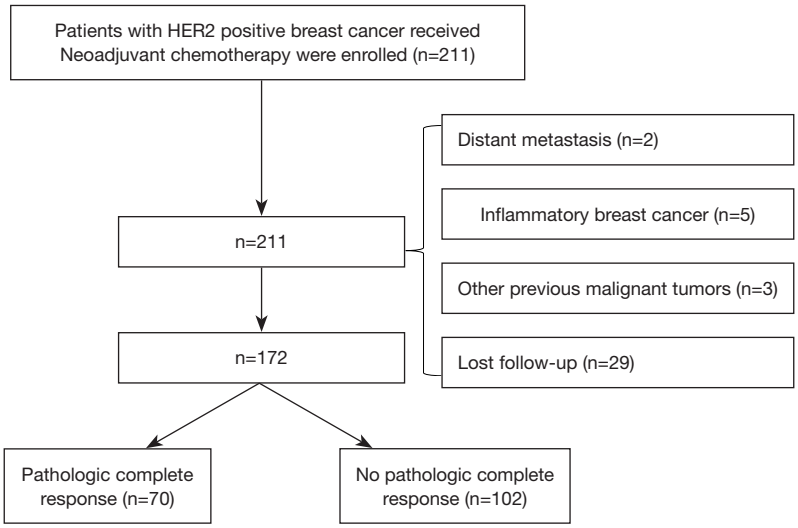

Figure 1 Inclusion process for the HER2 positive breast cancer patients receiving neoadjuvant chemotherapy. HER2, human epidermal growth factor receptor 2.

patients, a study has also shown that an increase in the SII level was related to a poor prognosis after adjuvant therapy (21). However, there is still a lack of research on the relationship between the SII and neoadjuvant chemotherapy in HER2 positive breast cancer patients; thus, we designed this study. We present this article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-55/rc).

Methods

General information

Sample size estimation: each variable needs to include at least 10 events, which has been widely accepted (also known as 10 events per variable) (22). The pathological complete response rate of HER2 positive breast cancer was about 60%, so the estimated sample size was more than 150 (23). This was a retrospective cohort study. The data of 172 HER2 positive breast cancer patients admitted to the Nuclear 215 Hospital of Shaanxi Province from January 2015 to January 2017 were retrospectively continuously collected. After neoadjuvant chemotherapy, the patients were divided into the complete response group (n=70) and the non-complete response group (n=102) based on whether or not they had achieved a pathological complete response (*Figure 1*).

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have HER2 positive (no special type) of invasive breast cancer with estrogen receptor and progesterone receptor negativity; (II) be a female aged 18–75 years; (III) have a primary tumor diameter >2 cm or axillary lymph node metastasis; (IV) have a Zubrod-Eastern Cooperative Oncology Group-World Health Organization performance status score of 0–1; (V) have received neoadjuvant chemotherapy combined with targeted therapy at the Nuclear 215 Hospital of Shanxi Nuclear Industry; and (VI) have available follow-up data. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had distant metastasis; (II) had inflammatory breast cancer; (III) had received anti-tumor therapy or radiotherapy for any malignant tumor in the past, excluding cured cervical carcinoma in situ, basal cell carcinoma, squamous cell carcinoma, and other malignant tumors; (IV) had also received a special treatment, such as neoadjuvant endocrine therapy; (V) had pregnancy-associated breast cancer; and/or (VI) had organ dysfunction in important organs, such as the heart, lung, liver and kidney.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Nuclear 215 Hospital of Shaanxi Province (No. 20220078). The requirement of individual consent for this retrospective analysis was waived.

Treatment

All the patients were treated with 4 cycles of Epirubicin + Cyclophosphamide and the following 4 cycles of Paclitaxel + Trastuzumab with 21 days as a cycle. The first 4 cycles used doxorubicin combined with cyclophosphamide, and the last 4 cycles used paclitaxel and trastuzumab. After the neoadjuvant chemotherapy, the patients received surgical treatment, and continued to use trastuzumab for 1 year after the surgery.

Follow-up

The follow-up was carried out in the form of outpatient appointments combined with telephone calls after the surgery. Breast ultrasound, chest computed tomography (CT), and abdominal CT were performed at least once every 6 months, and dynamic contrast-enhanced magnetic resonance imaging of the breast was performed once every 2 years. For patients in whom recurrence or metastasis was suspected, a bone scan or whole-body positron emission tomography-CT was performed.

Standard definitions

(I) HER2 positivity: before neoadjuvant chemotherapy, an ultrasound-guided biopsy was performed to obtain a breast cancer tissue sample and immunohistochemical staining was performed. According to the staining ratio and staining intensity of the HER2 protein on the cell membrane, the expression level of HER2 was defined as 0, 1+, 2+, 3+, where HER2 0 represents a negative staining result or the presence of staining on <10% of the tumor cells; HER2 1+ indicates that the light and barely visible cell staining intensity was displayed on >10% of the tumor cells; HER2 2+ indicates that the weak to moderate staining intensity of the intact cell membrane was displayed on 10–30% of the tumor cells; HER2 3+ indicates that the strong staining intensity of the intact membrane was displayed on >30% of the tumor cells. If HER2 3+ was defined as positive, for patients with HER2 2+, a fluorescence *in situ* hybridization test was performed. HER2 gene amplification was considered HER2 positive, otherwise it was considered negative. (II) Pathological complete response: a patient achieved a pathological complete response if no evidence of invasive breast cancer was found in the primary breast and lymph nodes in the metastatic region, or only carcinoma *in situ* was found. (III) SII: the following formula was used to calculate the SII: SII = (neutrophils percentage × platelets count)/lymphocytes percentage.

Study variables

The study variables were as follows: age at diagnosis, body mass index, lesion site, family history, diabetes, hypertension, hyperlipidemia, proliferation index of tumor cells (Ki-67), the SII, tumor size, lymph node metastasis, histological grade, number of lesions, recurrence and metastasis after surgery.

Statistical analysis

All the statistical analyses were performed using Statistical Package for the Social Science 26.0 (IBM, Chicago, USA). A 2-tailed P value <0.05 was considered statistically significant. In this study, the SII and other measurement data conformed to a normal distribution, and are expressed as the mean ± standard deviation, and the independent sample *t*-test was used to analyze differences between the two groups. The postoperative recurrence and other counting data are expressed as the number (percentage), and the chi-square test was used to analyze differences between the two groups. A receiver operating characteristic curve was used to analyze the value of the SII in predicting a pathological complete response after neoadjuvant chemotherapy. A multivariate logistic regression analysis was conducted to explore the risk factors of postoperative recurrence or metastasis in breast cancer. When the area under the curve is 0.7–0.9, it indicates that it has certain clinical significance. When the area under the curve is greater than 0.9, it indicates that the prediction accuracy is high.

Results

Comparison of the clinical characteristics of the two groups

The SII level of the complete response group was significantly lower than that of the non-complete response group (587.43±175.97 *vs.* 821.82±231.58; P=0.000). Additionally, the tumor size (4.68±1.53 *vs.* 5.45±1.59 cm; P=0.002), rate of lymph node metastasis (20.00% *vs.* 50.00%; P=0.000), 5-year recurrence rate (12.86% *vs.* 27.45%; P=0.022), and 5-year metastasis rate (5.71% *vs.* 15.69%; P=0.045) (*Table 1*) were significantly decreased in the complete response group compared to the non-complete response group.

Table 1 Comparison of the clinical characteristics of the two groups

Variables	Complete response group (n=70)	Non-complete response group (n=102)	t/χ^2 value	P value
Age at diagnosis (years)	46.33±16.83	47.30±14.88	0.400	0.689
Body mass index (kg/m^2)	23.59±3.70	24.37±3.94	1.323	0.188
Site of lesion			2.574	0.109
Left	27 (38.57)	52 (50.98)		
Right	43 (61.43)	50 (49.02)		
Family history	2 (2.86)	3 (2.94)	0.001	0.974
Diabetes	4 (5.71)	7 (6.86)	0.091	0.762
Hypertension	6 (8.57)	7 (6.86)	0.173	0.677
Hyperlipidemia	5 (7.14)	9 (8.82)	0.157	0.692
Surgery			0.062	0.803
Breast-conserving surgery	12 (17.14)	19 (18.63)		
Mastectomy	58 (82.86)	83 (81.37)		
Ki-67 (%)	41.31±22.83	44.18±24.36	0.777	0.439
SII	587.43±175.97	821.82±231.58	7.165	0.000
Tumor size (cm)	4.68±1.53	5.45±1.59	3.195	0.002
Lymph node metastasis	14 (20.00)	51 (50.00)	15.892	0.000
Histological grade			0.059	0.809
Grade II	33 (47.14)	50 (49.02)		
Grade III	37 (52.86)	52 (50.98)		
Number of lesions			0.157	0.692
Single lesion	65 (92.86)	93 (91.18)		
Multiple lesions	5 (7.14)	9 (8.82)		
5-year recurrence rate	9 (12.86)	28 (27.45)	5.236	0.022
5-year metastasis rate	4 (5.71)	16 (15.69)	4.017	0.045

Data are expressed as mean ± standard deviation or n (%). SII, systemic immune-inflammation index.

Value of the SII and tumor size in predicting no pathological complete response in the HER2 positive breast cancer patients after neoadjuvant chemotherapy

The SII level had some value in predicting which HER2 positive breast cancer patients would fail to achieve a pathological complete response after neoadjuvant chemotherapy. The area under the curve (AUC) was 0.773 [95% confidence interval (CI): 0.705–0.804; P=0.000]. The best diagnostic threshold was 755.10, the sensitivity was 0.618, and the specificity was 0.800. The tumor size had some value in predicting which HER2 positive breast cancer patients would fail to achieve a pathological complete response after neoadjuvant chemotherapy. The AUC was 0.639 (95% CI: 0.557–0.722; P=0.002). The best diagnostic threshold was 4.95 cm, the sensitivity was 0.598, and the specificity was 0.543 (*Figure 2*).

Related factors of the HER2 positive breast cancer patients who achieved a pathological complete response after neoadjuvant chemotherapy

A SII >755.10 and lymph node metastasis were adverse

factors for indicating which HER2 positive breast cancer patients would achieve a pathological complete response after neoadjuvant chemotherapy (P<0.05) (*Table 2*).

Correlation between the SII and postoperative recurrence within 5 years of surgery

The SII level had some value in predicting recurrence in 5 years after surgery, and had an AUC of 0.828 (95% CI: 0.757–0.900; P=0.000) (*Figure 3*). A SII >755.10 was a risk factor for recurrence within 5 years of surgery [P=0.001, relative risk (RR): 4.945 (95% CI: 1.949–12.544)] (*Table 3*).

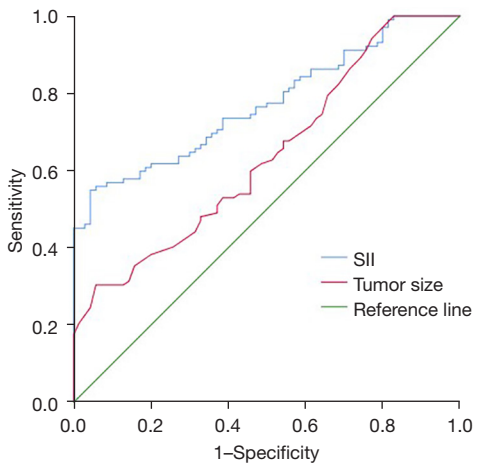

Figure 2 Value of the SII and tumor size in predicting no pathological complete response in the HER2 positive breast cancer patients after neoadjuvant chemotherapy. SII, systemic immune-inflammation index; HER2, human epidermal growth factor receptor 2.

Correlation between the SII and postoperative metastasis within 5 years of surgery

The SII level had some value in predicting metastasis within 5 years of surgery, and had an AUC of 0.837 (95% CI: 0.756–0.917; P=0.000) (*Figure 4*). A SII >755.10 was a risk factor for metastasis within 5 years of surgery (P=0.014, RR: 4.553 (95% CI: 1.362–15.220)] (*Table 4*).

Discussion

Neoadjuvant chemotherapy plays an important role in the diagnosis and treatment of breast cancer. The efficacy of neoadjuvant chemotherapy is directly related to the overall survival rate of patients after surgery. Thus, it is of

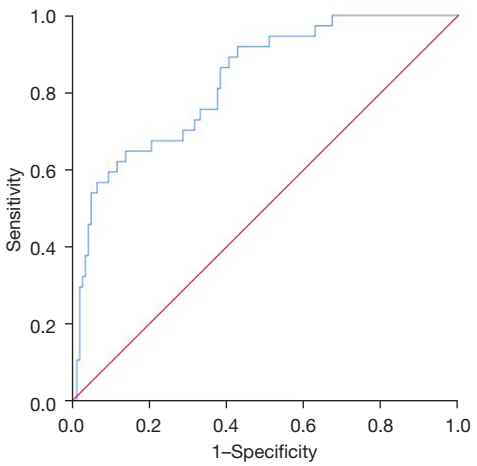

Figure 3 Value of the SII in predicting recurrence within 5 years of surgery. SII, systemic immune-inflammation index.

Table 2 Related factors of the HER2 positive breast cancer patients who achieved a pathological complete response after neoadjuvant chemotherapy

Variables	B	Standard error	Wald	P value	RR (95% CI)
A SII >755.10	–1.762	0.375	22.098	0.000	0.172 (0.082–0.358)
Tumor size >4.95 cm	–0.464	0.355	1.702	0.192	0.629 (0.313–1.262)
Lymph node metastasis	–1.222	0.387	9.997	0.002	0.295 (0.138–0.628)
Constant	5.918	1.067	30.785	0.000	371.704

HER2, human epidermal growth factor receptor 2; SII, systemic immune-inflammation index; RR, relative risk; CI, confidence interval.

Table 3 Risk factors of postoperative recurrence within 5 years of surgery

Variables	B	Standard error	Wald	P value	RR (95% CI)
A SII >755.10	1.598	0.475	11.326	0.001	4.945 (1.949–12.544)
Tumor size >4.95 cm	–0.018	0.461	0.001	0.970	0.983 (0.398–2.427)
Lymph node metastasis	2.668	0.508	27.617	0.000	14.404 (5.326–38.954)
Constant	–4.811	1.136	17.926	0.000	0.008

SII, systemic immune-inflammation index; RR, relative risk; CI, confidence interval.

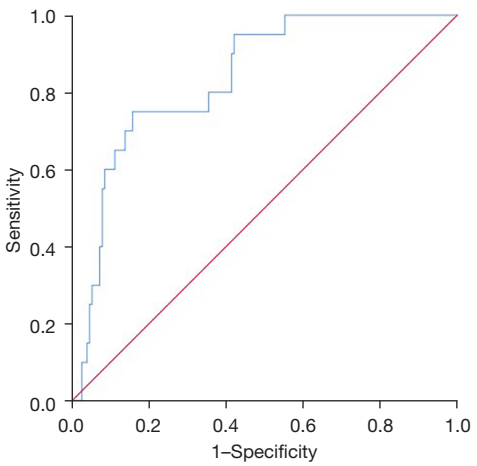

Figure 4 Value of the SII in predicting metastasis within 5 years of surgery. SII, systemic immune-inflammation index.

great significance to predict the efficacy of neoadjuvant chemotherapy.

This study explored the relationship between the SII level and neoadjuvant chemotherapy efficacy in HER2 positive breast cancer patients. We found that the SII level in patients with a pathological complete response after neoadjuvant chemotherapy was significantly reduced, and the SII level had a high value in predicting a pathological complete response after neoadjuvant chemotherapy, The multivariate regression analysis showed that a SII >755.10 was an adverse factor for HER2 positive breast cancer patients to achieve a pathological complete response after neoadjuvant chemotherapy ($P<0.05$). After 5 years of follow-up, we also found that an increase in the SII was a risk factor for recurrence and metastasis.

As stated above, the SII is calculated as follow: SII = (neutrophils percentage × platelets count)/lymphocytes percentage. An increase in the SII level indicates an increase in the level of neutrophils and platelets, and a decrease in the level of lymphocytes. Neutrophils represent the level of inflammation in patients. An increased level of inflammation is conducive to angiogenesis in the tumor microenvironment and the immune escape of tumors, which in turn lead to the rapid proliferation and metastasis of breast cancer cells (24). Tumor cells release active factors that promote the synthesis of platelets, accelerate the synthesis of platelets, and lead to a high platelet count, which is also a common laboratory manifestation of cancer (25).

Additionally, the compensatory enhancement of bone marrow hematopoietic function leads to the acceleration of platelet synthesis, which leads to the increase of platelets. Platelets promote the proliferation and metastasis of tumor cells and form a malignant cycle with the invasion and the metastasis of tumors (25). At present, research in breast cancer patients has confirmed that an increase in platelets is related to poor patient prognosis (26-28).

Lymphocytes are the main immune mechanism by which the body kills tumor cells. When the level of lymphocytes decreases, the ability of the body to kill malignant tumors decreases, which in turn leads to the immune escape of tumor cells, and ultimately a poor prognosis (29-31).

Based on the above-mentioned evidence, scholars synthesized these 3 indicators to form a new indicator; that is, the SII. At present, research has confirmed the role of the SII level in breast cancer patients, which is related to patient prognosis, and also has a clear correlation with the efficacy of neoadjuvant chemotherapy for triple-negative breast cancer patients (15-21). However, the relationship between the SII level and the efficacy of neoadjuvant chemotherapy in patients with HER2 positive breast cancer remains unclear. This study confirmed that the SII level affected the efficacy of neoadjuvant chemotherapy in patients with HER2 positive breast cancer.

Table 4 Risk factors for postoperative metastasis within 5 years of surgery

Variables	B	Standard error	Wald	P value	RR (95% CI)
A SII >755.10	1.516	0.616	6.062	0.014	4.553 (1.362–15.220)
Tumor size >4.95 cm	0.283	0.558	0.258	0.612	1.328 (0.445–3.964)
Lymph node metastasis	2.826	0.775	13.306	0.000	16.884 (3.698–77.091)
Constant	–4.296	1.400	9.414	0.002	0.014

SII, systemic immune-inflammation index; RR, relative risk; CI, confidence interval.

Limitations

This study was a retrospective clinical study, which failed to explore the molecular mechanism by which the SII level affects neoadjuvant chemotherapy efficacy in HER2 positive breast cancer patients.

Conclusions

The SII was associated with the prognosis and efficacy of neoadjuvant chemotherapy in HER2 positive breast cancer patients. For patients with an increased SII level before neoadjuvant chemotherapy, the treatment plan should be strengthened, which may in turn improve their prognosis.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-55/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-55/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-55/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-55/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Nuclear 215 Hospital of Shaanxi Province (No. 20220078). The requirement of individual consent for this retrospective analysis was waived.

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