

Increased systemic immune-inflammation index independently predicts poor survival for hormone receptor-negative, HER2-positive breast cancer patients

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Purpose: We sought to examine the role of pretreatment systemic immune-inflammation index (SII) in hormone receptor-negative, human epidermal growth factor receptor 2+ (HER2+) breast cancer patients.

Patients and methods: 155 HER2+ patients treated in our hospital from September 3, 2002, to September 21, 2012, were retrospectively enrolled. SII was established as neutrophil x platelet/lymphocyte counts. The median value of SII was used as cut-off value. We used the Kaplan-Meier method to evaluate the overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS). To comparatively evaluate the survival rates between patients from two groups, we used the log-rank test. For identifying independent factors of prognosis, we used the Cox regression model, applying multivariate statistics.

Results: Analyses show that HER2+ patients with high and low SII had median DFS of 15.1 and 31.5 months, respectively ($P<0.001$), while the median DMFS in HER2+ patients with high SII was 18.4 and in patients with low SII was 33.0 months ($P=0.001$), and the median OS were 54.5 and 71.1 months respectively in high and low SII patients, respectively ($P=0.002$). Multivariate analysis had revealed increased SII independently linked to poor DFS (HR =1.46, 95% CI: 1.01–2.11, $P=0.045$). The difference between SII and DMFS bore no statistical significance. (HR =1.40, 95% CI: 0.96–2.03, $P=0.078$), while high SII independently predicted short OS (HR =1.51, 95% CI: 1.02–2.25, $P=0.038$).

Conclusion: Our findings suggest that increased SII independently predicts poor survival for hormone receptor-negative, HER2+ breast cancer patients. Prospective studies are, however, required to confirm the role of SII in the prognosis of patients with HER2+ before clinical use.

Keywords: breast cancer, SII, HER2, inflammation

Introduction

Breast cancer is still one of the primary reasons for cancer death among female patients, although treatment strategies have improved in recent years.¹ That the human epidermal growth factor receptor-2 (HER2) is overexpressed is reportedly a concern in about 20–25% of breast cancers and is generally linked to poor outcomes. Trastuzumab is a humanized monoclonal antibody that acts against HER2's extracellular domain. The antibody is integral in the treatment of patients with HER2+ tumors, given its beneficial features in both early and metastatic

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situations. In addition to Trastuzumab, newer drugs, such as Ado-Trastuzumab Emtansine, Pertuzumab, and Lapatinib that also target HER2 have boosted the treatment of HER2+ breast cancer, subsequently improving survival rates and the quality of life of patients. However, death tolls from HER2+ breast cancer remain high.² HER2+ breast cancer frequently recurs after first-line treatment, resulting in metastasis and ultimately death.³ It is, therefore, particularly essential to evaluate HER2+ breast cancer patients' prognosis, which is affected by several clinicopathological parameters, such as tumor size, lymph node status, patient age, and molecular biology characteristics.^{4,5}

In the past, several investigations have paid more attention to inflammation and have established cancer-related inflammation to have a significant part in the development and prognosis of cancer.^{6–11} Systemic inflammation can be monitored using biochemical or hematologic markers, including elevated C-reactive protein, leukocyte, hypoalbuminemia, neutrophil, and platelet cell numbers.^{12–14} If these factors are combined, they can be used to derive predictive inflammatory scores. Examples of such scores are lymphocyte ratios for platelets (PLR) and neutrophil (NLR), and the Glasgow Prognostic Score. The disapproving role of elevated NLR and PLR has been vigorously scrutinized in various cancer types before, including breast cancer, lung cancer, ovarian cancer, colorectal cancer, gallbladder cancer, cervical cancer, gastric cancer.^{14–24}

Liquid biopsy, while being a noninvasive and dynamic detector tool in oncology, also offers several clinical benefits, including diagnosis, prognosis, treatment selection, and monitoring disease burdens.^{25,26}

Recently, an integrated indicator that is known as a systemic immune-inflammation index (SII), centered on peripheral platelet, neutrophil, and lymphocyte counts and defined as $\text{neutrophil} \times \text{platelet} / \text{lymphocyte}$, has been assessed in various cancers.²⁷ This indicator is noninvasive and offers a dynamic detection procedure during therapy. This indicator could be more suited in reflecting the balance between host inflammatory and immune status.²⁷ Although SII has been inspected in various cancers, including colorectal cancer, nasopharyngeal carcinoma, hepatocellular carcinoma, pancreatic cancer, gastric cancer, and prostate cancer,^{10,27–34} researchers are still to comprehend its part in patients with breast cancer fully. Our investigation aimed to examine the predictive significance of SII in patients with HER2+ breast cancer.

Materials and methods

Subjects

155 hormone receptor-negative, HER2+ patients treated in our hospital from September 3, 2002, to September 21, 2012, were retrospectively enrolled. All patients were pathologically diagnosed. Progesterone receptor and estrogen receptor were negative when the immunohistochemistry test to be less than 1% of the positive invasive tumor nuclei. HER2 status was considered negative when the immunohistochemical result was equal to 0 or with the confirmation of negativity with fluorescence in situ hybridization. We excluded patients who had inflammatory breast cancer, liver, hematological, infectious, immune, inflammatory diseases and other tumors. The Ethical Committee of Shandong Cancer Hospital approved our investigation. Because of the characteristic of a retrospective study, the habitual written informed consent was not required, and all data was anonymous.

We set August 6, 2018, as the deadline for follow-up. Patients were regularly followed up every three and six months after surgery until the end of follow up or death. We frequently used magnetic resonance imaging, ultrasound imaging, computed tomography, and tumor biomarkers to evaluate patients' tumor status. The criteria for determining relapse and distant metastasis is elucidated in the RECIST guideline (version 1.1). Relapse denotes both local and regional relapses, defined by the occurrence of detectable relapsing masses in the ipsilateral breast, ipsilateral chest wall, surgical scars, or local lymphatic drainage area. The classic clinical and radiographic and/or histological determination of distant detectable metastases larger than 0.2 mm confirm the presence of distant metastases. The overall survival (OS) begins with surgery up to the point of death or lost follow-up, disease-free survival time (DFS) represents the time beginning from surgery up to the first disease recurrence, death or lost follow-up, and distant metastasis-free survival (DMFS) covers surgery and spans the first distant metastasis phase, death or lost follow-up.

Data collection

Data for differential blood counts were collected within 3 days before surgery or neoadjuvant chemotherapy. We collected neutrophil counts alone, platelet counts alone, and lymphocyte counts alone and then calculated the corresponding NLR (neutrophil/lymphocyte ratio), PLR (platelet/lymphocyte ratio), and SII (neutrophil \times platelet/

lymphocyte).²⁷ Patients were partitioned into two groups of high or low SII following the median value (cut-off value), as well as in two groups each of high or low NLR, PLR, lymphocytes, platelets, and neutrophils in the Cox regression. The treatment approaches involved carrying out surgery, chemotherapy, and radiotherapy. All the patients were subjected to breast-conserving surgery or radical mastectomy. Patients received chemotherapy with Anthracyclines, Cyclophosphamide, and Paclitaxel during a treatment period spanning between 4 and 8 cycles (a median value of 5.7 cycles). Targeted therapy was used with Trastuzumab during a 1 year treatment period. The postoperative radiotherapy was performed with 50–60 Gy/25–30 fractions. Platelet count, lymphocyte count, neutrophil count, lymph node involvement, tumor differentiation, lymphovascular invasion, age, tumor stage, and surgical types for enrolled patients were evaluated. Tumor stage was evaluated by the 7th American Joint Committee on Cancer (AJCC) staging system.³⁵

Statistical analysis

We used SPSS 21 software (SPSS, Chicago, IL, USA) to analyze data. We used the Kaplan-Meier method to evaluate the DFS, DMFS, and OS, and the Log-rank test to evaluate survival differences between patients partitioned into two groups according to the SII obtained. Chi-square or Fisher exact tests were employed, when necessary, to assess the association between SII and clinicopathological parameters, while the Cox regression model helped in the multivariate analysis to identify independent factors of prognosis. Differences at $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

Characteristics of the 155 HER2+ patients in our study are presented in Table 1. There are 31 young patients (age ≤ 35) and 124 older patients (age > 35). 70, 64, and 21 HER2+ patients were at stage III, II, and I, respectively, according to the 7th AJCC stage. 77 patients had high SII (SII > 578), and 78 patients had low SII (SII ≤ 578). There were 17, 76, 52, and 10 HER2+ patients with well, middle, poor, and unknown differentiation, respectively. Follow-up duration lasted 57.6 months (10.4–158.2 months). By the end of our study, 119 patients had died, 137 of them had experienced recurrence, all 155 had developed distant metastasis, and 9 had eventually gone missing during follow-up.

Univariate analysis

The median DFS in high and low SII HER2+ patients were 15.1 and 31.5 months, respectively (HR=1.88, 95% CI: 1.34–2.65, $P < 0.001$, Figure 1, Table 2), the median DMFS in high SII HER2+ patients was 18.4, while that in patients with low SII was 33.0 months (HR=1.81, 95% CI: 1.28–2.55, $P = 0.001$, Figure 2, Table 2), and the median OS were 54.5 and 71.1 months in high and low SII patients, respectively (HR=1.79, 95% CI: 1.24–2.60, $P = 0.002$, Figure 3, Table 2). Besides, tumor stage, Ki-67 differentiation, lymph nodes involvement, lymphocytes, NLR and PLR also correlated with DFS, DMFS, OS ($P < 0.05$).

Multivariate analysis

Lymphocytes, NLR, PLR, and SII, alongside other clinicopathological parameters that were statistically significant after the univariate analysis were further evaluated using the multivariate Cox regression for DFS, DMFS, and OS. According to results from multivariate analysis, increased amounts of lymphocytes were independently linked to better OS (HR=0.62, 95% CI: 0.40–0.97, $P = 0.039$, Table 3), but no statistical significances were noted between lymphocytes and DMFS (HR=0.72, 95% CI: 0.48–1.08, $P = 0.116$, Table 3) and between lymphocytes and DFS (HR=0.76, 95% CI: 0.51–1.12, $P = 0.174$, Table 3). NLR did not predict any of DFS (HR=1.38, 95% CI: 0.96–1.99, $P = 0.081$, Table 3), DMFS (HR=1.32, 95% CI: 0.92–1.91, $P = 0.130$, Table 3), or OS (HR=1.32, 95% CI: 0.90–1.95, $P = 0.153$, Table 3) independently. PLR was also not an independent prognosticator for DFS (HR=1.23, 95% CI: 0.83–1.82, $P = 0.296$, Table 3), DMFS (HR=1.36, 95% CI: 0.92–2.02, $P = 0.114$, Table 3), or OS (HR=1.34, 95% CI: 0.88–2.04, $P = 0.167$, Table 3). Increased SII was independently linked to poor DFS (HR=1.46, 95% CI: 1.01–2.11, $P = 0.045$, Table 3), but there was no statistical significance between SII and DMFS (HR=1.40, 95% CI: 0.96–2.03, $P = 0.078$, Table 3), and high SII independently predicted short OS (HR=1.51, 95% CI: 1.02–2.25, $P = 0.038$, Table 3). Furthermore, tumor stage, Ki-67 and tumor differentiation were independent predictors for DFS, DMFS, OS in patients with HER2+ breast cancer ($P < 0.05$). We, therefore, note that SII has the best prognostic value among the 4 evaluated indices.

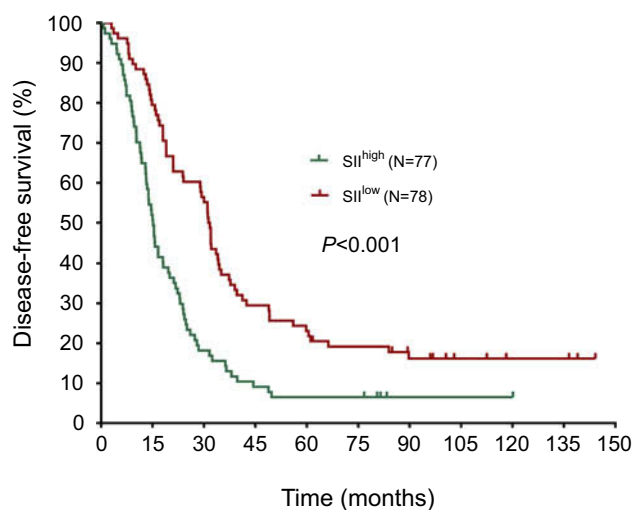
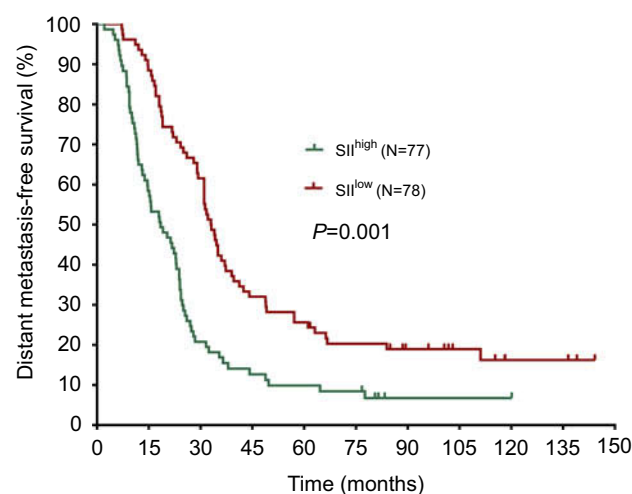
Correlation findings between SII and baseline characteristics

Table 4 displays the correlation between SII and baseline characteristics. Patients with a higher tumor stage have

Table 1 Patient characteristics of 155 hormone receptor-negative, HER2+ breast cancer patients

Parameters	Number	%
Age (years)		
≤35	31	20.0
>35	124	80.0
Tumor stage		
T1	29	18.7
T2	84	54.2
T3	35	22.6
T4	7	4.5
Tumor differentiation		
I	17	11.0
II	76	49.0
III	52	33.5
Unknown	10	6.5
Lymph node involvement		
N0	56	36.1
N1	34	21.9
N2	25	16.1
N3	40	25.8
AJCC stage		
I	21	13.5
II	64	41.3
III	70	45.2
Pathological type		
IDC	126	81.3
ILC	29	18.7
Ki-67		
≤30%	98	63.2
>30%	57	36.8
Surgery		
Breast-conserving surgery	15	9.7
Radical mastectomy	140	90.3
Radiotherapy		
Yes	92	59.4
No	63	40.6
Chemotherapy		
Adjuvant chemotherapy	129	83.2
Neoadjuvant chemotherapy	26	16.8
Targeted therapy		
Yes	81	52.3
No	74	47.7
SII		
≤578	78	50.3
>578	77	49.7

Abbreviations: AJCC, American Joint Committee on Cancer; SII, systemic immune-inflammation index; IDC, Intraductal Carcinoma; ILC, Intralobular Carcinoma.

**Figure 1** Disease-free survival rates of 155 patients with hormone receptor-negative, HER2+ breast cancer according to low and high SII (systemic immune-inflammation index).**Figure 2** Distant metastasis-free survival rates of 155 patients with hormone receptor-negative, HER2+ breast cancer according to low and high SII (systemic immune-inflammation index).

increased SII ($P=0.038$) and the positivity of lymph nodes metastasis correlated with high SII ($P=0.012$). We did not find significant correlations with SII for other baseline characteristics.

Discussion

SII prognoses have already been reported in prostate cancer, pancreatic cancer, nasopharyngeal carcinoma, colorectal cancer, hepatocellular carcinoma, and gastric cancer.^{10,27–29,31–34,36} Hu et al²⁷ initially identified SII as a novel and independent prognostic pointer in hepatocellular carcinoma, with higher preoperative SII patients presenting

Table 2 Univariate analysis for DFS, DMFS and OS

Parameters	DFS		DMFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)						
≤35	1		1		1	
>35	0.65 (0.43–0.97)	0.038	0.61 (0.41–0.92)	0.020	0.86 (0.56–1.33)	0.514
Tumor stage						
T1	1		1		1	
T2–4	2.99 (1.84–4.86)	<0.001	2.94 (1.81–4.78)	<0.001	3.51 (2.01–6.12)	<0.001
Tumor differentiation						
I–II	1		1		1	
III	3.33 (2.26–4.88)	<0.001	3.14 (2.13–4.62)	<0.001	2.71 (1.83–4.02)	<0.001
Lymph node involvement						
N0	1		1		1	
N1–3	2.20 (1.54–3.17)	<0.001	2.14 (1.49–3.07)	<0.001	2.34 (1.58–3.48)	<0.001
Pathological type						
ILC	1		1		1	
IDC	0.86 (0.62–1.28)	0.621	0.92 (0.75–1.41)	0.381	1.13 (0.83–1.39)	0.614
Surgery						
Breast-conserving surgery	1		1		1	
Radical mastectomy	1.57 (0.86–2.84)	0.135	1.53 (0.84–2.78)	0.157	2.07 (1.04–4.10)	0.037
Ki-67						
≤30%	1		1		1	
>30%	2.65 (2.11–4.15)	<0.001	2.89 (1.82–5.36)	<0.001	2.93 (1.94–4.62)	<0.001
Radiotherapy						
No	1		1		1	
Yes	1.04 (0.74–1.46)	0.836	0.99 (0.70–1.39)	0.952	0.84 (0.59–1.22)	0.364
Chemotherapy						
Adjuvant chemotherapy	1		1		1	
Neoadjuvant chemotherapy	0.85 (0.55–1.34)	0.493	0.92 (0.59–1.44)	0.714	1.18 (0.71–1.96)	0.517
Targeted therapy						
Yes	1		1		1	
No	1.07 (0.76–1.49)	0.692	0.96 (0.68–1.35)	0.819	1.04 (0.72–1.50)	0.839
Neutrophils						
≤3.61	1		1		1	
>3.61	1.11 (0.79–1.56)	0.518	1.06 (0.75–1.48)	0.729	1.22 (0.85–1.75)	0.276
Lymphocytes						
≤1.65	1		1		1	
>1.65	0.63 (0.43–0.91)	0.015	0.61 (0.42–0.89)	0.010	0.57 (0.37–0.86)	0.008
Platelets						
≤224	1		1		1	
>224	1.05 (0.75–1.48)	0.742	1.18 (0.84–1.65)	0.332	1.28 (0.89–1.84)	0.181
NLR						
≤2.3	1		1		1	
>2.3	1.44 (1.02–2.03)	0.034	1.41 (1.00–1.99)	0.045	1.54 (1.06–2.23)	0.022

(Continued)

Table 2 (Continued).

Parameters	DFS		DMFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
PLR						
≤160	1		1		1	
>160	1.68 (1.20–2.36)	0.003	1.78 (1.26–2.51)	0.001	1.69 (1.17–2.44)	0.005
SII						
≤578	1		1		1	
>578	1.88 (1.34–2.65)	<0.001	1.81 (1.28–2.55)	0.001	1.79 (1.24–2.60)	0.002

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; OS, overall survival; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; IDC, Intraductal Carcinoma; ILC, Intralobular Carcinoma.

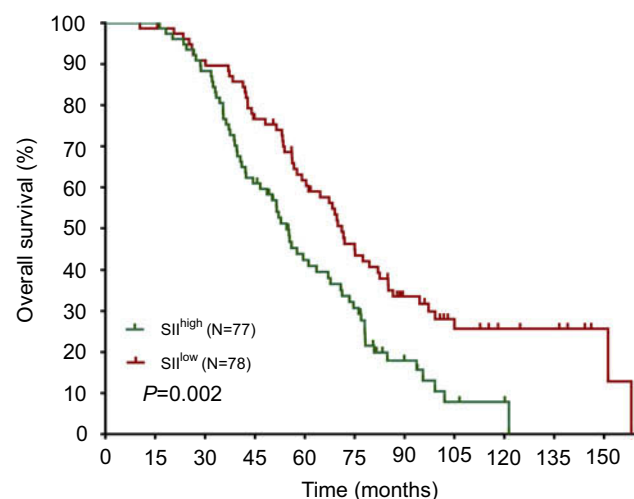


Figure 3 Overall survival rates of 155 patients with hormone receptor-negative, HER2 + breast cancer according to low and high SII (systemic immune-inflammation index).

increased recurrence rates and surviving lesser than their lower SII counterparts. Tong et al³² in examining the association between SII and each of therapy response and overall patient survival at stage III of non-small cell lung cancer, proved SII's prognostic value was independent. Studies on the prognostic significance of preoperative SII in patients with gastric cancer revealed that high SII correlated with poor clinicopathological characteristics and could act as a predictor of inferior prognosis.

Mounting research findings have established an existing prognostic relationship between different cancer types and the inflammatory system, typified by the pretreatment tallies of inflammatory cells, such as lymphocytes, neutrophils, and monocytes.^{37–43} Lymphocytes that infiltrate tumors could serve to prevent tumor development and spread through their antitumor immune response; lymphocytes are associated with better survival chances in cancer patients.^{44,45} Platelets, on the other hand, may not only be able to promote

the angiogenesis and metastases of tumors but could as well protect tumor cells from the impact of antitumor immune response by shielding them.⁴⁶ Neutrophils are an inflammatory and immune parameter renowned for their role in tumor proliferation and metastasis owing to their release of inflammatory mediators (matrix metalloproteinase-9, neutrophil elastase, and interleukin-8).⁴⁷

Our research has, for the first time, presented the clinical role of SII in Chinese patients with HER2+ breast cancer. We report that increased SII independently predicts short DFS and OS in HER2+ breast cancer patients. These findings are consistent with previous investigations.^{28,36,48} Prominent among those is Jiang et al's³³ substantiation of the independent predictive role of SII for survival in nasopharyngeal carcinoma, where tumor stage, differentiation, and lymphovascular invasion independently associated with bad survival for nasopharyngeal cancer patients.

A 1-year trastuzumab therapy is the standard treatment for high-risk, early Her2+ breast cancer patients. However, the Her2-targeted therapy played no significant role on prognosis as shown in Table 2. In this retrospective study, early stage patients (AJCC I and II) accounted for over 50% of the cases. Those who underwent the Her2-targeted therapy were mainly AJCC stage III individuals. And tumor stage is an independent predictor of DFS, DMFS and OS. A simple separation into two groups, designated “targeted therapy” or “non-targeted therapy” could weaken the role of targeted therapy on prognosis. This study was conducted on a small sample size; only 81 of the 155 patients received targeted therapy, with it possible that the effect of targeted therapy could be influenced by simple grouping easily.

The poor prognosis in this study, when compared to previously reported investigations, may be due partly to poor compliance to normative adjuvant therapy by some Chinese patients.⁴⁹ The lesser standard form of adjuvant

Table 3 Multivariate analysis for DFS, DMFS and OS

Parameters	DFS		DMFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)						
≤35	I		I		/	/
>35	0.79 (0.51–1.21)	0.285	0.72 (0.47–1.11)	0.142	/	/
Tumor stage						
T1	I		I		I	
T2–4	2.32 (1.39–3.89)	0.001	2.31 (1.38–3.89)	0.001	2.73 (1.50–4.97)	<0.001
Tumor differentiation						
I–II	I		I		I	
III	2.42 (1.54–3.81)	<0.001	2.34 (1.49–3.66)	<0.001	1.85 (1.20–2.87)	0.005
Lymph node involvement						
N0	I		I		I	
N1–3	1.21 (0.77–1.87)	0.396	1.16 (0.75–1.81)	0.485	1.22 (0.75–2.00)	0.409
Surgery						
Breast-conserving surgery	/		/		I	
Radical mastectomy	/	/	/	/	1.58 (0.73–3.39)	0.238
Ki-67						
≤30%	I		I		I	
>30%	1.98 (1.36–2.68)	0.001	2.06 (1.74–3.92)	<0.001	2.31 (1.81–3.46)	<0.001
Lymphocytes						
≤1.65	I		I		I	
>1.65	0.76 (0.51–1.12)	0.174	0.72 (0.48–1.08)	0.116	0.62 (0.40–0.97)	0.039
NLR						
≤2.3	I		I		I	
>2.3	1.38 (0.96–1.99)	0.081	1.32 (0.92–1.91)	0.130	1.32 (0.90–1.95)	0.153
PLR						
≤160	I		I		I	
>160	1.23 (0.83–1.82)	0.296	1.36 (0.92–2.02)	0.114	1.34 (0.88–2.04)	0.167
SII						
≤578	I		I		I	
>578	1.46 (1.01–2.11)	0.045	1.40 (0.96–2.03)	0.078	1.51 (1.02–2.25)	0.038

Notes: Lymphocytes, NLR, and PLR are evaluated using the multivariate Cox regression for DFS, DMFS, and OS alongside other clinicopathological parameters that were found to be statistically significant after the univariate analysis. Only each of lymphocytes, NLR, and PLR alone are listed in this table.

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; OS, overall survival; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index.

therapy contributed to the poor survival. Furthermore, only 81 of 155 patients received targeted therapy in this study, with the outcome of worse survival. Findings from a study investigating the prognostic significance of derived NLR in 310 patients who had HER2+ breast cancer and underwent neoadjuvant chemotherapy, amassing a median follow-up time of 62.5 months (9.6–138.5 months) established 270 cases of recurrent or metastatic disease, 246 dead cases, and 16 lost follow-up cases.⁵⁰ These cases had poor prognoses comparative to those in our study.

Despite the novelty and potential of our studies, there are some limitations to it. Firstly, our investigation consisted of a single-center retrospective study without a validation group, and it consisted of a relatively small sample size. Furthermore, factors such as hypercholesterolemia, metabolic syndrome, abnormal thyroid function, smoking, and alcohol consumption may potentially affect SII. That notwithstanding, if proper validation is made in the future, the study could serve as a potential boost in the fight against HER2 breast cancer.

Table 4 Correlation between SII and baseline characteristics

Parameters	SII ≤ 578	SII > 578	P-value
Age (years)			
≤ 35	13	18	0.322
> 35	65	59	
Tumor stage			
T1	20	9	0.038
T2–4	58	68	
Tumor differentiation			
I–II	53	40	0.119
III	22	30	
Lymph node involvement			
N0	36	20	0.012
N1–3	42	57	
AJCC stage			
I	14	7	0.158
II–III	64	70	
Pathological type			
ILC	12	17	0.310
IDC	66	60	
Surgery			
Breast-conserving surgery	11	4	0.101
Radical mastectomy	67	73	

Abbreviations: AJCC, American Joint Committee on Cancer; SII, systemic immune-inflammation index; IDC, Intraductal Carcinoma; ILC, Intralobular Carcinoma

Conclusion

Our results suggest that increased SII independently predicts poor survival for patients with HER2+ breast cancer. However, further in-depth studies are required to confirm the potential role of SII in HER2+ breast cancer patients before contemplations of any potential clinical use.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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