ORIGINAL RESEARCH

Prognostic significance of systemic immune-inflammation index in triple-negative breast cancer

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Introduction: The prognostic significance of the systemic immune-inflammation index (SII) in breast cancer is unknown. Here, we aimed to explore the connection between pretreatment SII and the survival of patients with triple-negative breast cancer (TNBC).

Methods: We enrolled 160 TNBC patients treated in our hospital between May 2000 and June 2012. We employed the Kaplan-Meier curve and log-rank test to assess overall survival (OS), disease-free survival (DFS), and distant metastasis-free survival (DMFS). We identified the prognostic significance of SII using the Cox regression model.

Results: The Kaplan-Meier curve revealed the median OS as 44.2 and 82.4 months in high and low SII TNBC patients, respectively ($P<0.001$). According to univariate and multivariate analyses, increased SII correlated with poor OS (HR =2.91, 95% CI: 2.00–4.23, $P<0.001$; HR =2.60, 95% CI: 1.74–3.88, $P<0.001$). The DFS and DMFS of patients with high SII were 18.8 and 23.8 months, respectively, while those of patients with low SII were 29 and 45.2 months, respectively, ($P<0.001$). Further univariate analyses showed a significant correlation between SII and DFS and DMFS ($P<0.01$), while results from multivariate analyses suggested that SII is an independent prognostic factor for DFS ($P=0.045$), but not for DMFS ($P=0.078$). The area under the receiver operating characteristics curves for SII to differentiate between long and short OS, DFS, and DMFS were 0.69, 0.60, and 0.64, respectively.

Conclusion: Our findings may point to SII having an independent prognostic significance in TNBC patients. Prospective in-depth studies, using a larger sample size, are required to further investigate the precise role of SII in TNBC before clinical use.

Keywords: SII, prognosis, immunity, inflammation, triple-negative breast cancer

Introduction

Triple-negative breast cancer (TNBC) is a heterogeneous disease characterized by the negative expression of the human epidermal growth factor receptor 2 (HER2), progesterone receptor, and estrogen receptor.[1,2] TNBC usually correlates with pushing margins of invasion, high histological grade, high levels of proliferation, young age, high recurrence and metastases rates, advanced disease,[3] and poor clinical outcomes.[4,5] So, predicting the prognosis of TNBC patients is particularly vital.

In recent years, liquid biopsy techniques have been widely employed to investigate the diagnostic and prognostic markers for breast cancer and other tumors. For example, circulating tumor cells have an unfavorable prognostic value in breast cancer patients.[6,7] Besides, exosomes have been shown to have diagnostic and

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prognostic values in various tumors.[8–10] Gene expression signatures, such as MAD2L1 and BUB1, have prognostic significance in breast cancer patients.[11–14] However, the above methods may be limited in clinical use because of the high cost and complexity of measurements. Thus, we would like to focus on the inflammation index, an easily obtained and cheap index, to predict the survival of breast cancer patients.

Cancer-related inflammation has been found to play a significant part in the development and prognosis of cancer.[15–17] Some biochemical or hematological markers, such as increase in platelet, lymphocyte, neutrophil, white cell counts, C-reactive protein levels, and hypoalbuminemia, could trigger a systemic inflammatory response.[18–21] A combination of these factors has been used to obtain prognostic scores for inflammation, for example, lymphocyte ratio (PLR) for platelet, lymphocyte ratio (NLR) for neutrophil, and the Glasgow Prognostic Score. The adverse role of elevated NLR and PLR has already been studied intensely in various cancers, including non-small cell lung cancer, cervical cancer, gallbladder cancer, ovarian cancer, colorectal cancer, breast cancer, and gastric cancer.[19,22–30]

The systemic immune-inflammation index (SII) is determined by platelet × neutrophil/lymphocyte, which could be better poised to mirror the sense of balance of the host inflammatory and immune status.[31] Though SII has been used before in investigating different cancers, including colorectal cancer, nasopharyngeal cancer, gastric cancer, pancreatic cancer, hepatocellular cancer, and prostate cancer,[31–38] it has yet to be applied comprehensively in studies involving breast cancer. Our research evaluated the clinical significance of SII, an easily obtained and cheap index, in TNBC patients.

Materials and methods
### Patient selection and data collection
This study is a retrospective investigation sanctioned by the Ethics Committee of China-Japan Union Hospital. All data were anonymous. Written informed consent was obtained from all patients. 160 TNBC patients undergoing treatment at our hospital between May 2000 and June 2012 were enrolled for the test. Patients enrolled had their TNBC histologically confirmation and received surgery accompanied by adjuvant chemotherapy or neoadjuvant chemotherapy. Exclusion criteria: patients suffering from an infectious disease 3 months before enrollment;

Table 1 Clinicopathologic parameters of 160 TNBC patients

Variables	Number (100%)
Age (years)	
≤35	23 (14.4)
>35	137 (85.6)
T stage	
pT1	38 (23.8)
pT2	93 (58.1)
pT3	25 (15.6)
pT4	4 (2.5)
Pathology	
Invasive ductal carcinoma	121 (75.6)
Invasive lobular carcinoma	39 (24.4)
Tumor differentiation	
G1	12 (7.5)
G2	93 (58.1)
G3	53 (33.1)
Unknown	2 (1.3)
Ki-67	
≤30%	86 (53.8)
>30%	74 (46.2)
Chemotherapy	
Adjuvant	128 (80.0)
Neoadjuvant	32 (20.0)
Adjuvant radiotherapy	
Yes	103 (64.4)
No	57 (35.6)
Type of surgery	
Breast-conserving surgery	31 (19.4)
Radical mastectomy	129 (80.6)
N stage	
pN0	71 (44.4)
pN1	51 (31.9)
pN2	23 (14.4)
pN3	15 (9.4)
AJCC stage	
I	26 (16.3)
II	85 (53.1)
III	49 (30.6)
SII	
≤557	80 (50.0)
>557	80 (50.0)

Abbreviations: TNBC, triple-negative breast cancer; AJCC, American Joint Committee on Cancer; SII, systemic immune-inflammation index.

patients with coronary artery disease, immune disease, inflammatory disease, and hematological diseases; with metastatic or inflammatory breast cancer; or using
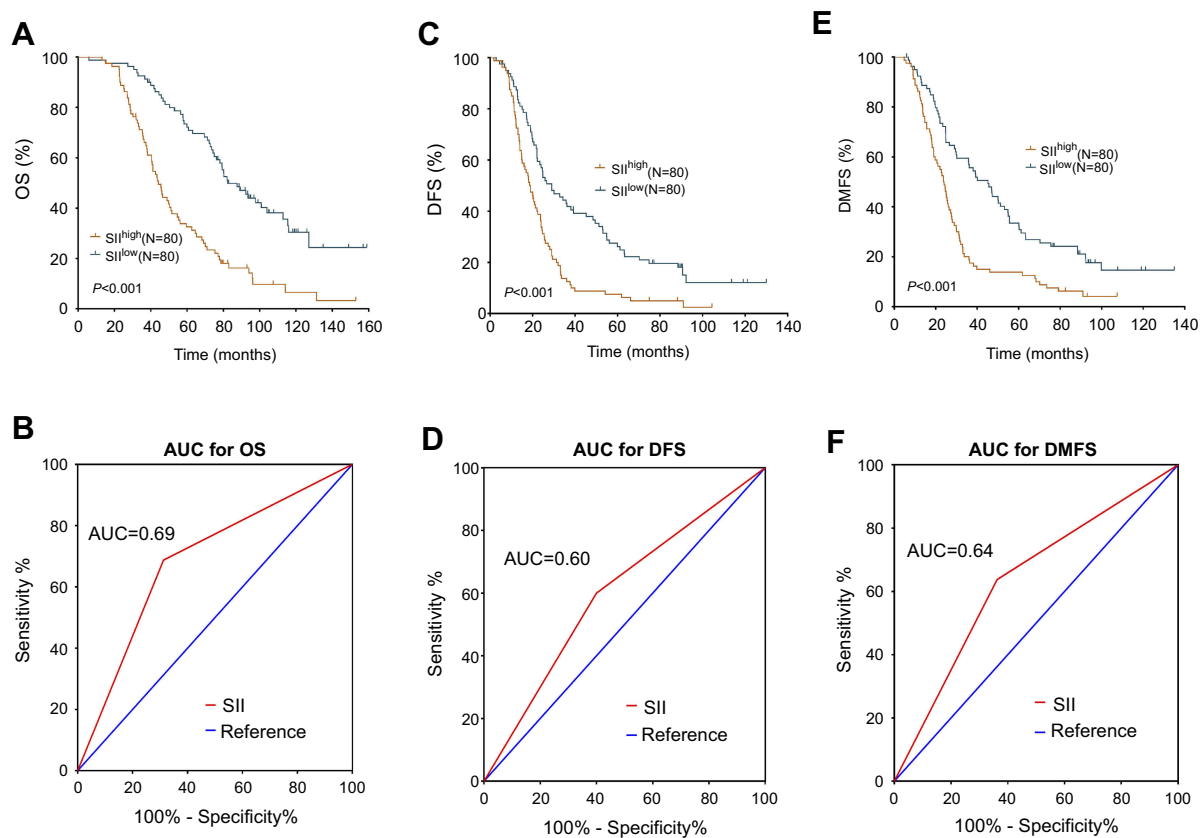
Figure 1 Kaplan-Meier and ROC curves for 160 TNBC patients. (**A**) OS as derived by the SII. (**B**) AUC of SII to differentiate between long and short OS. (**C**) DFS as derived by the SII. (**D**) AUC of SII to differentiate between long and short DFS. (**E**) DMFS as derived by the SII. (**F**) AUC of SII to differentiate between long and short DMFS.
Abbreviations: ROC, receiver operating characteristic curve; TNBC, triple-negative breast cancer; OS, overall survival; SII, systemic immune-inflammation index; AUC, area under the curve; DFS, disease-free survival; DMFS, distant metastasis-free survival.

immunosuppressive or anti-inflammatory drugs (including steroids, rapamycin, anti-lymphocyte, and globulin) before enrollment. 32 patients were excluded based on the above criteria.

Patients received regular follow-up every 3 months following adjuvant treatment until they died or lost follow-up. Follow-up included assessing disease progression, confirming patient death, and lost follow-up. The status of the disease was evaluated using ultrasound imaging, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission computed tomography. September 2018 was set as the deadline for follow-up. Disease-free survival (DFS) time referred to the period from surgical resection to the first disease recurrence, metastasis, lost follow-up, or death. Overall survival (OS) represented the stretch from surgery up till death or lost follow-up. Distant metastasis-free survival (DMFS) covered the spell from surgical resection to the first distant metastasis, lost follow-up, or death.

All patients were exposed to the following treatments: adjuvant and neoadjuvant chemotherapy, breast-conserving surgery and a radical mastectomy, and adjuvant radiotherapy with 50–60 Gy. A 3+ score or a fluorescence in situ hybridization for 1+ and 2+ patients confirmed a positive HER2 status, while an immunohistochemical score of 0 represented a negative status. Progesterone and estrogen receptors were negative and were determined by the immunohistochemistry test to be 1% of the positive invasive tumor nuclei. Data for age, pathology, tumor size, lymph node metastasis, tumor stage [according to the 7th American Joint Committee on Cancer (AJCC) stage],[39] lymphovascular invasions, histological grade, and anti-tumor treatment were collected. Data for differential blood counts were collected within the 7 days preceding surgery or neoadjuvant chemotherapy. The counts of platelets, neutrophils, and lymphocytes were extracted from our hospital's online records. Chemotherapy regimens included paclitaxel + anthracyclines + cyclophosphamide and anthracyclines + paclitaxel.

Statistical analysis

The SPSS 21.0 software (SPSS, Chicago, IL, USA) was used to perform data analysis. SII was determined by platelet × neutrophil/lymphocyte. The median value of SII (557) was used to distinguish between high and low SII. DFS, DMFS, and OS were obtained with the help of the Kaplan-Meier method. The log-rank test was used to compare the differences in DFS, DMFS, and OS between patients from the two groups. Receiver operating characteristics (ROC) curves were employed to evaluate the ability of SII to differentiate between good and reduced survival. Multivariate analyses to identify independent prognostic factors in TNBC patients was carried out using the Cox regression model. Statistical significance was established at $P<0.05$ for differential results.

Results

Characteristics that are representative of the 160 TNBC patients are displayed in Table 1. Results show that the median follow-up time was 61.7 months (5.9–159.0 months). Among the 160 TNBC patients, 143 and 140 of them experienced tumor recurrence and distant metastases, respectively, and 119 of them died. Two patients lost follow-up in DFS,

Table 2 Association between clinicopathologic parameters/SII and OS in TNBC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
≤35	I		/	
>35	0.86 (0.52–1.4)	0.552	/	/
T stage				
pT1	I		I	
pT2–4	1.99 (1.26–3.14)	0.003	1.72 (1.04–2.86)	0.035
Pathology				
Invasive ductal carcinoma	I		/	
Invasive lobular carcinoma	0.95 (0.92–1.01)	0.723	/	/
Tumor differentiation				
G1–2	I		I	
G3	3.06 (2.09–4.49)	<0.001	2.02 (1.34–3.06)	0.001
Ki-67				
≤30%	I		I	
>30%	2.87 (1.98–3.79)	<0.001	1.96 (1.27–2.81)	0.006
Chemotherapy				
Adjuvant	I		/	
Neoadjuvant	0.9 3(0.67–1.26)	0.468	/	/
Adjuvant radiotherapy				
Yes	I		/	
No	1.24 (0.81–1.52)	0.356	/	/
Type of surgery				
Breast-conserving surgery	I		I	
Radical mastectomy	2.69 (1.56–4.65)	<0.001	2.54 (1.46–4.42)	0.001
N stage				
pN0	I		I	
pN1–3	1.67 (1.15–2.43)	0.006	1.04 (0.70–1.56)	0.820
SII				
≤557	I		I	
>557	2.91 (2.00–4.23)	<0.001	2.60 (1.74–3.88)	<0.001

Abbreviations: TNBC, triple-negative breast cancer; SII, systemic immune-inflammation index; OS, overall survival.

Table 3 Association between clinicopathologic parameters/SII and DFS in TNBC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
≤35	I		I	
>35	0.65 (0.43–0.97)	0.038	0.79 (0.51–1.21)	0.285
T stage				
pT1	I		I	
pT2–4	2.99 (1.84–4.86)	<0.001	2.32 (1.39–3.89)	0.001
Pathology				
Invasive ductal carcinoma	I		/	
Invasive lobular carcinoma	0.965 (0.942–1.005)	0.836	/	/
Tumor differentiation				
G1–2	I		I	
G3	3.33 (2.26–4.88)	<0.001	2.42 (1.54–3.81)	<0.001
Ki-67				
≤30%	I		I	
>30%	2.06 (1.26–2.85)	<0.001	1.61 (1.12–2.34)	0.013
Chemotherapy				
Adjuvant	I		/	
Neoadjuvant	1.13 (0.58–1.63)	0.627	/	/
Adjuvant radiotherapy				
Yes	I		/	
No	1.38 (0.62–1.73)	0.428	/	/
Type of surgery				
Breast-conserving surgery	I		/	
Radical mastectomy	1.57 (0.86–2.84)	0.135	/	/
N stage				
pN0	I		I	
pN1–3	2.20 (1.54–3.17)	<0.001	1.21 (0.77–1.87)	0.396
SII				
≤557	I		I	
>557	1.88 (1.34–2.65)	<0.001	1.46 (1.01–2.12)	0.045

Abbreviations: TNBC, triple-negative breast cancer; SII, systemic immune-inflammation index; DFS, disease-free survival.

and 1 patient lost it in OS. One-half of the patients (80) had a low SII ($\leqq557$), and the other half (80) had a high SII (>557). According to the 7th AJCC, 26 (16.3%), 85 (53.1%), and 49 (30.6%) patients were in stages I, II, and III, respectively. 31 (19.4%) patients underwent breast-conserving surgery, while 129 (80.6%) patients received a radical mastectomy. 39 (24.4%) patients were diagnosed with lobular cancer, while 121 (75.6%) patients had ductal cancer. 12 (7.5%), 93 (58.1%), and 53 (33.1%) TNBC patients suffered from histopathological grades I, II, and III, respectively.

The Kaplan-Meier curve revealed the median OS in TNBC patients with high and low SII to be 44.2 and 82.4 months, respectively, (P<0.001, Figure 1A). The area under the curve (AUC) of ROC for SII to differentiate between long and short OS was 0.69 (Figure 1B). Results from univariate analyses showed increased SII correlating with poor OS (HR =2.91, 95% CI: 2.00–4.23, P<0.001; Table 2). Furthermore, the T stage, Ki-67, tumor differentiation, surgery type, and N stage correlated with the OS of TNBC patients (P<0.01; Table 2). According to multivariate

analyses, elevated SII correlated independently with poor OS (HR =2.60, 95% CI: 1.74–3.88, $P<0.001$; Table 2).

Median DFS in TNBC patients displayed high and low SII to be 18.8 and 29 months, respectively ($P<0.001$, Figure 1C). The AUC of ROC for SII to differentiate between long and short DFS was 0.60 (Figure 1D). Univariate analyses showed increased SII correlating with poor DFS (HR =1.88, 95% CI: 1.34–2.65, $P<0.001$; Table 3). Besides, age, Ki-67, tumor differentiation, N stage, and T stage correlated significantly with poor DFS of TNBC patients ($P<0.05$; Table 3). According to multivariate

analyses, elevated SII correlated independently with poor DFS (HR =1.46, 95% CI: 1.01–2.12, $P=0.045$; Table 3).

The median DMFS was 23.8 and 45.2 months in high and low SII TNBC patients, respectively ($P<0.001$, Figure 1E). The AUC of ROC for SII to distinguish between long and short DFS was 0.64 (Figure 1F). Univariate analyses showed increased SII correlating with poor DMFS (HR =1.81, 95% CI: 1.28–2.55, $P=0.001$; Table 4). Moreover, age, Ki-67, T stage, tumor differentiation, and N stage correlated with DMFS of TNBC patients ($P<0.05$; Table 4). According to multivariate analysis, elevated SII did not correlate

Table 4 Association between clinicopathologic parameters/SII and DMFS in TNBC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
≤35	I		I	
>35	0.61 (0.41–0.92)	0.020	0.72 (0.47–1.11)	0.142
T stage				
pT1	I		I	
pT2–4	2.94 (1.81–4.78)	<0.001	2.32 (1.38–3.89)	0.001
Pathology				
Invasive ductal carcinoma	I		/	
Invasive lobular carcinoma	0.96 (0.95–1.01)	0.756	/	/
Tumor differentiation				
G1–2	I		I	
G3	3.14 (2.13–4.62)	<0.001	2.34 (1.49–3.66)	<0.001
Ki-67				
≤30%	I		I	
>30%	2.21 (1.62–2.91)	<0.001	1.89 (1.34–2.61)	0.007
Chemotherapy				
Adjuvant	I		/	
Neoadjuvant	0.92 (0.49–1.51)	0.824	/	/
Adjuvant radiotherapy				
Yes	I		/	
No	1.19 (0.71–1.96)	0.637	/	/
Type of surgery				
Breast-conserving surgery	I		/	
Radical mastectomy	1.53 (0.84–2.78)	0.157	/	/
N stage				
pN0	I		I	
pN1–3	2.14 (1.49–3.07)	<0.001	1.16 (0.75–1.81)	0.485
SII				
≤557	I		I	
>557	1.81 (1.28–2.55)	0.001	1.40 (0.96–2.03)	0.078

Abbreviations: TNBC, triple-negative breast cancer; SII, systemic immune-inflammation index; DMFS, distant metastasis-free survival.
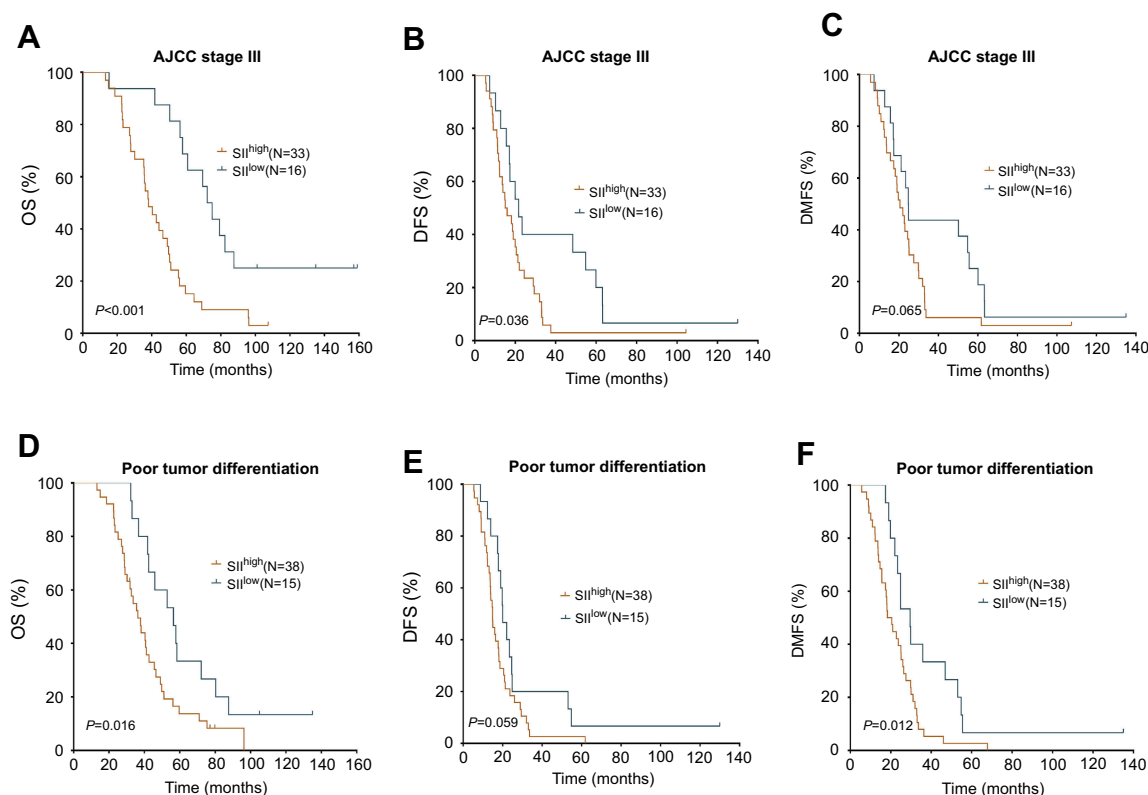
Figure 2 Kaplan-Meier curves for patients with AJCC stage III and poor tumor differentiation. In patients with AJCC stage III, OS (**A**), DFS (**B**), and DMFS (**C**) as derived by the SII. In patients with poor tumor differentiation, OS (**D**), DFS (**E**), and DMFS (**F**) as derived by the SII.
Abbreviations: AJCC, American Joint Committee on Cancer; OS, overall survival; DFS, disease-free survival; DMFS, distant metastasis-free survival.

independently with poor DMFS (HR =1.40, 95% CI: 0.96–2.03, P=0.078; Table 4).

For patients with AJCC stage III, increased SII predicted poorer OS and DFS than decreased SII (P<0.001, =0.036, Figure 2A–B) but not DMFS (P=0.065, Figure 2C). For patients with poor tumor differentiation, elevated SII indicated poor OS and DMFS (P=0.016, =0.012, Figure 2D and F) but not DFS (P=0.059, Figure 2E).

Discussion

Our study represents the first study aimed at assessing the clinical significance of SII in TNBC patients. As reported above, increased SII correlated with poor DFS, DMFS, and OS in TNBC patients and its prognostic role carried on into the multivariate analysis, which was consistent with previous findings from investigations of other tumors. According to Huang et al,[40] high SII was associated with poor outcomes in the evaluation of the prognostic value of preoperative SII in gastric cancer patients. To date, SII's role in prognosis has been investigated in different tumors.[31–35,37,38,40–42] Hu et al[31] were the first researchers to propose SII as having

a novel, independent prognostic role in Chinese hepatocellular cancer patients. Patients with elevated SII had higher recurrence and reduced survival rates than patients with decreased SII. Hu et al's finding has received backing from numerous other investigations. Tong et al[38] demonstrated the correlation between SII and tumor response post-treatment and survival in non-small cell lung cancer patients, proving its independent prognostic role. Jiang et al[37] showed that elevated SII predicts poor survival for nasopharyngeal cancer patients independently. Our results, in concomitance with all these reports, point to SII having a role to play in major cancer types, including breast cancer.

Accumulating studies have substantiated the association between cancer and the inflammatory system. Counts of the peripheral inflammatory cells, such as monocytes, lymphocytes, and neutrophils, before treatment, have validated the significant link between prognosis and the inflammatory system in different types of cancers.[21,28,43–50] As an integrated parameter, the prognostic value of SII in cancers may be explained by the function of platelets, neutrophils, and lymphocytes. Platelets promote tumor angiogenesis and

metastases and shield tumor cells from the antitumor immune response.[51] Neutrophils are inflammatory and immune parameters that play a part in the proliferation and metastasis of tumors by releasing such inflammatory mediators as neutrophil elastase, interleukin-8, and matrix metalloproteinase-9.[52] Contrary to platelets and neutrophils, lymphocytes infiltrate tumors and are associated with better survival in cancer patients, since their immune response can prevent tumor growth and metastasis.[53,54]

Although our investigation of SII in TNBC patients provided room for optimism, it had its drawbacks. First, we lacked external validation. Second, we could not avoid a selection bias of a retrospective, single-center study. Third, while diseases that impacted SII were excluded, some patients who carried these diseases might still have participated in the research if their medical records were not logged electronically.

Conclusion

We have revealed in our investigation that SII is a potential biomarker that could predict DFS and OS in TNBC, suggesting that SII's role could be significant in the growth, proliferation, and prognosis of breast cancer cells. Given, therefore, that SII can be obtained easily, it could eventually be introduced in clinical use to identify progressive TNBC if more in-depth studies with little to no nuance are carried out to ascertain its specificity.

Disclosure

The authors report no conflicts of interest in this work.

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