

Systemic immune-inflammation index and ultrasonographic classification of breast imaging-reporting and data system predict outcomes of triple-negative breast cancer

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Introduction: This research was conducted to explore the relationship between the systemic immune-inflammation index (SII) and breast imaging-reporting and data system (BI-RADS) classification using ultrasonography and the survival of patients with triple-negative breast cancer (TNBC) in a cohort of Chinese.

Methods: A total of 215 TNBC patients treated at our hospital between November 2008 and March 2016 were enrolled in this study. We used the log-rank test and Kaplan–Meier curves to assess the overall survival (OS) and disease-free survival (DFS) differences between groups. The prognostic role of SII and other clinicopathological characteristics in TNBC patients were identified using the Cox regression model.

Results: Patients with low and high SII had median OS of 60.9 and 40.3 months, respectively, (HR=3.78, 95% CI: 2.16–4.15, $P<0.001$); while the median DFS was 22.4 months and 14.4 months for TNBC patients with low and high SII, respectively (HR =3.16, 95% CI: 1.82–4.02, $P<0.001$). For patients with grade 5 ultrasonographic BI-RADS classification, the median DFS and OS were 41.2 and 16.5 months, respectively, whereas, it was 57.7 and 21.3 months, respectively, for those with BI-RADS grades 3–4 ($P<0.01$). According to multivariable analyses, increased SII was a risk factor that independently predicted poor OS (HR =2.96, 95% CI: 2.18–3.98, $P<0.001$) and DFS (HR = 2.85, 95% CI: 1.62–3.81, $P=0.005$). In addition, tumor stage, BI-RADS, and histological grade also independently predicted poor OS ($P=0.002$, <0.001 , 0.004).

Conclusion: Pretreatment SII and BI-RADS 5 were independent indicators for prognosis in TNBC patients. It is imperative to conduct prospective studies to evaluate the potential role of SII in patient selection, treatment guidance, and design of clinical trials.

Keywords: TNBC, SII, inflammation, prognosis, immunity

Introduction

Currently, breast cancer is the most common cancer in women, with a yearly increasing incidence in China.¹ Although the mortality rates of breast cancer have decreased in recent years due to advances in tumor therapy, the disease is still one of the most common causes of cancer mortality among women.² The prognosis of breast cancer is affected by several factors, including molecular, biological characteristics (such as human epidermal growth factor receptor 2 [HER2], hormonal receptors, and molecular subtypes) and clinicopathological parameters (such as the age of patient, lymph node status, tumor size, etc).^{3–5}

Triple-negative breast cancer (TNBC) accounts for ~10%–20% of any newly diagnosed breast cancer. It is defined as the negative expression of HER2 and hormonal receptors.⁶ Progression and relapse are commonly observed in TNBC women. The peak of recurrence takes place within the first 3–5 years after diagnosis.⁷ TNBC has a characteristic of an intrinsic, aggressive tumor pathology, including histological grade, high levels of proliferation, frequency of TP53 mutations, and mitotic index, which lead to large tumor sizes, as well as poor clinical outcomes.^{8,9} Therefore, it is particularly important to explore factors for the prognosis of TNBC in patients.

In recent years, many researchers have paid attention to inflammation and found that cancer-related inflammation played an essential role in cancer development and prognosis.^{10–13} Systemic immune-inflammation index (SII) is an indicator that is based on peripheral neutrophil, lymphocyte, and platelet counts, and defined as (platelet \times neutrophil)/lymphocyte, a potential indicator capable of establishing balance between inflammatory and immune status in the host.¹⁴ SII has been investigated in various cancers, including nasopharyngeal carcinoma, prostate cancer, colorectal cancer, pancreatic cancer, gastric cancer, and hepatocellular carcinoma.^{14–21} However, the role of SII in breast cancer patients has not been well understood. Therefore, this research was focused on exploring the clinical significance of SII in TNBC patients.

Materials and methods

Patient enrollment

The present study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of The Affiliated Hospital of North Sichuan Medical College. Written forms of informed consent were not required for individual patients because the study was retrospective, and all the data in the analysis were anonymous.

A total of 215 patients diagnosed with TNBC from November 2008 to March 2016 at our hospital were retrospectively included. We enrolled patients with histological confirmation of TNBC and they underwent surgery with neoadjuvant chemotherapy and adjuvant chemotherapy. We excluded patients with inflammatory diseases, immune diseases, coronary artery diseases, and hematological diseases; suffering from an infectious disease within 2 weeks of enrollment; using anti-inflammatory or immunosuppressive drugs prior to enrollment; with metastatic or inflammatory breast cancer. Data for differential blood counts were collected prior to anticancer treatment.

Collection of clinicopathological parameters

Negative estrogen receptor and progesterone receptor were defined as 1% of invasive tumor nuclei observed in the immunohistochemistry test. Negative HER2 status implies that the immunohistochemistry result was 0; positive HER2 means that the result was 3+ or positivity for 1+ and 2+ patients was confirmed by fluorescence in situ hybridization. All patients underwent radical mastectomy or breast-conserving surgery. The treatment methods for patients included chemotherapy (neoadjuvant and adjuvant chemotherapy), adjuvant radiotherapy, and surgery (mastectomy or breast-conserving surgery). Chemotherapy strategies included anthracyclines + cyclophosphamide + paclitaxel (AC-T) for 163 (76%) patients and docetaxel + carboplatin (TP) for 52 (24%) patients. Data for platelet count, neutrophil count, and lymphocyte count, as well as age, tumor size, breast imaging-reporting and data system (BI-RADS), lymph node metastasis, lympho-vascular invasion, histological grade, and antitumor treatment were collected. The SII was defined by the formula: (neutrophil \times platelet)/lymphocyte.

Follow-up

Patient follow-up was regularly conducted; every three months within the first 2 years after surgery, and then every 6 months from that point until death or lost follow-up from the study. Ultrasound imaging, positron emission computed tomography, magnetic resonance imaging, and computed tomography were used to assess disease status. The contents of follow-up included the extent of disease progression, loss of follow-up, and death. The deadline for follow-up was December 2017. Disease-free survival (DFS) time refers to the period from surgery to the first recurrence of disease, while overall survival (OS) was defined as the period from pathological diagnosis to death.

Statistical analyses

The Kaplan–Meier analysis was applied to evaluate the DFS and OS. Comparison of the differences in survival between patients from the two groups was performed using the log-rank test. We used the Cox regression model for multivariable analysis to clarify independent factors for prognosticating TNBC in patients with breast cancer. Patients were divided into high or low SII groups according to the median index value. Chi-squared tests and Fisher's exact tests were used to evaluate the correlation between clinicopathological parameters and SII. $P < 0.05$ was considered statistically significant. The SPSS 21.0 software (IBM Corporation, Armonk, NY, USA) was used for data analysis.

Results

Patient information

Table 1 summarizes the characteristics of the 215 TNBC patients at baseline in this study. One hundred eighty-one patients underwent radical mastectomy, while 34 patients received breast-conserving surgery. One hundred sixty-eight patients had ductal carcinoma, while 47 patients had lobular carcinoma. There were 138 and 77 patients with histopathological grades I, II, and III, respectively. Based on the American Joint Committee on Cancer staging system, 30, 114, and 71 patients were at stages I, II, and III of the disease, respectively. The median (range) value of SII was 624 (138–1,682), which was used to divide high and low SII.

Table 1 Baseline characteristics of 215 TNBC patients

Parameters	N=215	%
Age (years)		
≤50	155	72
>50	60	28
Type of surgery		
Breast-conserving surgery	34	16
Radical mastectomy	181	84
Tumor stage		
pT1	45	21
pT2	125	58
pT3	39	18
pT4	6	3
Tumor histology		
Ductal carcinoma	168	78
Lobular carcinoma	47	22
Histologic grade		
I–II	138	64
III	77	36
Lympho-vascular invasion		
Yes	30	14
No	185	86
Lymph node status		
pN0	88	41
pN1	71	33
pN2	32	15
pN3	24	11
AJCC stage		
I	30	14
II	114	53
III	71	33
Chemotherapy		
Neoadjuvant chemotherapy	45	21
Adjuvant chemotherapy	170	79
Adjuvant radiotherapy		
Yes	135	63
No	80	37
SII		
≥624	108	50
<624	107	50

Abbreviations: AJCC, American Joint Committee on Cancer; TNBC, triple-negative breast cancer.

One hundred twenty-five and 90 patients were identified as BI-RADS 5 (high BI-RADS) and BI-RADS 3–4 (low BI-RADS), respectively. The median time for follow-up was 49.2 months (4–105 months). At the end of follow-up, 71 (33%) patients were still alive, 5 (2%) patients lost follow-up, and 139 (65%) patients had died. One hundred seventy-one patients had recurrent or metastatic cancer, of whom 136 died. Three patients died without any recurrence or metastasis.

Relationship between clinicopathological parameters and SII

The association between SII and clinicopathological parameters is shown in Table 2. Histologic grade, lymph node status, and tumor stage positively correlated with SII ($P<0.001$, $P=0.002$, $P=0.004$, respectively). We did not find a statistically significant correlation between other clinicopathological parameters and SII in our study ($P>0.05$, Table 2).

Kaplan–Meier and univariable analysis

The median DFS for patients with TNBC who had low and high SII was 22.4 months and 14.4 months, respectively, (HR=3.16, 95% CI: 1.82–4.02, $P<0.001$; Table 3, Figure 1), while the

Table 2 Association between SII and clinicopathological parameters

Parameters	SII <624	SII ≥624	P
Age (years)			
≤50	80	75	0.448
>50	27	33	
Type of surgery			
Breast-conserving surgery	18	16	0.712
Radical mastectomy	89	92	
Tumor stage			
pT1	31	14	0.004
pT2–4	76	94	
Histologic grade			
I–II	92	46	<0.001
III	15	62	
Lymph node status			
pN0	55	33	0.002
pN1–3	52	75	
AJCC stage			
I	20	10	0.051
II–III	87	98	
Chemotherapy			
Neoadjuvant chemotherapy	25	20	0.406
Adjuvant chemotherapy	82	88	
Adjuvant radiotherapy			
Yes	65	70	0.574
No	42	38	

Abbreviations: AJCC, American Joint Committee on Cancer; SII, systemic immune-inflammation index.

median OS was 60.9 and 40.3 months for patients who had low and high SII, respectively (HR =3.78, 95% CI: 2.16–4.15, $P<0.001$; Table 3, Figure 2). The median DFS for patients with BI-RADS 5 was 16.5 months, while it was 21.3 months for those with BI-RADS 3–4 (HR =1.74, 95% CI: 1.23–2.45, $P=0.001$; Table 3, Figure 3). The median OS was 41.2 and 57.7 months for patients with BI-RADS 5 and 3–4, respectively (HR =2.35, 95% CI: 1.61–3.42; $P<0.001$; Figure 4, Table 3).

Multivariable analysis

Multivariable analysis showed that elevated SII was an independent risk factor for poor DFS (HR =2.85, 95% CI: 1.62–3.81, $P=0.005$; Table 4) and for poor OS (HR =2.96, 95% CI: 2.18–3.98, $P<0.001$; Table 4). Moreover, tumor stage, BI-RADS, and histological grade independently associated with poor OS for patients with TNBC ($P=0.002$, $P<0.001$, $P<0.004$, Table 4).

Table 3 Univariable analysis for DFS and OS in TNBC

Variables	DFS			OS		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
>50 vs ≤50	0.91	0.78–1.25	0.170	0.93	0.69–1.51	0.290
Type of surgery						
Radical mastectomy vs breast conserving surgery	1.38	0.73–1.72	0.212	1.33	0.87–1.61	0.239
Tumor stage						
pT2–4 vs pT1	2.23	1.61–3.15	0.005	2.93	2.16–3.82	<0.001
BI-RADS						
5 vs 3–4	1.74	1.23–2.45	0.001	2.35	1.61–3.42	<0.001
Histologic grade						
III vs I–II	3.05	2.64–4.25	<0.001	3.77	2.53–4.96	<0.001
Lympho-vascular invasion						
Yes vs no	1.63	1.24–2.26	0.018	1.81	1.36–2.65	0.014
Lymph node status						
pN1–3 vs pN0	2.56	1.13–2.72	0.003	3.05	1.61–4.16	0.002
Chemotherapy						
Neoadjuvant vs adjuvant	1.10	0.62–1.62	0.426	1.11	0.72–1.61	0.704
Chemotherapy options						
AC-T vs TP	1.22	0.84–1.39	0.391	1.15	0.89–1.31	0.514
Adjuvant radiotherapy						
Yes vs no	1.02	0.59–1.36	0.510	1.07	0.65–1.52	0.685
SII						
≥624 vs <624	3.16	1.82–4.02	<0.001	3.78	2.16–4.15	<0.001

Abbreviations: AC-T, anthracyclines + cyclophosphamide + paclitaxel; BI-RADS, breast imaging-reporting and data system; DFS, disease-free survival; OS, overall survival; SII, systemic immune-inflammation index; TNBC, triple-negative breast cancer; TP, docetaxel + carboplatin.

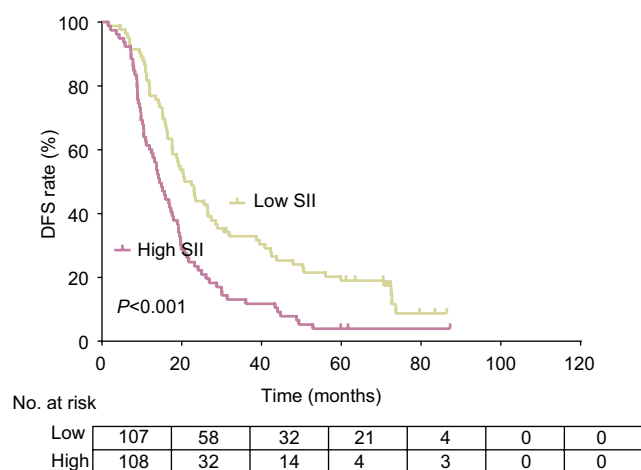


Figure 1 DFS rates for 215 patients with TNBC as indicated by SII ($P<0.001$).
Abbreviations: DFS, disease-free survival; SII, systemic immune-inflammation index; TNBC, triple-negative breast cancer.

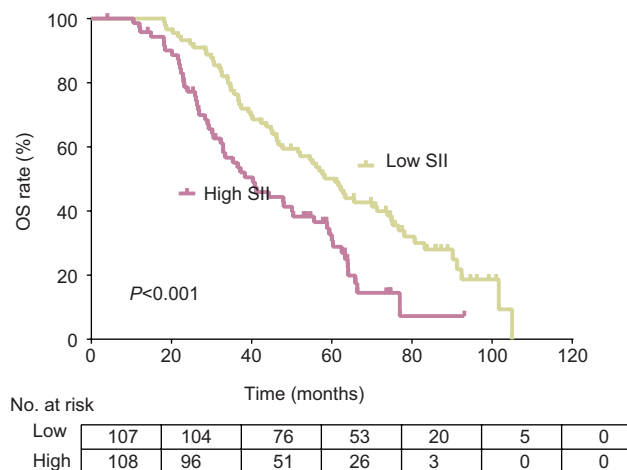


Figure 2 OS rates for 215 patients with TNBC as indicated by SII ($P<0.001$).
Abbreviations: OS, overall survival; SII, systemic immune-inflammation index; TNBC, triple-negative breast cancer.

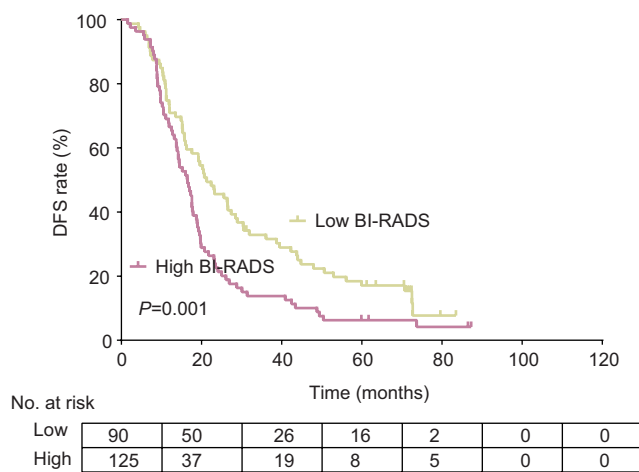


Figure 3 DFS rates for 215 patients with TNBC as indicated by BI-RADS ($P=0.001$).
Abbreviations: BI-RADS, breast imaging-reporting and data system; DFS, disease-free survival; TNBC, triple-negative breast cancer.

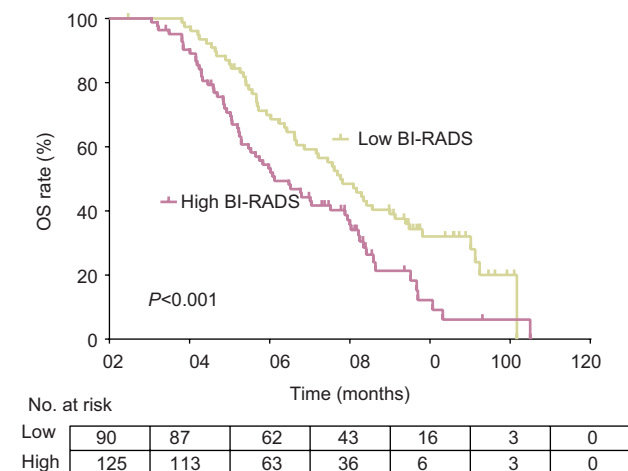


Figure 4 OS rates for 215 patients with TNBC as indicated by BI-RADS ($P<0.001$).
Abbreviations: BI-RADS, breast imaging-reporting and data system; OS, overall survival; TNBC, triple-negative breast cancer.

Discussion

Several studies have demonstrated the association between the inflammatory system and tumors. The number of peripheral inflammatory cells before treatment, including lymphocytes, monocytes, and neutrophils, have shown the strong link between the prognosis of different kinds of cancer and the inflammatory system.^{22–32} Neutrophils, reportedly, is an indicator of inflammatory and immune response; their involvement in the proliferation and metastasis of tumor by releasing inflammatory factors, such as neutrophil elastase, matrix metalloproteinase-9, and interleukin-8 has been elucidated.³³ In addition, platelets have been shown to play a role in promoting angiogenesis and metastases of tumors, as well as shielding tumor cells to protect them from antitumor immune responses.³⁴ In contrast, tumor-infiltrating lymphocytes are involved in the prevention of tumor growth and spread, by initiating antitumor immune response, and correlate with better survival in cancer patients.^{35,36}

Until now, the values of SII in prognosis have been reported in nasopharyngeal carcinoma, prostate cancer, colorectal cancer, pancreatic cancer, gastric cancer, and hepatocellular carcinoma.^{14–17,19–21,37,38} Hu et al¹⁴ reported, for the first time, the role of SII in hepatocellular carcinoma as a novel and independent prognostic indicator. Compared with the patients who had lower SII, patients with higher SII before treatment had shorter survival time and increased recurrence rates. Jiang et al²¹ also showed SII as an independent predictor for survival in patients with nasopharyngeal carcinoma, while Huang et al³⁹ reported that high SII values correlated with poor clinicopathological features and could be used to identify poor prognosis.

Table 4 Multivariable analysis for DFS and OS in TNBC

Variables	DFS			OS		
	HR	95% CI	P	HR	95% CI	P
Tumor stage pT2–4 vs pT1	2.25	1.52–2.81	0.014	2.06	1.45–3.56	0.002
BI-RADS 5 vs 3–4	1.59	1.12–2.26	0.009	2.18	1.481–3.22	<0.001
Lympho-vascular invasion Yes vs no	1.53	0.93–1.84	0.144	1.52	1.06–1.86	0.039
Histologic grade III vs I–II	3.03	1.61–3.48	0.010	2.66	1.88–3.25	0.004
Lymph node status pN1–3 vs pN0	1.80	0.92–2.16	0.056	2.16	1.81–2.48	0.014
SII ≥624 vs <624	2.85	1.62–3.81	0.005	2.96	2.18–3.98	<0.001

Notes: $P<0.008$ was considered as statistically significant for multiple comparisons by using Holm–Bonferroni correction.

Abbreviations: BI-RADS, breast imaging-reporting and data system; DFS, disease-free survival; OS, overall survival; SII, systemic immune-inflammation index; TNBC, triple-negative breast cancer.

In this study, we have shown that increased SII independently correlates with poor OS and DFS in TNBC patients, which is consistent with previously reported findings. Tong et al²⁰ proved SII's independent prognostic value when investigating the association between SII and OS and treatment response in patients with non-small-cell lung cancer at stage III. Furthermore, we found that tumor stage, BI-RADS, and histological grade also independently predicted poor DFS, while the same factors, alongside lympho-vascular invasion and lymph node status were independently associated with poor OS for patients with TNBC.

To the best of our knowledge, this study is the first research to explore the clinical significance of SII in Chinese TNBC patients. Nevertheless, there are some limitations in our study. Firstly, even though we ruled out patients with diseases that may influence the SII, some of the patients who took part in our study might have had these diseases but were not registered in the medical records. Secondly, the sample size for our study was small. Finally, this retrospective, single-center study inevitably had selection bias and lacked external validation.

Conclusion

This study indicates that SII may be associated with OS and DFS in TNBC patients and could be conveniently introduced in clinical practice for identifying TNBC patients with poor prognosis. It, however, still requires prospective studies to evaluate the possible role of SII in selecting patients, guiding treatments, and designing clinical trials.

Disclosure

The authors report no conflicts of interest in this work.

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