

Comparison of the Systemic Immune Inflammation Index with Prognostic Factors in Patients Operated for Breast Cancer

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Abstract: The aim of this study is to investigate the utility of the pre-operative systemic immune inflammation index (SII) as an independent prognostic factor in patients operated on for breast cancer. The clinical, pathological and laboratory data of 112 patients who were operated for breast cancer in Sivas Cumhuriyet University Surgical Oncology Department between January 1, 2014 and January 1, 2020 were retrospectively analyzed. Preoperative systemic immune-inflammation index (SII) was calculated. The SII cut-off value was set at 600. The SII value was compared with ca 15-3, histological grade, TNM classification, and tumor size which is an independent prognostic factor for breast cancer. All patients were women. The average age of the patients was calculated as 58.5 years. There was a significant relationship between SII and Ca 15.3, histological grade, tumor size, and anatomical stage obtained by TNM classification. The increase in the systemic immune-inflammation index (SII) as other prognostic values increase in our study suggests that this value can be used as an independent prognostic factor. We think that SII can be used as a prognostic factor in the clinic because it does not take much time to calculate it, it is easily accessible and its cost is low.

INTRODUCTION

Breast cancer is the second most common cause of mortality and morbidity in women worldwide. It is also one of the most common cancers in women worldwide¹. Although the incidence of breast cancer in the world is increasing, the number of people who have been treated and survivor for breast cancer is increasing gradually². Breast cancer treatment varies according to the stage and pathological diagnosis of the tumor. While the treatment option may be surgery, radiotherapy, chemotherapy, endocrine treatment or their combination may also be the treatment option³. At the same time, clinical results of breast cancer patients are unsatisfactory due to the ineffectiveness of prognostic factors. Therefore, it is necessary to define new and effective prognostic factors in order to regulate breast cancer treatment and to increase survival.

Some prognostic factors such as lymph node invasion, menopause, age, pathological stage, histological type, molecular subtype, and tumor size affect the course of breast cancer⁴. Determining the number of peripheral blood cells can help us gain insight into the inflammation of tumor cells. In this way, it can make it easier for us to organize the treatment of the disease. Many recent studies have shown that parameters such as neutrophil (N), white blood cell (W), lymphocyte (L), monocyte (M), platelet count (P), C reactive protein (CRP), neutrophil lymphocyte ratio (NLR) in systemic circulation and systemic inflammatory response index (SIRI) are high inflammatory biomarkers and these can be considered as prognostic factors for malignant tumors⁵⁻⁸. A new prognostic factor has been identified for patients with cancer called the systemic immune-inflammation index (SII). SII is associated with N, L and P numbers and calculated as $SII = N \times P / L$. It has been shown that SII is associated with the survival and clinical outcomes of cancer patients^{9, 10}.

Various tumor markers such as Ca 15-3 are used for breast cancer¹¹⁻¹³. Although Ca 15-3 increases mostly in metastatic breast cancers, it can be detected in high concentrations in various subtypes of breast cancer. Ca 15-3 may also be elevated in gastric cancer, ovarian cancer lung cancer, pancreatic cancer¹⁴⁻¹⁷. Although it is known that Ca15-3 has little role in early breast cancer diagnosis, it has been shown that it can be used as a prognostic factor¹⁸⁻²⁵.

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The histology of breast carcinoma is evaluated by the scoring system modified by Elston and Ellis, which Bloom made in 1950 and was used by Bloom and Richardson in 1957²⁶⁻²⁸. In this scoring system, the grade of tumor cells are scored between 1-3 according to the nuclear properties, mitosis numbers and ratio of tubule structures. Grade 1-well differentiated (3-5 points), grade 2-moderately differentiated (6-7 points), grade 3-poorly differentiated (8-9 points). This scoring reflects the potential malignancy grade of the tumor cells²⁶. The relationship of many factors with this histological grade system, which is accepted as a prognostic factor, has been investigated²⁹.

TNM staging system was developed for breast cancer by Pierre Dennoix in France in the 1940s and 1950s³⁰. The TNM staging we currently use is the algorithm contained in the book American Joint Committee on Cancer (AJCC), which published its first edition in 1977^{30,31}.

The anatomical stage of breast cancer is evaluated between 0 and 4 according to the size of the tumor (T), the number of lymph nodes involved (N), and distant metastasis (M)³².

In this study, it was investigated whether it is possible to use SII as an independent prognostic factor in the clinic by comparing SII values with ca 15-3, tumor size, histological grade and anatomical stage, which are considered prognostic factors.

MATERIALS and METHODS

Ethical approval

Since the article we wrote was not prepared by taking biological samples (blood, urine, serum, etc.) from humans, not based on the study of biological samples previously taken, did not evaluate personal information and their relationship with diseases and was not a study in which experimental procedures (drugs, etc.) were applied to humans, ethics committee approval was not required.

Patients and study design

The clinical, pathological and laboratory data of 112 patients who were operated for breast cancer between January 1, 2014 and January 1, 2020 were retrospectively analyzed. Laboratory values (neutrophil, lymphocyte, platelet, ca15-3 values) of the patients 3 days before surgery were used. Clinico-pathological data were retrieved from their retrospectively recorded files. Calculated by the formula $SII = P (10^9/L) \times N(10^9/L) / L(10^9/L)$. Clinico-pathological data includes gender, age, tumor size, histopathological tumor grade (modified scart-bloom richardson), anatomical stage.

Statistical analysis

The normality ranking of the data used in the study was achieved by the Shapiro-Wilk test. It was observed that the order of normality was not provided. Mann Whitney U test was used in paired comparisons, and Kruskal Wallis H test was used in multiple comparisons. Chi Square was used for comparison of categorical data. Analysis results were interpreted at a 95% confidence level.

RESULTS

112 patients were studied. All of the patients were women, their average age was 58.5. It was observed that 45 patients underwent Breast-Conserving Surgery (BCS), and 67 patients underwent Modified Radical Mastectomy (MRM). When the histopathological of the tumors were examined, it was found that 11 invasive malignant

epithelial tumors, 2 invasive lobular carcinomas, 2 invasive papillary carcinomas, 3 invasive medullary carcinomas, 2 mixed invasive carcinomas, 1 stony ring cell carcinoma, 4 ductal carcinoma insitu, 87 unspecified invasive ductal carcinomas.

When tumor size was compared with SII, it was seen that as the tumor size increased, SII increased significantly. While the median value of tumor size was found to be 13 in patients with SII less than 600, it was found that the median value of tumor size was 50 in patients with SII greater than 600 (Table 1).

Table 1. Relationship between SII and tumor size (mm) SII: Systemic immun-inflammation index IQR: Inter Quantile Range SII cut-off value = 600

SII	Size (mm)				P
	%25	%75	Median	IQR	
<600	10,00	22,00	13,00	12	<0,001
>600	27,00	88,00	50,00	59	

It was observed that as Ca 15-3 increased, SII also increased significantly. While the median value of ca 15-3 was found to be 15.34 in patients with SII less than 600, it was found that the median value of ca 15-3 was 76.5 in patients with SII greater than 600 (Table 2).

Table 2. Relationship between SII and ca 15-3 (U/ml) SII: Systemic immun-inflammation index IQR: Inter Quantile Range SII cut-off value = 600

SII	Ca 15-3 (U/ml)				P
	%25	%75	Median	IQR	
<600	11,28	23,00	15,34	11.72	<0,01
>600	23,30	113,00	76,50	89.7	

It is observed that as the histological grade of the tumor increases, SII also increases significantly. While the number of patients with SII less than 600 in grade 1 was 23, the number of patients with SII greater than 600 in grade 1 was 2, the number of patients with SII less than 600 in grade 2 was 6, the number of patients with SII greater than 600 in grade 2 was 44, and the number of patients with SII less than 600 in grade 3 was 0 while the number of patients with SII greater than 600 in grade 3 was found to be 37 (Table 3).

Table 3. Relationship between SII and histological grade SII: Systemic immun-inflammation index BR: Bloom Richardson SII cut-off value = 600

Gra-de.BR	1,00	Count	SII		Total	P
			<600	>600		
Gra-de.BR	1,00	Count	23	2	25	<0,001
		% within Grade.BR	92,0 %	8,0 %	100,0 %	
	2,00	Count	6	44	50	
		% within Grade.BR	12,0 %	88,0 %	100,0 %	
	3,00	Count	0	37	37	
		% within Grade.BR	0,0 %	100,0 %	100,0 %	
Total	Count	29	83	112		
	% within Grade.BR	25,9 %	74,1 %	100,0 %		

It is seen that as the tumor stage increases, SII also increases significantly. While in patients with SII values less than 600; 3, 11, 13, 1, 0, 0, 1 patients were detected in stages 0, 1, 2a, 2b, 3a, 3c, 4, respectively, in patients with SII greater than 600; 0, 1, 32, 19, 17, 14, 0 patients were detected in stages 0, 1, 2a, 2b, 3a, 3c, 4 were identified, respectively (table 4).

Table 4. Relationship between SII and grade determined by anatomical stage SII: Systemic immun-inflammation index SII cut-off value = 600

Stage	0	Count	SII		Total	P
			<600	>600		
			3	0	3	<0,001
		% within evere	100,0 %	0,0%	100,0 %	
	1	Count	11	1	12	
		% within evere	91,7 %	8,3%	100,0 %	
	2a	Count	13	32	45	
		% within evere	28,9 %	71,1 %	100,0 %	
	2b	Count	1	19	20	
		% within evere	5,0%	95,0 %	100,0 %	
	3a	Count	0	17	17	
		% within evere	0,0%	100,0 %	100,0 %	
	3c	Count	0	14	14	
		% within evere	0,0%	100,0 %	100,0 %	
	4	Count	1	0	1	
		% within evere	100,0 %	0,0%	100,0 %	
Total		Count	29	83	112	
		% within evere	25,9 %	74,1 %	100,0 %	

DISCUSSION

Recently, many studies have been conducted on systemic inflammatory response and prognostic factors in cancer patients. These studies have shown that systemic inflammatory response can predict tumor behavior and patient survival, and thus can be used as an independent prognostic factor^{10,33-35}. SII is a new systemic immune inflammation index. SII represents the inflammatory and immune status of the patient. It has been proven that SII can be used as a preoperative biomarker in various tumors^{10,33-36}.

SII is calculated using the formula neutrophil count x platelet count / lymphocyte count. Since the SII index is calculated by the numbers of neutrophil platelet lymphocytes, the change of these cells directly affects the SII index. Neutrophils can increase tumor activity by secreting various inflammatory mediators such as vascular endothelial growth factor, interleukin (IL) -6, IL-10, and IL-22³⁷. Platelets can protect cancer cells from being broken down by natural killer cells³⁸. Lymphocytes can affect the growth of the tumor with the cytokines they secrete, and it does this by inhibiting the proliferation and migration of cancer cells³⁹. On the other hand, lymphocytes play a role in cancer immune surveillance and thus prevent the progression of cancer⁴⁰. Therefore, cancer patients with low lymphocyte count give inadequate response to immunological reactions⁴¹.

The relationship of SII with various types of cancer has been investigated. Hu et al. showed that SII is a prognostic factor related to local recurrence in patients with hepatocellular cancer³⁵. Whang et al. showed that the SII value in patients with gastric cancer is related to local lymph node metastasis, distant metastasis, age, and tumor invasion¹⁰. Similar results were found with gastric and hepatocellular cancers in studies conducted to evaluate the relationship between lung cancer and SII³⁶. The results of a large-scale study on breast cancer involving 2642 patients in 2020 showed that SII is an independent prognostic factor for breast cancer⁴². In the study conducted by Li et al. with 161 breast cancer patients, it was shown that SII elevation in luminal breast cancer increased resistance to endocrine treatment, and

TNM staging and SII were shown to be independent prognostic factors in breast cancer⁴³. The results of the study conducted by Jiang et al. showed that SII is a poor prognostic factor for nasopharyngeal cancer patients⁴³. The results of our study show that SII can be used as an independent prognostic factor for clinical evaluation of breast cancer and other cancers.

In this study, SII was compared with ca 15-3, histological grade, tumor size and anatomic stage which is considered as a prognostic factor for breast cancer. SII was found to be correlated with prognostic factors. It was also observed that high SII was associated with high malignancy, metastatic lymph node, high stage, high histological grade, high ca15-3, high tumor size.

There are some restrictions for this study. The first is that it has been applied in a small number of patients in a small center. The second is that it was made in one center. It would be more useful to compare the results of different centers with more patients.

Conclusion

As a result, we think that SII, like other prognostic factors, can be used as an independent prognostic factor for breast cancer. We think that multicenter studies with larger numbers of patients may be useful to evaluate the prognostic relationship between breast cancer and SII.

Conflict of interest

The authors declare that they have no conflict of interest.

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