MSD

Medical Science and Discovery
ISSN: 2148-6832

Effect of systemic immune-inflammation index on prognostic parameters and survival in patients with breast cancer under the age of 40 years

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ABSTRACT

Objective: Systemic immune inflammation index, which is one of the systemic inflammatory markers obtained by using peripheral blood cells, neutrophils, lymphocyte and platelet counts, has been previously shown to be prognostic in many types of cancer, and it has been also shown in previous studies that SII was associated with prognosis in patients who received adjuvant and neoadjuvant therapy in breast cancer. In our study, the evaluation of the potential prognostic importance of SII in patients with breast cancer diagnosed before the age of 40 was aimed.

Material and method: For the study, demographic, histopathological, clinical and file data of 129 patients who were diagnosed with breast cancer in the tertiary medical oncology outpatient clinic and were 40 years old and younger at the time of diagnosis were recorded retrospectively. SII was calculated according to the neutrophil count x platelet number/lymphocyte (NxP / L) formula, and those below the optimal cut-off value obtained by ROC analysis were classified as low SII, and those above it as High SII. The relationship between breast cancer clinicopathological variables and SII was evaluated by Chi-Square test. While the effect of SII on survival was evaluated by Kaplan Meiermethod, the Logrank test was used to evaluate survival in low and high groups.

Results: For the study, 1400 patients diagnosed with breast cancer were reviewed and 129 patients who were under the age of 40 at the time of diagnosis were included. Patients who had insufficient follow-up or whose pre-treatment hemogram values could not be reached, who had medication use that could affect their hemogram parameters, and those with inflammatory diseases were not included. The median age in the study was 35, and the youngest patient was 21 years old. In the study group, based on the SII cut-off value of 720 calculated according to the roc analysis, 73 patients were in the low SII group and 56 patients were in the high SII group. When the relationship between prognostic factors of the patients and SII was examined, no statistically significant relationship was observed between age, hormone receptor status, Her-2 status, histological subtype, clinical stage, grade, Ki 67 status, lymph node involvement and SII. However, in the survival analysis, although the median value could not be reached between the two groups, there was a significant difference in overall survival with SII ($p = 0.051$) and it was observed that survival was worse in the high SII group, and the 3 and 5-year survival rates were worse in the high group compared to the low ones.

Conclusion: In our study, we reached the conclusion that SII can be an independent prognostic factor for survival in patients with breast cancer diagnosed at 40 years of age or younger. Considering the SII status together with other prognostic factors in diagnosis, a more intensive treatment plan can be made for the patients. However, well-designed prospective studies including more patients are needed for the routine use of SII.

Keywords: Breast cancer, prognosis, systemic immune inflammation index, SII

Received 18-12-2020

Accepted 15-01-2021

Available Online: 18-01-2021

Published 30-01-2021

http://dx.doi.org/10.36472/msd.v8i1.452

INTRODUCTION

Breast cancer is the most common cancer among women all over the world, ranks 2nd among cancer deaths in women. (1). In the United States, it is estimated that 279,000 patients will be diagnosed with breast cancer in 2020 and approximately 43,000 patients will die due to breast cancer (1).

Mortality rates tend to decrease due to the development of examinations that allow early diagnosis of breast cancer and the successes achieved in systemic treatment over the past years. The risk of developing breast cancer increases with age; however, although breast cancer can also develop in young women, those diagnosed before the age of 40 are 6.6% of all cases, while those under 35 years old constitute 2.4% (2).

Breast cancer has a more aggressive course in cases under the age of 40, and the tumor generally tends to be larger, higher grade, more hormone receptor (HR) negative and epidermal growth factor 2 (HER-2) being positive. In younger patients, the frequency of triple-negative (ER (-) PR (-) HER2 (-)) tumors also increases (3).

Since breast cancer is a heterogeneous tumor with different genomic subtypes, it differs in prognosis. Tumor size, stage, histological subtype, lymph node involvement, hormone receptor (HR) status, epidermal growth factor 2 (HER2) status, grade survival, and prognosis are histopathological factors used to determine.

Also, age is accepted as an independent prognostic factor in breast cancer patients (4).

However, up-to-date and reliable prognostic parameters are still needed to personalize the treatment of breast cancer patients and improve survival.

Tumor microenvironment and cancer-associated inflammation play an important role in tumor development and prognosis (5).

Tumor micro environment includes neutrophils, monocytes, lymphocytes, and platelets, and in recent years studies evaluating the prognostic effect of inflammatory biomarkers in breast cancer patients, parameters such as neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR) have been confirmed to be an independent prognostic factor (6).

The systemic immune-inflammation index (SII) is a parameter calculated using platelet, neutrophil, and lymphocyte counts, reflecting the balance between host immune and inflammation status.

SII has previously been studied in colorectal, gastric, and pancreatic cancers and has been shown to be prognostic. The prognostic effect of SII has been investigated in patients with breast cancer before neoadjuvant therapy and in the adjuvant period in various subtypes, and the results are controversial (7, 8, 9, 10).

In our study, we aimed to evaluate the relationship of SII with other prognostic parameters and the effect on survival in patients diagnosed with breast cancer before the age of 40.

MATERIAL AND METHODS

The study, which was designed retrospectively, included patients who were diagnosed with breast cancer between 2006 and 2020, aged 40 years and younger, and admitted to the Medical Oncology Outpatient Clinic. The study was initiated after obtaining approval from the ethics committee of Afyon Health Sciences University. After obtaining written consents from the patients, histopathological, clinical and file data were recorded retrospectively.

Patients who were diagnosed with confirmed breast cancer histopathologically, over the age of 18, in the age of 40 years and younger, with regular file data and regular follow-up were included in the study.

Study exclusion criteria were determined as;

1) Patients with active infections or using steroids at the time of the hemogram
2) Ductal or Lobulercarcinoma in-situ
3) Patients who do not have sufficient follow-up and file data cannot be reached
4) Those with acute or chronic inflammatory diseases
5) Those diagnosed with hematological disease
6) Without hemogram data at the time of diagnosis
7) Male breast cancer.

Patients' age, histology, tumor size, lymph node metastasis status, histological grade, ER, PR, HER-2 status, Ki-67 index, operation type and treatment characteristics were obtained from the file and by reviewing the hospital information system. SII was calculated with the formula (neutrophil x platelet / lymphocyte) using the platelet (10^3/ µL), neutrophil (10^3/ µL), and lymphocyte (10^3/ µL) counts obtained from the preoperative hemogram examinations. The SII cut-off value was calculated by performing ROC analysis. The value obtained in max sensitivity and specificity was used as the SII value cut-off value.

After the treatment was completed, the patients were followed up every 3 months for the first 2 years, every 6 months between the 2nd and 5th years, and once a year after 5 years. Disease-free survival (DFS) in patients was calculated according to the time from diagnosis until the development of first disease recurrence, Overall survival (OS) was calculated according to the date of death from any cause or the last control date.

Statistical Analysis

The SPSS v. 20.0 Software (SPSS; Chicago, IL, USA) program was used in all analyses and a p value of < 0.05 was considered statistically significant. Descriptive statistics including patient age, tumor stage, clinical presentation, histopathological type, grade, immune histochemical findings, Ki 67 status were presented as frequencies and percentages of categorical variables and means and standard deviations of quantitative variables. Chi-square or Fisher's exact tests were employed for categorical variables. The relationship between SII and pathological parameters was evaluated by Roc curves, The Kaplan Meier method was used for OS and log-rank test was used to evaluate the survival differences between patients divided into two groups according to the optimal cut-off point.

http://dx.doi.org/10.36472/msd.v8i1.452

RESULTS

For the study, 1400 patients diagnosed with breast cancer in the tertiary medical oncology outpatient clinic were reviewed and 129 patients aged 40 and under at the time of diagnosis were included. The clinic-pathological characteristics of the patients are shown in Table 1.

The median age in the study was 35, and the youngest patient was 21 years old. Median body mass index (BMI) was 26.3 (19-40), smoking history was present in 7.8% (10 patients), 14 patients (10.9%) had a family history of breast cancer and only 1 patient was in the postmenopausal period. The most common clinical presentation was a palpable mass (86%), pain was the reason for the clinical presentation in 10 patients. Breast cancer was diagnosed in 5 (3.9%) patients during the controls performed for any reason. Considering histological subtypes, 115 (89%) patients had invasive ductal carcinoma, 5 patients (3.9%) had medullary carcinoma, 2 (1.6%) patients had invasive lobular carcinoma, and 7 patients had other histological subtypes.

It was seen that the right/left breast placement (64/65) was equal. Pathologically, in immuno histochemical evaluation, 105 (81.4%) of the patients were ER (+), 97 (75 %) were PR (+) and 34 (26.4%) were HER-2 (+). The number of triple-negative patients was 17 (13.2%). When the histological grades were examined, Grade 2 (39.5%) disease was the most common. Lymphovascular invasion was present in 38.8% of the patients, the perineural invasion was detected in 19% of the patients. When evaluated according to the stages of T, the most common clinical was T2 (37.2% 48 patients) while the most common with N1 patient ratio (32% 41 patients) was the lymph node involvement. According to the AJCC 7th staging system, the ratios of stage 1/2/3 patients were 26 (21.7%) / 58 (45%) / 26 (20.2%), respectively, and 13.2% of the patients were at the metastatic stage at the time of diagnosis. The most common type of surgery performed in patients who underwent surgery was breast-conserving surgery (50.4%). Adjuvant radiotherapy (RT) and chemotherapy (CT) were applied in 73.6% of patients, and 93 patients (72.1%) were given adjuvant hormonotherapy. The most commonly used hormonotherapy was determined as tamoxifen and LHRH (61.2) treatment. Neoadjuvant therapy was given to 12 (9.3%) patients. The median Ki67 level was 30 (2-90) in 87 patients whose Ki 67 data were available, while there were 47 (54%) patients below 30 and 40 (46%) patients above 30. Recurrence was observed in 26 patients during follow-up, and recurrence/metastasis development was served in 9 patients after adjuvant therapy. While 2 patients had second primary breast cancer, only 8 patients died in the study group. The diagnostic stages of those who died consisted of stage 3 and stage 4 patients (75%) at most.

In the study group, based on the SII cut-off value of 720 calculated according to the ROC analysis, 73 patients were in the low SII group and 56 patients were in the high SII group. When the relationship between prognostic factors of the patients and SII was examined, no statistically significant relationship was observed between age, hormone receptor status, Her-2 status, histological subtype, clinical-stage, grade, Ki 67 status, lymph node involvement and SII. Although it did not reach statistical significance according to SII levels, it was observed that the patients in the higher group had more advanced clinical stage and T stage and were younger patients. (Table 2)

However, in the survival analysis, although the median value could not be reached between the two groups, there was a difference between the two groups with SII in overall survival but statistical significance could not be reached ($p = 0.051$) and it was observed that survival was worse in the SII high group (figure 1 Kaplan-Meier).

Considering the 3-year and 5-year survival rates of the patients, it was seen that it was 98% and 98% in the Low SII group, respectively, while it was 89% and 69% in the high SII group. The 3 and 5-year survival rates were worse in the high group than in the low group. (Figure 2)

Table 1. General characteristics of the study group

		Number	%
Age	≤35	78	60.5%
	>35	51	39.5%
Family history	Present	14	10.9%
	Absent	111	86.0%
Histological Type	Invasive Ductal	115	89.1%
	Invasive lobuler	2	1.6%
	Medullary	5	3.9%
	Other	7	5.4%
Breast side	Right	64	49.6%
	Left	65	50.4%
Hormone receptor status (HR)	HR +	106	82.2%
	HR -	23	17.8%
HER-2 status	Her-2 +	34	26.4%
	Her-2 -	95	73.6%
AJCC Stage at Diagnosis	I	28	21.7%
	II	58	45.0%
	III	26	20.2%
	IV	17	13.2%
Type of Surgery	BCS	65	50.4%
	MRM	54	41.9%
Adjuvant Radiotherapy	Present	95	73.6%
	Absent	32	24.8%
Adjuvant Chemotherapy	Present	95	73.6%
	Absent	34	26.4%
Recurrence	Present	26	20.2%
	Absent	100	77.5%
Grade	I	15	11.6%
	II	51	39.5%
	III	46	35.7%
T stage	T1	32	24.8%
	T2	75	58.1%
	T3	13	10.1%
	T4	5	3.9%
SII	≤720	73	56.6%
	>720	56	43.4%
Ki67	≤30	44	50.5 %
	>30	43	49.5%

BCS (breast conservative surgery), **MRM** (modified radical mastectomy)

http://dx.doi.org/10.36472/msd.v8i1.452

Table 2. Clinicopathologic characteristics of the patients according to SII groups

	Category	SII 720 (73)	SII> 720 (56)	P value
Age (n/%)	≤35	38 (59.4)	40 (61.5)	0.472
	> 35	26 (40.6)	25 (38.5)	
ER Status (n/%)	Negative	16 (25)	8 (12.3)	0.510
	Positive	48 (75)	57 (87.7)	
PR status (n/%)	Negative	20 (31.3)	12 (18.5)	0.690
	Positive	44 (68.7)	53 (81.5%)	
HER-2 status (n/%)	Negative	45 (70.3)	50 (76.9)	0.257
	Positive	19 (29.7)	15 (23.1)	
AJCC stage (n/%)	Stage I	15 (53.6)	13 (46.4)	0.680
	Stage II	38 (65.5%)	20 (34.5)	
	Stage III	15 (57.7)	11 (42.3)	
	Stage IV	5 (29.4)	12 (70.6)	
Grade (n/%)	Good	11 (73.3)	4 (26.7)	0.164
	Moderate	25 (49)	26 (51)	
	Poor	29 (63)	17 (37))	
Lymph Node Status (n/%)	N0	32 (61.5)	20 (38.5)	0.880
	N1	26 (59.1)	18 (40.9)	
	N2	8 (61.5)	5 (38.5)	
	N3	7 (50)	7 (50)	
Breast side (n/%)	Right	27 (42.2)	37 (56.9)	0.670
	Left	37 (57.8)	28 (43.1)	
Surgery Type (n/%)	BCS	39 (60.9)	26 (41.3)	0.210
	MRM	24 (37.5)	30 (47.6)	
Ki 67 Status (n/%)	≤30	19 (43.2)	25 (56.8)	0.124
	>30	28 (65.1)	15 (34.9)	
Histological Type (n/%)	Invasive ductal carcinoma	55 (85.9)	60 (92.3)	0.245
	Invasive lobular carcinoma	2 (3.1)	0 (0)	
	Other	7 (11.1)	5 (7.7)	

SII: systemicimmune-inflammatoryindex, **ER:** estrogenreceptor, **PR:** progesterone receptor, **BCC:** breast , conservative surgery, **MRM:** modified radical mastectomy,

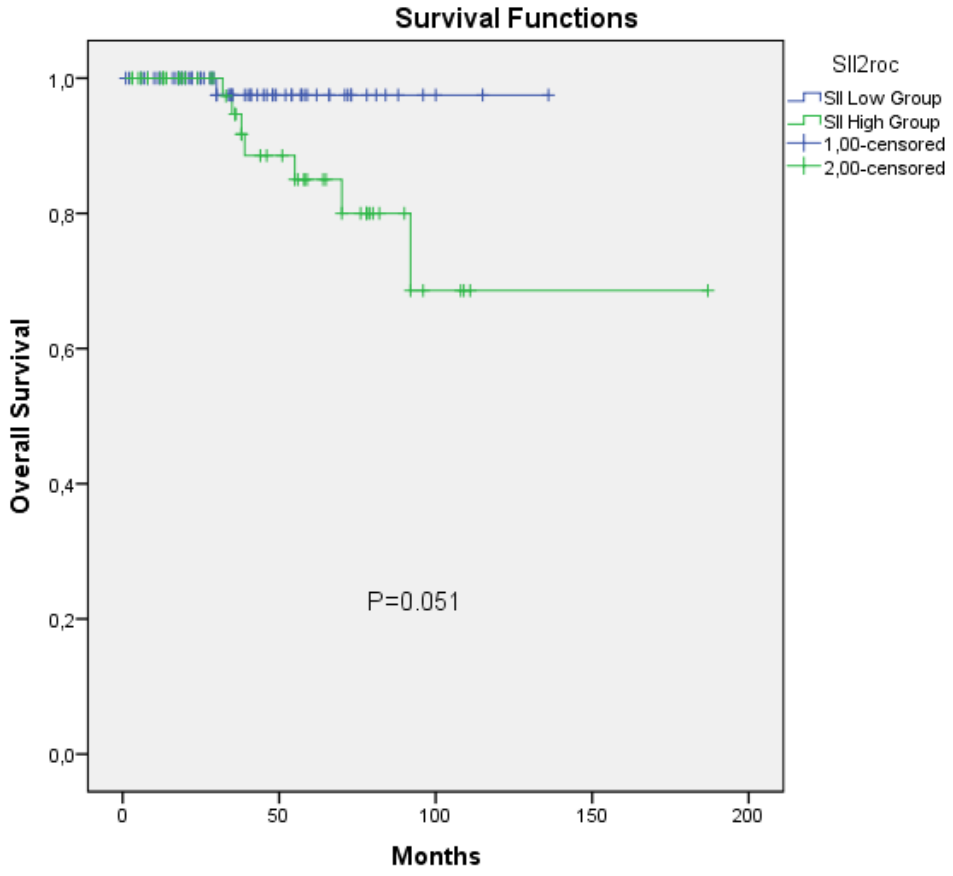

Figure 1: The effect of SII on OS in breast cancer under 40 years old female

http://dx.doi.org/10.36472/msd.v8i1.452

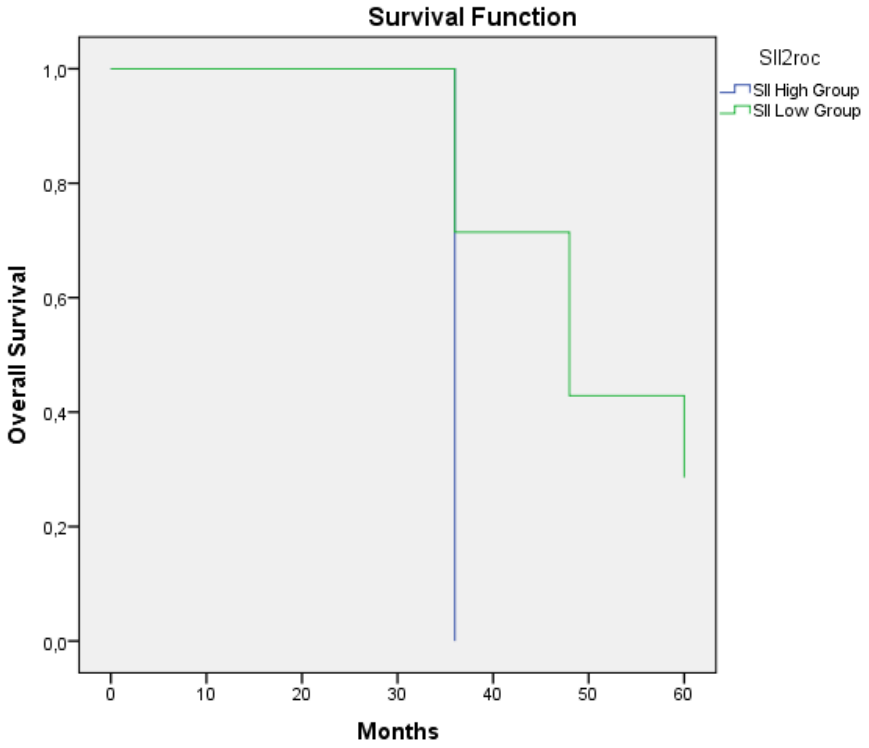

Figure 2: The 3 years and 5 years survival according to the SII groups

DISCUSSION

SII, an index based on inflammation, has previously been studied in patients with breast cancer in the adjuvant and neoadjuvant period, and according to our current knowledge, our study is the first study evaluating SII in breast cancer patients under the age of 40. In our study, we found that SII was associated with survival in breast cancer patients under the age of 40, and survival was statistically significantly worse in patients in the high SII group (P=0.051) (Figure 1).

In previous studies, it has been shown that high SII levels may be an independent prognostic factor in patients with gastric cancer, lung cancer, and hepatocellular cancer. (**11, 12, 13**)

Due to the increasing number of studies, information on the relationship between the inflammatory system and cancer is increasing. It has been confirmed in various cancer types that there was a significant relationship between pre-treatment monocyte, lymphocyte, neutrophil and platelet counts, inflammatory system and prognosis (**14, 15**). Platelets lead to tumor angiogenesis and the development of metastasis and form a shield of protection for tumor cells against antitumor immuneresponse (**16**).

Neutrophilsplay a role in the inflammatory and immuneresponse that plays a role in the proliferation and metastasis of the tumor by secreting various cytokines and inflammatory mediators (**17**). While lymphocytes have protective effects against tumor growth and metastasis, the prognosis is better in lymphocyte infiltrated tumors (**18**). Considering all of these, it is obvious that SII, a parameter determined by the use of platelets, neutrophils and lymphocytes may be prognostic in cancers.

In the study of Liu et al. on the evaluation of the prognostic effect of SII in triple-negative breast cancer patients, they have found that increased SII levels were associated with shorter disease-free survival (DFS) and overall survival (OS). They have also shown that these patients had more advanced T stages, their tumor grades had worse differentials, and Ki67 levels were statistically significantly higher (**10**).

In the study conducted by Jiang et al. with patients with Her2 (+) breast cancer who received adjuvant trastuzumab treatment, they have found that survival was significantly affected in patients with a cut off value of more than 442, which was determined according to the ROC analysis, and that these patients had shorter DFS and OS. Again, in this study, no significant relationship has been found between known prognostic factors such as ER status, tumor size, lymph node involvement and SII.

Similar results have been obtained in the study of Sun Y et al. with patients with hormonereceptor-negative Her2 (+) breast cancer (**8**).

In our study, we found that higher SII levels in young breast cancer patients were worse prognostic and although the median value in terms of OS could not be reached, it was associated with short survival, but statistical significance could not be reached difference between the two groups. The 3 and 5-year survivals were significantly shorter in the high SII groups (Figure 2).

When the relationship between previously defined prognostic factors and SII was evaluated, similar to Jiang L.'s study, no significant relationship was found in our study, however, patients in the high SII group were younger, had more

advanced T stage and AJCC clinical-stage, although they did not have statistical significance.

Chen Li et al., in their study evaluating the pre-treatment SII levels in patients receiving neoadjuvant chemotherapy, have found that patients with low SII levels had better DFS and OS times, and 3, 5, and 10-year DFS and OS times were better (9). In our study, in line with these findings, 3 and 5-year survival was better in the low SII group.

Although our study is current and has not been performed in breast cancer patients under the age of 40 before, it has many restrictions. The first is that it includes a relatively small number of patients from a single center and is retrospective, secondly, it has a short follow-up period, and the third is that all patients under the age of 40 are included. We think that more significant results can be obtained in studies when more homogeneous and more specific subgroups are included. However, the use of different cut-off values for SII in the literature creates limitations in terms of comparison with other studies. Although SII is an independent predictor in many cancers, its sensitivity and specificity are not high. Prospective randomized and well-designed studies are needed for optimization of the appropriate cut-off value.

CONCLUSION

SII can be used as an easy-to-apply and easily repeatable, inexpensive, and effective marker to show the prognosis in many cancers. Our study is the first study in which the systemic immune inflammation index (SII), which is an index based on peripheral inflammation, was evaluated in patients with breast cancer diagnosed below the age of 40, and our findings show that patients with higher SII levels at the time of diagnosis have statistically significantly worse prognosis. At the time of diagnosis, more intensive treatments can be planned by considering the SII status in addition to classical prognostic indicators in young breast cancer patients. However, to clarify the SII prognostic value, it needs to be validated in larger, multi-center clinical studies.

Acknowlegment: None

Author contributions: HD, İB; Design of the study and data collection. **HD;** review of the literature, analyzes and writing of the manuscript.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical issues: All authors declare originality of research.

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