ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 26(1): 171-174, 2021
DOI: 10.5505/ejm.2021.71542

The Role of Peripheral Blood Inflammatory Markers in the Staging of Breast Cancer

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ABSTRACT

This study aims to evaluate the importance of neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) in the staging of breast cancer.
One-hundred patients with breast cancer between January 2005 and December 2019 were reviewed retrospectively. Clinical and demographic data of patients were reviewed from the hospital records. Age, gender, pre-treatment complete blood count results and stages were analyzed from patient files.
The median NLR, PLR, and SII values of the T3 stage were higher than the T1 and T2 stages. While there was no difference between the groups according to the N stage, a difference was found between the peripheral blood inflammatory markers of Stage I, II, and III groups. The median NLR, PLR, and SII values of stage III were higher than the stage II and III.
As a result, NLR, PLR, LMR, and SII may be valuable in breast cancer staging.

Key Words: Breast Cancer, Neutrophil-to-lymphocyte ratio, Lymphocyte-to-monocyte ratio, Platelet-to-lymphocyte ratio, Systemic immune-inflammatory index

Introduction

Breast cancer (BC), the most common cancer in women, leads to cancer-related deaths between the ages of 40 and 59 (1). It is thought that inflammation caused by cancer is a prognostic factor, and studies on this subject have increased in recent years. The leukocytes and tumor-associated macrophages in the neoplastic tissue microenvironment, play a crucial role. Transcription factors, signal converter, and transcription-3 activator, cytokines, and their chemokines lead to tumor angiogenesis, tumor cell survival and proliferation (2).

Studies linking neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR) to cancers are increasing (3-5). Although there are studies about the prognostic importance of these values in breast cancer, very few of them investigated inflammatory markers in staging (6,7). To the best of our knowledge, there is no study examining the role of NLR, PLR, LMR, and SII in BC staging. This study aims to investigate the importance of NLR, LMR, PLR, and SII in the staging of breast cancer.

Material and Methods

One-hundred patients with breast cancer between January 2005 and December 2019 were reviewed retrospectively. Patients with previously untreated breast cancer who had medical and follow-up records were included in the study. Metastatic disease, high CRP levels, diabetes mellitus, infectious diseases, rheumatologic diseases, inflammatory diseases, hematological disease, usage of non-steroid anti-inflammatory drugs, and missing medical records were the exclusion criteria of the study. Clinical and demographic data of patients were reviewed from the hospital records. Age, gender, pre-treatment, complete blood count results, and tumor stages were analyzed from patient files. NLR and PLR were calculated as the absolute count of neutrophils and platelets, divided by the absolute lymphocyte count. LMR was calculated as the absolute count of lymphocyte divided by the absolute monocyte

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Received: 27.10.2020, **Accepted:** 30.12.2020

Table 1. Demographic characteristics of the patients

Age, median (range)	55 (29-79)
Histopathology, n (%)	
Invasive ductal carcinoma	87 (87)
Invasive lobular carcinoma	13 (13)
T stage, n (%)	
T1	27 (27)
T2	58 (58)
T3	15 (15)
N stage, n (%)	
N0	48 (48)
N1	35 (35)
N2	14 (14)
N3	3 (3)
Stage	
I	17 (17)
II	65 (65)
III	18 (18)

Table 2. Comparison of NLR, LMR, PLR, and SII levels of patients according to T stage

	T1 n:27	T2 n:58	T3 n:15	P
NLR	1.82 (1.33-2.50)	1.86 (1.55-2.34)	3.15 (2.33-4.41)	0.001
LMR	5.10 (4.14-7.21)	5.39 (4.44-6.63)	4.19 (3.16-5.25)	0.087
PLR	116 (92.7-142.2)	126 (97.7-167.0)	174 (121.6-207.5)	0.023
SII	546 (339.5-867.5)	530 (425.1-676.0)	938 (607.8-1172.5)	0.014

NLR, Neutrophil-lymphocyte ratio; LMR, Lymphocyte-monocyte ratio; PLR, Platelet-lymphocyte ratio; SII, systemic immune-inflammation index

count. SII was calculated by multiplying the NLR by the number of platelets.

Statistical Analysis: Statistical analyses performed via IBM SSPS Statistics for Windows v. 20.0 software (IBM Corp., Armonk, NY). In descriptive statistical analyses, frequencies (percentages) was used for categorical variables; median (interquartile range) was used for non-parametric variables. Kruskal-Wallis test was used for comparisons of continuous variables. When a statistical difference was detected in the Kruskal-Wallis test, the groups were evaluated in pairs with the Mann-Whitney-u test. Thus, it was determined which groups made the difference. A p value of <0.05 was considered statistically significant.

Results

The median age of patients with breast cancer (87 IDC, 13 ILC) included in the study was 55 years (range: 29-79). The demographic characteristics and TNM staging of the patients are shown in Table 1.

The patients were divided into three groups according to the T stage as T1, T2, and T3. When the patients were evaluated according to the T stage, statistically significant differences were found between the groups (Table 2). The median NLR levels of those with tumor stage T3 were higher than those with T1 ($p=0.004$) and T2 ($p=0.002$). The median PLR value of patients with stage T3 was higher than patients with stage T1 ($p = 0.019$). The median SII value of T3 stage patients was significantly higher than the T2 stage patients ($p = 0.011$).

While there was no difference between the groups according to the N stage, a difference was found between the peripheral blood inflammatory markers of Stage I, II, and III groups (Table 3 and 4).

The median NLR, PLR, and SII values of stage III were higher than the stage II and I (Table 4).

Table 3. Comparison of NLR, LMR, PLR, and SII levels of patients according to the N stage

	N0 n:48	N1 n:35	N2-3 n:17	p
NLR	1.88 (1.51-2.37)	1.80 (1.42-2.54)	2.69 (1.91-3.16)	0.067
LMR	5.63 (4.43-7.02)	4.92 (4.18-5.95)	4.33 (3.96-6.63)	0.238
PLR	117 (95.3-155.5)	130 (106.9-168.5)	164 (102.1-202.7)	0.100
SII	541 (339.4-697.4)	590 (368.2-760.6)	792 (501.8-1094.0)	0.116

NLR, Neutrophil-lymphocyte ratio; LMR, Lymphocyte-monocyte ratio; PLR, Platelet-lymphocyte ratio; SII, systemic immune-inflammation index

Table 4. Comparison of NLR, LMR, PLR, and SII levels of patients according to disease stage

	I n:17	II n:65	III n:18	p
NLR	1.38 (1.27-2.05)	1.89 (1.56-2.49)	2.69 (1.91-3.00)	0.016
LMR	6.72 (5.68-7.81)	5.06 (4.16-6.02)	4.57 (3.96-6.63)	0.021
PLR	98 (82.5-134.9)	132 (104.6-170.6)	157 (102.0-207.6)	0.046
SII	435 (305.4-640.7)	555 (426.0-743.9)	749 (501.8-1094.0)	0.068

NLR, Neutrophil-lymphocyte ratio; LMR, Lymphocyte-monocyte ratio; PLR, Platelet-lymphocyte ratio; SII, systemic immune-inflammation index

Stage III group's median NLR value was higher than Stage I ($p = 0.012$). The median LMR value of the Stage I group was higher than Stage II and III groups (p-value was 0.034 and 0.036, respectively).

Discussion

In this study, we evaluated the role of peripheral inflammatory markers in breast cancer staging. The study findings showed that NLR, PLR, LMR, and SII are markers that can aid in breast cancer staging. It has been demonstrated that high NLR, PLR, SII, and low LMR may be associated with the advanced TNM stage.

BC is a highly heterogeneous disease that offers a wide variety of clinicopathological features. Patients with stage I-III disease classified by the International Association for Cancer Controls (UICC) require mastectomy/lumpectomy +/- adjuvant chemotherapy. There is a 10% to 40% chance of recurrence after definitive treatment, depending on the underlying molecular subtype of the tumor and the TNM stage (8). Although there are many studies in the literature evaluating the relationship between inflammatory markers and cancer prognosis, studies evaluating these markers' relationship with tumor stage are very rare (6). Elyasinia et al. showed a correlation between NLR and T stage in patients with BC (6). In our study, the median NLR, PLR, and SII values of the T3 stage were higher than the T1 and T2 stages.

In a study showing that NLR may be associated with lymph node metastasis in breast cancer, it has been shown that high NLR can predict lymph node metastasis in patients with axillary lymph node dissection, although sentinel lymph node biopsy is negative (9). Our study found that the median NLR of the N2-3 group was in an increasing trend compared to the N0 and N1 groups. We thought that the low number of patients in the N2-3 group might have affected this result.

Neutrophils suppress the lymphocytes', NK cells', and activated T cells' cytolytic activity to inhibit the immune system. Also, a low lymphocyte count has negative effect in patients with cancer. Host cell-mediated immunity is expected to have significant effects in destroying micrometastases and remaining tumor cells. Tumor infiltration by lymphocytes has been reported to demonstrate an effective antitumor cellular immune response and increased lymphocyte infiltration associated with a better prognosis (10, 11).

Recent studies have reported that tumor size, pathologic tumor, node, metastasis (TNM) staging is significantly associated with the prognosis of patients with breast cancer (12). However, most of these factors are often obtained under the requirement of core biopsies and with the aid of molecular technique, which is invasive and costly. Based on this idea, we found that cheaper and more easily measurable NLR, PLR, and LMR values can guide us in staging.

The main limitations of this study are that it is a retrospective study and a single-center experience. Also, the number of patients in this study is low.

This study's main finding is that NLR, PLR, LMR, and SII values, which can be obtained with a simple complete blood count, can guide the staging of BC. NLR, PLR, and LMR may be valuable in breast cancer staging, but more studies are needed in this area.

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