

## The relationship between the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio and tumor characteristics in patients with breast cancer

Inflammatory markers in breast cancer

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### Abstract

**Aim:** Many studies nowadays increasingly enlighten the nature of relationship between cancer and inflammation. NLR and PLR are proinflammatory indicators that are related to many clinicopathological characteristics of many types of cancer. In this study, we aimed to find out the relationship between NLR and PLR values and tumor characteristics in patients with breast cancer that are operated with help of basic and inexpensive peripheral blood test results.

**Material and Methods:** A database of 94 female patients who were operated in the Department of Surgical Oncology of the Medical School of Ankara University was studied. All blood sample tests, pathology reports, immunohistochemical staining results of the patients were retrospectively scanned. Patient demographics and pathological properties of tumor obtained from the database. The NLR and PLR values were taken from the peripheral blood cell count. Data were presented as average value±standart deviation(SD), and maximum-minimum values. Later data were analyzed.

**Results:** NLR values were significantly different accordingly to T stage of tumor ( $=11.452$ ;  $p=0.022$ ). On the other hand, the PLR value did not show a significant differentiation according to tumor size ( $=5.865$ ;  $p=0.209$ ). It has been seen that this differentiation is between T1 and T2; T1 and T3 statistically. ( $U=251.000$   $p=0.003$ ;  $U=54.000$ ,  $p=0.021$ ).

**Discussion:** The NLR value is significantly related to the tumor size. But further research is needed to see the clinical reflection and added value to the clinical practice of these results.

### Keywords

Breast cancer; Neutrophil-Lymphocyte ratio (NLR); Platelet-Lymphocyte ratio (PLR)

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## Introduction

Nowadays, breast cancer is the most common cancer among women and the second most common reason for cancer-associated women deaths [1]. Despite significant progress in recent years, approximately 20% of patients with breast cancer experience distant metastasis or relapse within 5 years because of late diagnosis [2,3]. Therefore, some diagnostic biomarkers such as free-floating tumor cells in serum, DNA, miRNA, lncRNA, and exosome have been developed to screen and detect cancer in the early stages. However, their clinical use is still limited because of the uncertainty and high cost of these biomarkers [4]. Lately, PLR and NLR parameters, which are determined from peripheral venous blood tests, are closely related to poor prognosis, relapse, and mortality in solid tumors as prognostic indicators [5,2].

Even if their numbers are limited, similar studies have been carried out comparatively on breast cancer subtypes [6], in elderly patient groups [7] and in healthy control groups, and similar results were obtained [7]. It is now accepted that cancer dependent chronic inflammatory process is closely related to cancer development course.

It is increasingly accepted that as components of the systemic inflammatory response, lymphocytes, neutrophils, and platelets have an essential role in carcinogenesis and tumor progression [9, 10]. Many authors recommend inflammation-based scoring systems. However, clinical applications are not at a level that can be used in routine practice, and there is no consensus on optimal limit levels. The Glasgow prognostic score is an inflammation-based prognostic scoring like NLR and PLR obtained from peripheral blood-based inflammatory components [5,6]. Neutrophils are known to support the potential of circulating tumor cells to metastasize to distant organs by secreting circulating growth factors such as vascular endothelial growth factor (VEGF) and proteases [11].

Studies have shown that cytokines and chemokines produced by inflammatory cells and tumor cells can contribute to metastasis development [12]. As it can inhibit the immune system by suppressing cytotoxic T lymphocytes' activities, the neutrophilic response is associated with poor prognosis [13]. Lymphocytes that infiltrate the tumor are related to a better response to cytotoxic treatment and a better prognosis in patients with breast cancer [14]. Lymphocytes usually increase apoptosis through the cytokine microenvironment that they provide. They symbolize the immune response in the fight against cancer [15]. It is found that neutrophile-lymphocyte ratio (NLR) is an independent factor for negative outcomes in many solid tumors, including breast cancer. Fortunately, the determination of NLR depends on a minimal invasive peripheral venous blood test, which is highly specific and sensitive for evaluating the tumor's activity and its' interaction with microcirculation. These tests can be obtained easily in all routine clinics, and they do not require additional costs.

As these parameters obtained from peripheral blood tests are cheap and easily accessible, their predictive value is important for clinicians. Studies like this, which are carried on with breast cancer patients, will help the clinicians diagnose, treat, and predict overall survival. In this study, we aimed to show the

relationship between the NLR and PLR values obtained from the peripheral blood test results at the diagnosis and the characteristics of the tumor, and the clinical reflections of this relationship.

## Material and Methods

In this study, the database of 94 patients with breast cancer who were operated at the Surgical Oncology Clinic was examined retrospectively. Included data were obtained from preoperative routine blood tests, postoperative follow-up, and pathology reports. In this study, newly diagnosed primary or metastatic breast cancer cases that did not use any medication that can affect hematological parameters were included.

Therefore patients who are using steroids have hematological diseases, they have previously been diagnosed with malignancies, had acute or chronic inflammation signs before the operation, have recently received a blood transfusion, and were diagnosed with autoimmune disease. Patients with missing data in the database were also excluded. Demographic features and laboratory values of the patients were retrospectively scanned through the records of the hospital's medical database. Clinical characteristics including age, menopause status, diagnosis, TNM stage, pathological type, receptors (estrogen, progesterone, HER2) were gathered. Patients were staged according to the TNM staging system of the American Joint Committee on Cancer [16] (AJCC 8th edition, 2017). Recent preoperative neutrophile, platelet, and lymphocyte counts were obtained from medical blood test records. The absolute neutrophile number was divided by the total lymphocyte number to calculate the NLR, and the final platelet number was divided by the whole lymphocyte number to calculate the PLR.

When patients were admitted to the hospital, peripheral blood tests were done to prepare for surgery. Later, neutrophile, platelet, and lymphocyte counts were obtained through the medical database. Pathology reports and immunohistochemical staining results were analyzed to obtain tumor size, lymph nodes, estrogen, progesterone, HER2 receptors, and Ki-67 percentages.

All patients involved in this study were female. Demographic and clinicopathological features of the patients are shown in Table-1. Our study was approved by the Hospital Ethics Committee of the Ankara University, Medicine Faculty (Decision number: 110-625-20). Written informed consent was obtained from all participants.

## Statistical Analysis

Data are presented as average value±standard deviation (SD), and max-min values. Parametric test assumptions were examined before performing the difference analysis. Normality was checked with the Shapiro-Wilk test skewness and kurtosis. The homogeneity of the variances was checked with Levene's test. If the assumptions were satisfied, the difference analysis was performed using one-way analysis of variance (ANOVA); otherwise, the Kruskal-Wallis test was used. Paired comparisons were made using the Mann-Whitney U test. Statistical analyses are done at a 95% confidence interval. A P -value of less than 0,05 is considered statistically significant.

## Results

The characteristics of the patients participating in the study are shown in Tables 1 and 2.

**Table 1.** Demographic and clinicopathological characteristics of patients

Properties	Number (n)	Percentage (%)
<b>T Stage</b>		
T1	39	41.5
T2	40	42.5
T3	15	16
T4	0	0
<b>Receptor Status</b>		
ER (+)	77	82
ER (-)	17	18
PR (+)	71	75
PR (-)	23	25
HER2 (+)	60	64
HER2 (-)	34	36
<b>Menopausal Status</b>		
Premenopausal	32	34
Postmenopausal	62	66
<b>Axillary Involvement</b>		
Lymph node (+)	50	53
Lymph node (-)	44	47
<b>Side</b>		
Right Breast	43	46
Left Breast	51	54

**Table 2.** Preoperative blood count results and PLR and NLR values of patients

Properties	Median	Min-Max	Standard Deviation
Age	57,2	33-81	12,2
NLR Value	2,10	0,73-5,61	0,70
PLR Value	144,41	58,60-460,76	60,61
Neutrophile Count	4,11	1,65-10,50	1,33
Platelet Count	273,09	92-504	68,82
Lymphocyte Count	2,04	0,78-3,50	0,55
KI-67 (%)	26,83	0-99	21,53

According to the pathological diagnosis, the PLR values of the patients are not statistically significant;  $F(3,90) = 1.189$   $p > .05$ . Similarly, the patients' NLR values were not statistically significant according to the pathological diagnosis ( $F(3,90) = 1.648$   $p > .05$ ).

The NLR value showed statistically significant changes compared to T stage; ( $X^2 = 11.452$ ;  $p = 0.022$ ). The PLR value did not show statistically significant change according to the tumor size ( $X^2 = 5.865$ ;  $p = 0.209$ ). This difference is between T1 and T2, Statistical T1, and T3 tumors ( $U = 251.000$   $p = 0.003$ ;  $U = 54.000$   $p = 0.021$ ). As a result, it is seen that the NLR value increases significantly as the tumor size increases.

The PLR and NLR values were not statistically different according to the pathological axillary lymph node involvement ( $F(1,92) = 0.656$   $p > .05$ ;  $F(1,92) = 2.103$   $p > .05$ ).

There was no statistically significant difference in PLR and NLR values according to the receptor status of the tumor estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor (HER2) ( $p > .05$ ). Similarly, there was no statistically significant difference between menopausal status and PLR-NLR values ( $p > .05$ ).

## Discussion

In this study, we examined the relationship between NLR and PLR values with tumor characteristics. Our study showed that the NLR value statistically differs according to tumor diameter (T stage). This differentiation was evident, especially in between T1 and T2; T1 and T3 tumor sizes. This finding was invalid for PLR values. Likewise, no significant findings were obtained when comparing PLR and NLR values with the clinical pathology of the tumor and the demographic characteristics of the patients.

Inflammation and cancer; platelets play an essential role in tumor growth by increasing angiogenesis through VEGF (vascular endothelial growth factor) in cancer progression [17]. There is a direct relationship between platelet count and VEGF levels. While angiogenesis may contribute to metastasis through thrombocytosis, some studies have found that most VEGF levels are due to neutrophils. Neutrophils may also support tumor growth and metastasis by releasing reactive oxygen radicals (ROS), nitric oxide (NO), and arginase [18]

In contrast, lymphocytes represent the host immune response against malignancy by inducing cancer cell death and inhibiting tumor cell proliferation and migration [2,11]. A positive relationship was found between tumor diameter and NLR value in our study. Besides, NLR is an indicator of impaired cell-mediated immunity associated with systemic inflammation [12]. This shows that the cytokine microenvironment provided by neutrophils contributes to tumor growth.

Consequently, the numerators of NLR and PLR values, neutrophile, and platelet counts are considered negative outcome determinants, and their denominator, lymphocyte count, is considered a positive predictor of outcome. At the same time, NLR and PLR values are determinants of breast cancer risk [8,2]

Koh et al. (2015), who considered the relationship of NLR values with clinical outcomes, showed that an increase of NLR value is related to increased T stage, younger age, and positive HER2 status in their study with 2059 breast cancer patients. This outcome is coherent with the outcomes of the study by Azab et al. (2013) conducted with patients with operated breast cancer. This finding is consistent with the findings of Azab et al. (Azab et al., 2013) in their study with operated breast cancer patients. The study was evaluating the prognostic significance of the NLR value in 437 breast cancer patients. Patients with high NLR values were older. They also had more lymph node involvement and metastasis rates [19]. However, they could not define a significant correlation with relapse. Dirican et al. showed that high NLR values are significantly related to the T stage of the tumor, axillary lymph node status, and distant metastasis status. The study correlated the NLR value with disease-free survival and overall survival at 6-year follow-up in approximately 1500 patients using a cut-off value of 4 for

NLR [20].

On the other hand, Yersal et al. found no statistically significant difference with the distribution of NLR and PLR values in 255 breast cancer patients by lymphovascular invasion, tumor size, pathological lymph node involvement, and breast cancer subtypes. But they found that PLR values in patients with lymph node metastasis were higher than in others [21]. We could not find a significant relationship between breast cancer receptor type and NLR and PLR values. Breast cancer is divided into subgroups according to receptor types. Yersal et al. did not find a significant relationship between breast cancer subgroups and NLR and PLR values in their study on 255 breast cancer patients [21]. Yao et al. found that NLR value is an easily accessible and inexpensive preoperative prognostic indicator for triple-negative breast cancer (TNBC) [22]. Liu et al. found that high NLR values are related to decreased overall survival in HER2 (+) patients in the study on 318 triple-negative breast cancer (TNBC) patients [6].

### Conclusion

In summary, these results show that inflammation components are important triggers of tumor growth. This is consistent with the 'seed and soil' nature of cancer growth, according to Proctor [23].

The most significant limitation of our study is that it is observational and single-centered, and the comparison of clinicopathological features of the tumor requires a more extensive patient series. Before considering the clinical application of PLR and NLR values as cancer markers, further prospective research is needed. It must evaluate particular cut-off values and required optimal cut-off levels. NLR value has the potential of becoming an accurate prognostic indicator. Mechanisms underlying the high NLR value and response to anticancer treatment in breast cancer need further investigation. Clearer findings on NLR and its association with breast cancer prognosis will facilitate selecting patients who are more likely to benefit from medical and specific surgical approaches [24].

### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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### Conflict of interest

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