

## Neutrophil-Lymphocyte Ratio in Different Stages of Breast Cancer

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**Abstract-** Despite many advances in the treatment of breast cancer, it is still the second most common cause of death in women in the United States. It has been shown that inflammation plays a major role in the treatment of these cancers and inflammatory factors enhance tumor growth, invasion, metastasis, and vascularization. In this study, we would like to analyze peripheral blood neutrophil-lymphocyte ratio (NLR) in breast cancer patients and its correlation with disease staging. This cross-sectional analytic study was conducted in Imam Hospital, affiliated with Tehran University of Medical Sciences; a total of 195 female patients with breast cancer met the inclusion criteria. All of the patients had a complete blood count with leukocyte differential performed before chemotherapy. Medical records including pathology reports were also available. Data for all patients were collected prior to any surgical intervention. Exclusion criteria included clinical evidence of active infection, presence of hematological disorders, acute as well as chronic inflammatory or autoimmune diseases, or prior steroid therapy. Higher platelet count was significantly associated with the higher stage. The stage was not associated with the hemoglobin level. There was no association between the tumor size and age of patients with NLR. There was a significant relationship between NLR and IDC. There was a significant relationship between IDC and NLRs of less than 8.1 and greater than 3.3. There was a significant relationship between NLR and vascular invasion. There was no association between NLR and estrogen receptor and HER2. There was no significant relationship between the PLR and the cancer stage. In this study, NLR showed a significant relation with the disease staging. As the NLR increases the stage increases as well. Therefore, this ratio may be helpful in the preoperative evaluation of patients with breast cancer.

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**Keywords:** Breast cancer; Neutrophil; Lymphocyte; Stage

### Introduction

Breast cancer is the most common cancer in women. Despite much progress in treatment for breast cancer, but it is still as the second common cause of death in women in the United States (1).

Despite, the need for the staging of breast cancer to determine the survival rate of patients, this approach had imposed a lot of costs to the patient and also, need to intensive techniques, too (2). Clinical staging of breast cancer mainly is done through physical examination of the breast and the glands tissue including lymph above the clavicle, armpits, and a thorough neck examination (3). Axillary lymph node metastasis has only 99 percent accuracy. Mammography, chest radiograph, and the other findings of the initial tumor size during the surgery

such as invasion to chest wall can provide some necessary information; this information has relation with staging (3,4).

According to the previous studies, increase in the neutrophil-lymphocyte ratio (NLR) might lead to an increase in the mortality of patients with breast cancer and a decreased survival in these groups of patients (5-12). These studies have detected an increase in the mortality rate in patients with high NLR (5-7). An increase in this ratio can increase the deaths rate of other cancers such as colorectal, lung, stomach, liver and pancreas as well (13-17).

The aim of this study is to evaluate the neutrophil-lymphocyte ratio in breast cancer patients and its correlation with disease staging.

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## Materials and Methods

This study was a cross-sectional study on patients with breast malignancy diagnosis who underwent surgical operation between April 2006 and March 2010. This study was done at Imam hospital, affiliated with Tehran University of Medical Sciences and it was approved by the ethics committee of the university.

Female patients with a confirmed diagnosis of breast cancer referred to the breast clinic of the hospital were included. All patients underwent whole blood cell count before the operation. Inclusion criteria were patients with no previous history of neoadjuvant therapy, no blood diseases, no acute inflammation, no autoimmune diseases, and no history of previous treatment with corticosteroid medications. Pathologic reports were also collected after the surgery. Tumor pathology reports including tumor size and tumor type were also recorded.

Statistical analysis was done using SPSS version 20 software. Student *t*-test and *chi*-square tests were used. The *t*-test was used to compare two sets of quantitative data. The level of 0.05 was considered as significant.

## Results

In this study, a total of 195 patients were evaluated with a mean age of 51.1±12.06 years (range: 29-78). The mean of WBC count was 7.4±1.8 (range: 3.7-13.1). The mean of lymphocyte percentage was 31.1±9.7 percent (range:6-82). The mean of neutrophil percentage was 63.7±10.5 percent (range: 12-92). The mean of platelet (PLT) count was 258.3±65.8 (range: 3.5-11.5), and the mean of Hemoglobin (Hg) level was 13.2±2.08 (9.7-36).

An increased number of PLT was correlated with a higher stage of cancer; ( $P=0.0001$ ) but Hg was not related with the stage ( $P>0.005$ ). Data are shown in Table 1. An NLR of less than 1.8 was seen in 36.4% of patients; 31.8% of patients had NLR between 1.8-2.45 and 15.9% had an NLR between 2.45-3.3. NLR of greater than 3.3 was found in 15.9%.

There was no significant relation between the age of patients and the tumor size ( $P>0.005$ ). The mean age of

patients with NLR of less than 1.8 was 53.2±11.7 years. The mean for the NLRs between 1.8-2.45, 2.45-3.3, and >3.3 was 49.08±13.08, 50.5±10.3, and 50.9±1.7 years respectively. The mean size of the tumor in NLRs less than 1.8, 1.8-2.45, 2.45-3.3 and >3.3 was 2.6±1.5, 2.6±1.5, 2.3±0.8 and 2.9±1.7, respectively.

According to the T stage of cancer patients were divided into three groups; <20 mm: T1 (36.9%), 2-2.5 mm: T2 (57.9%) and >5 mm: T3 (5.1%). NLR ratio in various T stages of the tumor is summarized in Table 2. There was no significant relation between NLR and the T stage of the disease.

According to the N, stage patients were divided into three groups; 1-3 lymph node: N1 (12.8%), 4-9 lymph node: N2 (14.4%) and >10 lymph node: N3 (8.2%). 64.6% of patients had no N stage. NLR ratio in various N stages of the tumor is summarized in Table 3. There was a significant relation between NLR and the N stage ( $P=0.001$ ).

In general, 30.3% of patients were at the stage 1A, 39 % were at stage 2A, 9.2% were at stage 2B, 13.3% were at stage A3, and 8.2% were at stage 3C. There was a significant relation was seen between NLR and total stage of cancer ( $P=0.001$ ). NLR ratio in various total stages of the tumor is summarized in Table 4 .

Invasive ductal carcinoma of the breast was not significantly correlated with NLR ( $P<0.05$ ); but there was a significant relation between invasive lobular carcinoma and NLR<1.8 and NLR>3.3 ( $P=0.038$ ). 32.3 percent had vascular invasions. 12 cases had the concurrent cardiovascular disease (6.2%). 37.4% had HER2 in grade 3 and 62.6 in grade 0-1. A significant relation was seen between vascular invasions and NLR ( $P=0.032$ ). There was no significant difference between the NLR and estrogenic receptors numbers ( $P>0.05$ ). There was no significant difference between the NLR and HER2 receptors ( $P>0.05$ ).

Platelet level of >109 was seen in 34.4%, 109-139 in 35.9%, 139-185 in 19.5% and >185 in 10.3% of patients. There was no significant relation between the total stage and platelet count.

**Table1. Platelet and hemoglobin level in various stages of breast cancer**

Total stage	Platelet (per microliter)	Hemoglobin (gr/dl)
1A	234.59±55.5	13.3±0.9
2A	271.8±62.2	13.3±2.9
2B	274.4±84.7	12.8±1.4
3A	238.9±74.8	12.8±1.8
3C	295.0±42.3	12.8±1.1

**Table 2. Neutrophil/ Lymphocyte ratio in various T stages of the tumor. Data are presented as number(percent)**

Neutrophil/ Lymphocyte ratio	Stage T1	Stage T2	Stage T3
<1.8	25 (35.2%)	42(56.2%)	4 (5.6%)
1.8-2.45	25 (40.3%)	35(56.5%)	2 (3.2%)
2.45-3.33	12 (38.7%)	19(61.3%)	0 (0%)
>3.3	10 (32.3%)	17(54.8%)	4 (12.9%)

**Table 3. Neutrophil/ Lymphocyte ratio in various N stages of the tumor. Data are presented as number(percent)**

Neutrophil/ Lymphocyte ratio	Stage N1	Stage N2	Stage N3
<1.8	14 (19.7%)	10(14.1%)	2 (2.8%)
1.8-2.45	3 (4.8%)	4(6.5%)	6 (9.7%)
2.45-3.33	2 (6.5%)	4(6.5%)	6 (19.4%)
>3.3	6 (29.4%)	10 cases (32.3%)	2 (6.5%)

**Table 4. Neutrophil/ Lymphocyte ratio in various stages (total stages) of the tumor. Data are presented as number(percent)**

Neutrophil/ Lymphocyte ratio	Stage 1A	Stage 2A	Stage 2B	Stage 3A	Stage 3C
<1.8	21 (29.6%)	28(39.4%)	12 (16.9%)	8 (11.3%)	2 (2.8%)
1.8-2.45	20 (32.3%)	32(51.6%)	0 (0%)	4 (6.5%)	6 (19.4%)
2.45-3.33	10 (32.3%)	11(35.5%)	0 (0%)	4 (12.9%)	6 (6.25%)
>3.3	8 (25.8%)	5 (16.1%)	6 (19.4%)	10 (32.3%)	2 (6.5%)

## Discussion

Prevalence of breast cancer in Iran is lower than Western countries, but breast cancer is the most common cancer in women. Studies have shown that inflammatory processes have supplied and boosted tumor growth, invasion, and metastasis (4,5,18,19). Previous studies have shown that increased neutrophil and platelet levels can play an important role in the development of complications after surgery and survival rate (8).

The lymphatic node involvement is the most important element to predict prognosis in these patients. Breast cancers have unpredictable behaviors, and its consequences can significantly be different in one patient with another patient (20). While the behavior of the cancer is depended on several factors, the role of inflammation is more important (21). According to a study, it was demonstrated that a high number of leukocytes available in a tumor might cause an increase in tumor growth (21,22).

In our study neutrophil-lymphocyte ratio in patients with breast malignancy; we also reviewed its relationship with the stage of the disease. According to our findings, an increase in NLR was correlated with the mortality rate. This ratio showed a significant difference in various stages of the disease. But there was no

significant difference between the age and tumor size, too. We also detected no significant difference between Her2 and ER with NLR. These findings are similar to another study done by Noh *et al.*, (23). In our study, there was a significant difference between NLR and N stage.

In a study (24), it was shown that with an increase in NLR, the lymph node number was increased. According to another study, an increase in this ratio can be associated with a decreased survival in patients with breast cancer (25). In a study by Koh Wha on breast cancer patients with positive ER/PR and HER2 and neoadjuvant chemotherapy, it was shown that age and tumor size, N stage and T stage were correlated with NLR; there was a significant difference between the NLR and ILC. However, It might be due to the chemotherapy performed before surgery and its effect on neutrophil and lymphocytes count (26).

In this study, with an increase in NLR, total stage of disease was increased. These tests are simply available and can be helpful in predicting survival and stage of the disease.

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