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Investigation Of The Clinicopathological Importance Of Neutrophil – To - Lymphocyte Ratio And Platelet – To - Lymphocyte Ratio In Breast Cancer

Meme Kanserinde Nötrofil - Lenfosit Oranı Ve Platelet - Lenfosit Oranının Klinikopatolojik Öneminin Araştırılması

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ABSTRACT

AIM: In this study, we aimed to examine whether the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values of women operated for breast cancer were associated with their clinicopathological features.

MATERIAL AND METHOD: The data of 463 females who were operated for breast cancer in our center between Januray 2015 and December 2020 were analyzed retrospectively. Age, menopausal status, hematological values, histopathological features of tumors, presence of hormone receptors, surgical and biopsy techniques were evaluated in detail. NLR and PLR values were calculated using the results of routinely performed hemogram test before the operation, and their relationships with all parameters were analyzed.

RESULTS: The mean age was 53.57±12.66 years. Postmenopausal women constituted 62.42% of the cases. A negative correlation was found between age and PLR (r=-0.125, p=0.007), but neither PLR nor NLR were found to be associated with menopause status (p>0.05). It was found that high NLR value was associated with high N stage (r=0.010, p=0.018), high TNM stage (r=0.125, p=0.007), high number of metastatic lymph nodes (r=0.112, p=0.016) and presence of extracapsular invasion (p=0.022). In addition, high PLR values were associated with low age (r=-0.125, p=0.007), progesterone receptor negativity (p=0.044) and high TNM stage (r=0.111, p=0.017).

CONCLUSION: The results of our study showed that high NLR and PLR values may be associated with poor prognostic factors. It was thought that it would be beneficial for clinicians and surgeons to consider these values in the follow-up of patients due to ease of use and swift results.

Keywords: Breast cancer, prognosis, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

ÖZET

AMAÇ: Bu çalışmada meme kanseri nedeniyle ameliyat edilen kadınların nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR) değerlerinin klinikopatolojik özellikleri ile ilişkili olup olmadığını incelemeyi amaçladık.

GEREÇ VE YÖNTEM: Merkezimizde Ocak 2015 – Aralık 2020 tarihleri arasında meme kanseri nedeniyle ameliyat edilen 463 kadının verileri retrospektif olarak incelendi. Yaş, menopoz durumu, hematolojik değerler, tümörlerin histopatolojik özellikleri, hormon reseptörlerinin varlığı, cerrahi ve biyopsi teknikleri detaylı olarak değerlendirildi. Ameliyat öncesi rutin olarak yapılan hemogram testi sonuçları kullanılarak NLR ve PLR değerleri hesaplandı ve tüm parametrelerle ilişkileri analiz edildi.

BULGULAR: Ortalama yaş 53,57±12,66 idi. Olguların %62,42'sini postmenopozal kadınlar oluşturmaktaydı. Yaş ve PLR arasında negatif yönde bir korelasyon bulundu (r=-0,125, p=0,007); ancak ne PLR ne de NLR menopoz durumu ile ilişkili değildi (p>0,05). Yüksek NLR değerinin yüksek N evresi (r=0,010, p=0,018), yüksek TNM evresi (r=0,125, p=0,007), yüksek metastatik lenf nodu sayısı (r=0,112, p=0,016) ve ekstrakapsüler invazyon varlığı (p=0,022) ile ilişkili olduğu bulundu. Ayrıca yüksek PLR değeri düşük yaş (r=-0,125, p=0,007), progesteron reseptör negatifliği (p=0,044) ve yüksek TNM evresi (r=0,111, p=0,017) ile ilişkiliydi.

SONUÇ: Çalışmamızın sonuçları, yüksek NLR ve PLR değerlerinin kötü prognostik faktörlerle ilişkili olabileceğini göstermiştir. Bu değerlerin hasta takibinde kolaylıkla kullanılabilir olması ve hızlı sonuç vermesi nedeniyle klinisyen ve cerrahlar için faydalı olacağı düşünülmüştür.

Anahtar Kelimeler: Meme kanseri, prognoz, nötrofil-lenfosit oranı, trombosit-

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INTRODUCTION

According to current reports, it is predicted that one out of every three people will suffer from at least one type of cancer in their lifetime. Today, along with cardiovascular diseases, cancer is one of the leading causes of death[1]. Breast cancer is the most common type of cancer in women and accounts for approximately 15% of cancer-related deaths[2,3]. It is rarely seen in men[4]. According to data from the World Health Organization, a total of 2.1 million women were diagnosed with breast cancer in 2018, and there were 627,000 deaths[2,3]. The diagnosis, follow-up and treatment of cancers has been the focus of researchers and important developments have occurred in recent years. However, even in the most common types of cancer (such as breast cancer), there are deficiencies in the classification of patients, and by extension, the decision for treatment methods.

Until recently, tumor staging was considered as the only reliable parameter that could dictate diagnosis, follow-up and treatment. However, new surgical approaches suggest that tumor staging alone may not be sufficient for these purposes. Many different factors related to the patient may play an important role in the treatment and subsequent process[5]. In addition, considering that a significant portion of deaths in breast cancer cases are due to recurrences, it is thought that the parameters related to recurrence should also be reviewed. Currently, hormone receptor status and relapse due to hormonal therapy are a few of the known mechanisms, but these parameters are often insufficient for early diagnosis of cases[6].

Recent studies stated that the parameters used to measure the systemic inflammatory response (lymphocyte, neutrophil, thrombocyte, etc.) might be associated with the prognosis and clinicopathological features of cancer[7-9]. An example of this is the Glasgow prognostic score (GPS), which is based on measurements of acute phase proteins in cancer patients and has come to be accepted as an independent parameter with prognostic value, similar to classifications based on tumor characteristics[10]. In addition, neutrophil, platelet and lymphocyte counts and different combinations of their ratios have been explored to determine the prognostic value of systemic inflammation in cancer patients[11]. In fact, research examining the relationship between cancer and the inflammatory response dates back over 100 years. These studies, which were based on the detection of inflammatory cells in samples taken from tumor cells, were largely limited by past technology and could not reach clear conclusions. In the last 25 years, this issue has regained value and it has been suggested that the inflammatory response caused by infection or other causes may be associated with approximately 20% of cancer-related deaths[12]. Studies investigating the relationship between inflammatory response and breast cancer have reported an increase in neutrophil and thrombocyte counts, and a decrease in lymphocytes. In addition, several studies have emphasized that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) had independent prognostic value[2,13]. It is also known that there is a difference in breast cancer patients in pre- and postmenopausal periods in terms of tumor size, tumor stage, lymph node metastasis and invasion characteristics, but there are limited studies examining the relationship between these features and systemic inflammatory response14. In the present study, we aimed to evaluate the relationship between the NLR / PLR values of women operated for breast cancer and the clinicopathological features of these cases.

MATERIAL AND METHOD

Study Population

In our study, the data of breast cancer patients who were operated between Januray 2015 - December 2020 in the Department of Surgical Oncology, Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye were reviewed retrospectively. Males, those who received neoadjuvant treatment, subjects diagnosed with comorbid primary cancer, autoimmune disorder, hematological malignancy or another active infection, those who had received corticosteroid therapy within the last 6 months, and patients who had missing data were excluded from the study. In addition, only cases with invasive cancer types were studied, and in situ cancers (DCIS, LCIS) were excluded.

The diagnosis of cases, the biopsy method applied, the types of operation, tumor localizations and stages, ki-67 score, menopausal status, general information about the treatments they received, and the relevant values in the hemogram tests were analyzed. In addition, patients were grouped according to their estrogen and progesterone receptor positivity, tumor invasion types and lymph node characteristics. These continuous and ordinal variables were examined to assess their possible relationships with NLR and PLR, and, in addition NLR and PLR values were compared according to groups formed with respect to patient- and tumor-related characteristics.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Q-Q and histogram plots were used to determine whether variables were normally distributed. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Spearman correlation coefficients were calculated for the assessment of relationships between continuous and ordinal variables. Between-groups comparisons were performed with the Mann-Whitney U test or Kruskal-Wallis test depending on group count. Two-tailed p values of less than 0.05 were considered to be statistically significant.

Ethical Approval

All procedures performed in studies involving human participants 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. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Eskisehir Osmangazi University (Decision number: 03, Decision date: 01/06/2021). Informed consent was obtained from all individual participants included in the study.

RESULTS

In the study, the information of a total of 463 patients who were operated for breast cancer was reviewed retrospectively. Ages ranged from 23 to 88 years and the mean value was 53.57 ± 12.66. All of the cases were females and 62.42% of them were in the postmenopausal period. In all cases, the involvement was unilateral and the cancer was in the right breast in more than half of the patients (54.21%). The majority of cases (86.18%) had a diagnosis of invasive ductal carcinoma. When the number of cases according to invasion types were analyzed, the most common was lymphovascular invasion (30.67%), followed by extracapsular (29.59%) and perineural invasion (25.49%), respectively. The median number of lymph nodes was 17 (IQR: 11-24). All examined information about the cases and data concerning tumor characteristics are summarized in

Table 1. Summary of patients and tumor characteristics (n=463).

Charecteristics	Frequency, n (%)	Charecteristics	Frequency, n (%)
Age	53.57 ± 12.66	Perineural invasion	118 (25.49%)
Gender, female	463 (100.00%)	Lymphovascular invasion	142(30.67%)
Menopause status		Extracapsular invasion	137 (29.59%)
Premenopausal	174 (37.58%)	Multifocal	94 (20.30%)
Postmenopausal	289 (62.42%)	Multicentric	61 (13.17%)
Side		T stage	
Right	251 (54.21%)	T1	147 (31.75%)
Left	212 (45.79%)	T2	262(56.59%)
Bilateral	0 (0.00%)	T3	42 (9.07%)
Diagnosis		T4	12 (2.59%)
Invasive ductal carcinoma	399 (86.18%)	N stage	
Invasive lobular carcinoma	28 (6.05%)	N0	209 (45.14%)
Others	**36 (7.78%)**	**N1**	**139 (30.02%)**
Biopsy method		N2	72 (15.55%)
Trucut	450(97.19%)	N3	43 (9.29%)
Excisional	9 (1.94%)	M stage	
Incisional	4 (0.86%)	M0	458 (98.92%)
Type of surgery		M1	5 (1.08%)
Mastectomy	320 (69.11%)	TNM stage	
Breast conserving surgery	143 (30.89%)	Stage 1	83 (17.93%)
Status of axilla		Stage 2	240(51.84%)
SLNB	130 (28.08%)	Stage 3	135 (29.16%)
SLNB + ALND	100 (21.60%)	Stage 4	5 (1.08%)
ALND	233 (50.32%)	Number of lymph nodes	17 (11-24)
Grade		Number of metastatic lymph	1 (0-4)
Grade 1	118 (25.49%)	Adjuvan chemotherapy	429(92.66%)
Grade 2	248 (53.56%)	Adjuvant radiotherapy	311 (67.17%)
Grade 3	97 (20.95%)	Hormonotherapy	404 (87.26%)
Estrogen receptor positivity	396 (85.53%)	Neutrophil (×1000/)mm	4.61 ± 1.55
Progesterone receptor positi	336 (72.57)	Lymphocyte (×1000/)mm	2.09 ± 0.68
cerbB2 positivity	195 (42.12%)	Platelet (×1000/)mm	266.92 ± 69.58
Ki-67 score		Neutrophil-Lymphocyte ratio	2.13 (1.6-2.86)
0-15	202 (43.63%)	Platelet-to-Lymphocyte ratio	126.67 (100.65-176)
16-30	139(30.02%)		
>30	122 (26.35%)		

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables
SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection

The mean lymphocyte, neutrophil and platelet counts and NLR and PLR values of all cases are given in Table 1. NLR values were very weakly correlated with N stage (r = 0.110, p = 0.018), TNM stage (r = 0.125, p = 0.007) and number of metastatic lymph nodes (r = 0.112, p = 0.016). PLR values showed an inverse very weak correlation with age (r = -0.125, p = 0.007), while there was a positive and very weak correlation with TNM stage (r = 0.112, p = 0.016). Data concerning PLR and NLR values in terms of their correlations with age, stage, Ki-67, T stage, N stage, TNM stage and the numbers of lymph nodes and metastatic lymph nodes are summarized in

Table 2. Relationships between NLR, PLR and continuous & ordinal variables

		Neutrophil-to-Lymphocyte ratio	Platelet-to-Lymphocyte ratio
Age	r	0.032	**-0.125**
	p	0.489	**0.007**
Grade	r	0.076	0.046
	p	0.104	0.319
Ki-67 score	r	0.053	0.001
	p	0.258	0.978
T stage	r	0.064	0.010
	p	0.171	0.831
N stage	r	**0.110**	0.043
	p	**0.018**	0.358
TNM stage	r	**0.125**	**0.111**
	p	**0.007**	**0.017**
Number of lymph nodes	r	0.012	0.036
	p	0.804	0.439
Number of metastatic lymph nodes	r	**0.112**	0.043
	p	**0.016**	0.355

r: Spearman correlation coefficient

The cases were grouped according to the presence of menopause, tumor localization, axilla status, presence of hormone receptors, type of invasion, surgical intervention technique, and treatment modalities. Comparisons of NLR and PLR values with respect to these groups were performed. It was determined that the NLR values of the cases with extracapsular invasion were significantly higher than those without (p = 0.022). PLR values were significantly lower in patients with progesterone receptor positivity compared to those with negativity (p = 0.044). No other significant differences were identified

Table 3. NLR and PLR with regard to patient- and tumor-related characteristics

	Neutrophil-to-Lymphocyte ratio	p	Platelet-to-Lymphocyte ratio	p
Menopause status				
Premenopausal	2.11 (1.71 - 2.68)		129.95 (103.37 - 169.92)	
Postmenopausal	2.14 (1.61 - 2.89)	0.643	124.32 (99.62 - 160.80)	0.116
Side				
Right	2.15 (1.65 - 2.89)		128.13 (100.00 - 168.38)	
Left	2.09 (1.64 - 2.81)	0.696	123.35 (99.81 - 163.85)	0.579
Diagnosis				
Invasive ductal carcinoma	2.13 (1.64 - 2.87)		125.62 (100.00 - 164.08)	
Invasive lobular carcinoma	2.08 (1.76 - 2.61)	0.981	139.35 (102.27 - 168.44)	0.644
Other invasive EP	2.12 (1.53 - 2.98)		126.36 (100.22 - 177.86)	
Type of surgery				
Mastectomy	2.20 (1.65 - 2.92)		129.69 (101.51 - 166.62)	
Breast-conserving surgery	2.00 (1.63 - 2.67)	0.053	121.05 (100.00 - 160.22)	0.320
Status of axilla				
SLNB	2.06 (1.51 - 2.96)		122.33 (101.43 - 161.19)	
SLNB + ALND	2.08 (1.66 - 2.63)	0.306	118.25 (97.18 - 165.86)	0.396
ALND	2.19 (1.73 - 2.84)		131.30 (103.09 - 166.26)	
Estrogen receptor				
Negative	2.33 (1.78 - 3.14)		144.02 (111.07 - 166.26)	
Positive	2.11 (1.61 - 2.83)	0.058	124.88 (99.81 - 164.19)	0.131
Progesterone receptor				
Negative	2.30 (1.75 - 3.00)		142.71 (104.29 - 166.26)	
Positive	2.11 (1.61 - 2.84)	0.160	122.64 (98.36 - 163.61)	**0.044**
cerbB2				
Negative	2.13 (1.63 - 2.83)		124.88 (99.08 - 164.94)	
Positive	2.12 (1.65 - 2.96)	0.741	128.67 (102.59 - 166.11)	0.749
Perineural invasion				
No	2.10 (1.63 - 2.79)		124.66 (99.62 - 164.00)	
Yes	2.29 (1.69 - 3.00)	0.199	132.05 (103.16 - 169.92)	0.225
Lymphovascular invasion				
No	2.09 (1.61 - 2.79)		124.55 (100.40 - 166.26)	
Yes	2.32 (1.72 - 3.00)	0.061	130.90 (100.00 - 161.62)	0.959
Extracapsular invasion				
No	2.10 (1.63 - 2.72)		124.49 (100.00 - 164.08)	
Yes	2.26 (1.71 - 3.24)	**0.022**	130.00 (102.33 - 167.69)	0.417
Multifocal				
No	2.11 (1.61 - 2.83)		124.66 (100.00 - 164.08)	
Yes	2.23 (1.71 - 2.95)	0.434	130.90 (101.43 - 167.69)	0.355
Multicentric				
No	2.09 (1.63 - 2.82)		124.04 (100.00 - 163.33)	
Yes	2.33 (1.70 - 3.00)	0.101	145.28 (112.56 - 168.46)	0.063
Adjuvant chemotherapy				
No	2.16 (1.65 - 3.40)		123.56 (96.04 - 176.19)	
Yes	2.12 (1.64 - 2.84)	0.556	126.67 (100.40 - 164.12)	0.913
Adjuvant radiotherapy				
No	2.24 (1.60 - 2.92)		125.81 (103.12 - 169.65)	
Yes	2.09 (1.65 - 2.83)	0.471	127.97 (100.00 - 162.35)	0.724
Hormonotherapy				
No	2.15 (1.71 - 3.00)		147.43 (104.50 - 169.38)	
Yes	2.11 (1.62 - 2.84)	0.438	124.88 (100.00 - 164.19)	0.169
Data are given as median (1st quartile - 3rd quartile) for continuous variables according to normality of				

DISCUSSION

For a long time, it was thought that cancerous cells could only reproduce by themselves as a result of genetic abnormalities, and the effect of tumor microenvironment on this proliferation was ignored. However, extensive research shows that tumor cells are susceptible to environmental conditions and host characteristics. Recent studies conducted in this context show that clinicopathological features of cancer patients and the systemic inflammatory response they create may be related to each other[15,16]. In this study, we found very weak but significant correlations between various prognosis-related characteristics and NLR and PLR values. In addition, NLR values appear to be increased by presence of extracapsular invasion, while PLR value is decreased in patients with progesterone receptor positivity.

A likely example showing the relationship between cancer and inflammatory response is the overproduction of platelet-derived growth factor in cancer cells, since it plays an active role in the growth of tumors. As such, platelet counts have been suggested to be an indicator of tumor activity[17,18]. In addition, it is thought that the inflammatory response occurring in the vicinity of cancer cells is associated with angiogenesis and invasion features, and that lymphocytes involved in the infiltration of malignant cells and neutrophils may exhibit prognostic properties in these cases[15,19]. There are studies showing that NLR and PLR values, which are indicators of the inflammatory response, are affected by the tumor microenvironment. In studies examining the relationship of NLR and PLR values with the clinical characteristics, prognosis and survival rates of cancer patients, it has been stated that high NLR and PLR values are associated with adverse survival in many cancer types, including colorectal, stomach, breast, prostate, liver, esophagus and pancreas cancers[11,16,20-23].

Although there are few such studies in breast cancer patients, these studies report that NLR and PLR values are independent prognostic factors[13,16]. In one of these studies, Koh et al. examined the relationship between NLR and PLR values and prognosis in breast cancer patients. They examined 1435 breast cancer cases and reported that high NLR and PLR values were associated with high mortality. It was emphasized that the prognostic value of NLR was found to be relatively better than PLR[16]. Azab et al. studied the relationship between NLR value and survival of patients with breast cancer in 2012 and divided the patients into 4 groups according to their NLR values. It was stated that the survival rate of those in the highest NLR quartile was significantly lower than the other 3 groups. They thought that the NLR values of patients in the highest quartile group could constitute a threshold value[24]. Although the majority of studies show that high NLR and PLR values are indicators of poor prognosis in breast cancer, there are few studies reporting that these parameters are not significantly associated with prognosis. Cihan et al. reported that leukocyte, neutrophil, lymphocyte counts, and NLR and PLR values had no relationship with prognosis in breast cancer. However, they stated in their study that the short duration of patient follow-up and the number of early-stage patients might have affected this result, and thus, cited this as a limitation of their study[25]. The effects of NLR and PLR values on prognosis and survival were not directly investigated in our study, but the relationship of these values with other factors directly affecting prognosis (stage, number of metastatic lymph nodes, invasion characteristics, presence of hormone receptors, etc.) was evaluated. NLR values were found to be significantly correlated with the number of metastatic lymph nodes, N stage, and TNM stage. In addition, the relationship between TNM stage and high PLR value was also significant.

Secondarily, when we assessed NLR and PLR values with respect to various patient- and tumor-related characteristics, presence of hormone receptors, which is considered to be one of the important prognostic factors in breast cancer, it was found that PLR was significantly lower in patients with positivity for progesterone receptors. In the examination performed according to the invasion characteristics of the tumor, which is also one of the important prognostic factors, a high NLR value was noted in tumors with extracapsular invasion. Considering the effects of these parameters on breast cancer prognosis, the relationship between high NLR & PLR values and poor prognosis was also supported by the data in our study.

Unal et al. examined the PLR values of 140 patients diagnosed with breast cancer and reported that the PLR value was significantly higher in postmenopausal patients ($p < 0.001$)[2]. As far as we know, there is no other study in the literature comparing menopausal status and PLR or NLR value. In our study, there was no significant difference in PLR or NLR values between premenopausal and postmenopausal women. In addition, when the relationship between age and NLR & PLR values was examined, regardless of the menopausal status of the cases, it was found that only the PLR value decreased significantly as the age increased ($r = -0.125$, $p = 0.007$). Although the sample size of our study is greater than the aforementioned study, it is evident that the current results are not sufficient to reach a clear conclusion on this issue and it is thought that the data should be supported by new research. Considering that our study included a highly heterogenous group of patients, we believe the assessment of possible relationships in future studies should exercise stratification based on clinical and/or pathological findings of patients.

CONCLUSION

The results of our study weakly support the consensus of previous studies and show that high NLR and PLR values are associated with poor clinicopathological features. In particular, the fact that NLR and PLR values are easy to measure and that they are calculated with the parameters found in the hemogram test requested from the patients in routine examinations show the value of these parameters in prognostic follow-up.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Author Contributions

AK: Substantial contributions to conception and design of the study and the article, data analysis and interpretation, drafting the article, final approval of

the version to be published.

DBO: Data analysis and interpretation, drafting the article.

HD: Data analysis and interpretation, drafting the article.

MU: Substantial contributions to conception and design of the study and the article.

BU: Substantial contributions to conception and design of the study and the article, data analysis and interpretation, drafting the article, final approval of the version to be published.

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