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Are Peripheral Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Radio Related with Breast Cancer-Related Lymphedema?

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ABSTRACT

Objective: To investigate peripheral neutrophil-lymphocyte ratio, which is an indicator of immunity and systemic inflammation, and platelet-lymphocyte ratio in patients with breast cancer and its affect on lymphedema.

Material and Methods: The patients were dichotomized into two groups, ones with breast cancer-related lymphedema (BCRL) and the control group cases with no identified BCRL. The BCRL group included 28 cases and the control group included 34. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) values were compared between the groups. Intra and intergroup correlation analysis for NLR/PLR, visual analog scale (VAS), Quick Disabilities of the Arm, Shoulder, and Hand Questionnaire (Q-DASH), and the volumetric and diametric differences between the upper extremities were computed.

Results: Neutrophil-to-lymphocyte ratio was significantly higher in the control group (p= 0.035). Platelet-to-lymphocyte ratio values yielded similar results (p= 0.161). There was no correlation between NLR/PLR values and outcome parameters (r≤ 0.3; p> 0.05).

Conclusion: Neutrophil-to-lymphocyte ratio and PLR are not clinically significant for lymphedema, pain, disability, physical function, and BCRL.

Keywords: Breast cancer related lymphedema, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte

ÖZ

Meme Kanseri ile İlgili Lenfödem ile Periferik Nötrofil-Lenfosit Oranı ve Platelet-Lenfosit Oranı İlişkili Midir?

Giriş: Bağışıklık ve sistemik inflamasyonun göstergesi olan periferik nötrofil-lenfosit oranı ve trombosit-lenfosit oranının meme kanseri olan hastalarda incelenmesi ve lenfödeme etkisinin araştırılması.

Gereç ve Yöntemler: Hastalar iki gruba ayrıldı. Meme kanseri ilişkili lenfödem (BRCL) grubu, lenfödemli 28 meme kanseri hastasını ve kontrol grubu lenfödem olmayan 34 meme kanseri hastasını içeriyordu. Nötrofil-lenfosit oranı (NLO) ve platelet-lenfosit oranı (PLO) gruplar arasında karşılaştırıldı. Her iki gruptaki NLO/PLO ve görsel analog skala (VAS) arasındaki korelation ve Hızlı Kol, Omuz ve El Değerlendirme Anketi (Q-DASH); BCRL grubunda üst ekstremiteler arasındaki hacimsel ve çevresel ölçüm farklılıkları analiz edildi.

Bulgular: Nötrofil-lenfosit oranı kontrol grubunda anlamlı derecede yüksekti (p= 0.035). Platelet-lenfosit oranı değerleri gruplar arasında benzerdi (p= 0.161). NLO/PL0 değerleriyle sonuç parametreleri arasında korelasyon yoktu (r≤ 0.3; p> 0.05).

Sonuç: Nötrofil-lenfosit oranı ve platelet-lenfosit oranı lenfödem ve ağrı, özürlülük, fiziksel fonksiyon veya BCRL'nin klinik değerlendirmeleri için önemli değildir.

Anahtar Kelimeler: Meme kanserine bağlı lenfödem, nötrofil/lenfosit oranı, trombosit/lenfosit oranı

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INTRODUCTION

Breast cancer is the most common female cancer and one of the leading causes of cancer mortality in women in the western world (1). Recent improvements in the management of the condition have led to increased survival rates and thus escalated incidences of long-term treatment-related complications. Breast cancer-related lymphedema (BCRL) is one of the most frequent problems encountered by patients undergoing breast cancer surgery. The problem itself has a great impact on both quality of life and social consequences. Breast cancer-related lymphedema results from iatrogenic damage in the transport capacity of the regional lymphatic system which leads to the interstitial collection of lymph fluid in the upper limb (2,3). Lymphatic fluid accumulation by definition is composed of proteins, cytokines, chemokines, recirculating lymphocytes, parenchymatous cell products, and residue of senescent cells (4). Lymphatic drainage insufficiency leads to a progressive inflammatory process involving immunologic responses that finally manifests as pain, inactivity, discomfort, and recurrent infections in patients with BCRL (1,2,5,6).

Numerous studies have investigated the relation of peripheral inflammatory cells to many diseases and malignities (1,7-11). Neutrophils and platelets are known to be involved in the regulation of immune and inflammatory responses and might have independent prognostic values in systemic inflammatory response (12).

In clinical practice, peripheral blood-based simples are generally used for the evaluation of peripheral indicators of systemic immunity and inflammation. These blood-based measurements commonly include the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). In previous studies, NLR and PLR have been associated with systemic inflammation and disease-free survival in breast cancer (1,7-11). Although there are many previous studies investigating the relationship between neutrophil lymphocyte ratio and platelet lymphocyte ratio in breast cancer, prognosis and complications of breast cancer, no study investigating neutrophil lymphocyte ratio and platelet lymphocyte ratio in lymphedema was found in the literature.

The present study aimed to analyze the peripheral NLR and PLR values in patients with breast cancer and analyze the impact of NLR and PLR on lymphedema progression.

MATERIALS and METHODS

The study included 62 patients in our outpatient clinic with a diagnosis of breast cancer and a history of surgical, chemotherapy, and radiotherapy treatment. We reviewed these files retrospectively for this study. Exclusion criteria were the presence of bilateral breast carcinoma and/or bilateral BCRL and active systemic or local infection and active immunologic treatment. The breast cancer patients were dichotomized into two groups, ones with breast cancer-related lymphedema (BCRL) and the control group cases with no identified BCRL. Inclusion criteria of the BCRL group (n= 28) was having a diagnosis of a unilateral upper extremity BCRL [n= 28; median age= 54 (32-70) years]. The control group (n= 34) consisted of patients diagnosed with unilateral breast cancer without lymphedema [n= 34; median age= 57 (31-73) years]. Age, body mass index (BMI) [body weight (kg)/height^2 (m^2)], education level, work status, affected breast, the history of malignancy diagnosis were recorded. The surveys included visual analog scale (VAS), Quick Disabilities of the Arm, Shoulder, and Hand Questionnaire (Q-DASH). The volumetric and diametric differences between the affected and unaffected extremities were examined. Platelet, neutrophil, and lymphocyte levels of the peripheral blood samples were also recorded. NLR was defined as the ratio between the absolute count of neutrophils and the absolute count of lymphocytes. PLR was computed by dividing the absolute number of platelets by the absolute number of lymphocytes (1).

Lymphedema Evaluation

Interlimb volume and size difference measurements were used for the diagnosis of BCRL at our outpatient clinic. Breast cancer-related lymphedema was diagnosed as a difference of ≥200 mL in the upper limb volume or a circumferential difference of ≥2 cm at any of the measurement points between the affected and non-affected upper extremities (13,14). The clinic's routine lymphedema measurement procedures are summarized below: Before the measurements were performed, patients were asked to remove all jewelry and watches from their hands and wrists. Volumetric measurement differences between the upper extremities were made using the water displacement method. A larger water container attached to another container with an overflow tube was filled with warm water up to a marked level at the lower border of the overflow tube. Each arm was submerged into the container in turn and the volume of water that was displaced was recorded. The circumferential measurement differences method was performed using a narrow, flexible non-stretch tape measure. Measurements were performed at the metacarpophalangeal joint, wrist, 10 cm distal to the lateral epicondyle, 10 cm proximal to the lateral epicondyle, and 20 cm proximal to the lateral epicondyle.

The lymphedema stage of all BCRL patients was recorded based on this categorization. Stage 1 presents with reversible pitting edema that subsides with limb elevation. As the edema advances and becomes more intense, evolves to a non-pitting and irreversible phase, and is rarely reduced by limb elevation alone, the second stage is developed. Stage 3 is characterized

by advanced lymphedema and pitting is absent. Skin changes can be seen at this stage, including thickening, hyperpigmentation, fibrosis, and increased skin folds (14-16).

Visual Analog Scale (VAS)

The severity of pain in the study was assessed using the VAS scale, which assesses subjective pain intensity. The scale is a 10 cm straight line with two sides marked: Having on the left side absolutely no pain and on the right as typed maximum pain. Pain levels were assessed by asking subjects to mark their pain level on the visual analog scale (17).

Q-DASH (the Quick Disabilities of the Arm, Shoulder, and Hand Questionnaire) This scale assesses the physical function and symptoms in patients with musculoskeletal disorders of the upper limb and is a shortened version of the DASH scale. Q-DASH consists of a disability/symptom scale (11 items) and two optional scales: Work (four items) and sports/ performing arts (four items). In the main part which questions the disability and symptoms, items ask regarding the severity of pain, activity-related pain, tingling, weakness and stiffness, difficulty in performing physical activities due to the upper extremity problems, and the effect of the upper extremity problems on social activities, work, and sleep. The latter two optional modules estimate the ability to work and the ability to perform sports and play musical instruments. Answers are given based on a one-to-five scale and each question is scored between one and five. The scores of three subscales of Quick DASH, the disability/symptom, work, and sports/performing arts scales, ranged between 0 (no disability) and 100 (most severe disability). The reliability and validity study of the Turkish version of the Q-DASH has been performed by Koldas Dogan et al. (18).

Statistical Analysis

Statistical analysis was performed using the SPSS statistical package (Version 17.0, SPSS Inc., Chicago, IL, USA). Normal continuous variables were described as mean ± standard deviation [p> 0.05 in Kolmogorov-Smirnov test or Shapiro-Wilk (n< 30)] and non-normal variables were described as median. Chi-square test was used to compare categorical expressions. Mann Whitney U test was used to analyze the non-normally distributed parameters. A p-value of 0.05 was taken as the level of significance.

Correlations between outcome scores and blood tests were analyzed using Spearman's correlation test. In determining the relationship between continuous measurements, the r coefficient value is respectively; 0-0.300 weak; 0.301-0.500 moderate, 0.501-0.700 good; 0.701-0.900 strong. It shows a very strong relationship between 0.901-1.000.

RESULTS

In the BCRL group, 14 patients were evaluated as lymphedema Stage 1, 13 patients Stage 2, and one patient Stage 3. Mean duration of BCRL was 14.4 months (range= 1 to 96 months). Clinical characteristics of the study population did not show statistically significant differences between the groups (p> 0.05), except for BMI, which was significantly higher in the BCRL group (p= 0.031). The clinical characteristics of each group were summarized in Table 1.

Median NLR values were 1.84 (0.95-8.3) in the BCRL group and 2.82 (0.8-13.0) in the control group. Neutrophil-to-lymphocyte ratio was significantly higher in the control group than the BCRL group (p= 0.034).

Platelet-to-lymphocyte ratio values were higher in the control group than the BCRL group median 10.5 (4.4-31.5); 8.46 (4-25.5), respectively. However, this ratio was not statistically significant (p= 0.122).

Neutrophil-to-lymphocyte ratio and PLR results are shown in Table 2. Correlations between outcome measure-

Table 1. Clinical characteristics of the study population

Characteristics	BCRL Group (n= 28)	Control Group (n= 34)	p
Age (years) [Med (Min-Max)]	54 (32-70)	57 (31-73)	0.370
Body mass index (kg/m^2) [Med (Min-Max)]	31.2 (21.4-43.8)	28.3 (22.8-35.5)	**0.031***
Duration of malignancy (months) [Med (Min-Max)]	24 (6-99)	32.5 (10-125)	0.386
Dominant extremity (right/left) (n)	22/6	27/7	0.589
Affected breast (right/left) (n)	22/12	14/14	0.182
Work status (Housewife/Active working/ Intermittent working/Retired) (n)	22/4/1/1	25/8/0/1	0.580
Education level (No School/Elementary School/ Middle School/High School/College/Master) (n)	0/8/9/4/4/3	1/3/13/6/9/2	0.306

BCRL: Breast cancer related lymphedema; SD: Standard deviation.

*: Statistically significant, Med (Min-Max): Mann Whitney U test (n): Chi-square test.

Table 2. Peripheral blood simple results of the study population (mean ± standard deviation)

Characteristics	BCRL Group (n= 28) Med (Min-Max)	Control Group (n= 34) Med (Min-Max)	p
Neutrophil/lymphocyte ratio (NLR)	1.84 (0.95-8.3)	2.82 (0.8-13.0)	0.034
Platelet/lymphocyte ratio (PLR)	8.46 (4-25.5)	10.5 (4.4-31.5)	0.122

BCRL: Breast cancer related lymphedema, Med (Min-Max): Mann Whitney U test.

Table 3. Correlation analysis results of NLR/PLR levels between outcome measurements of the BCRL population (n= 28)

Characteristics	Value*	Correlation Analysis Results of NLR**		Correlation Analysis Results of PLR***	
		r	p	r	p
Visual Analog Scale	0 (0-8)	0.025	0.889	0.106	0.556
Quick DASH****	15 (0-68)	0.31	0.861	0.020	0.913
Volumetric Measurement Difference Between Upper Extremities (mL)	461 (90-1840)	0.40	0.824	0.006	0.971
Circumferential Measurement Difference Between Upper Extremities (cm)					
Metacarpophalangeal joint	0.5 (0-4)	-0.064	0.632	0.068	0.708
Wrist	1 (0-5)	-0.098	0.460	-0.072	0.687
10 cm distal to the lateral epicondyle	2.5 (0-10)	-0.027	0.837	0.030	0.865
10 cm proximal to the lateral epicondyle	2.5 (1-12)	-0.055	0.678	-0.024	0.893
20 cm proximal to the lateral epicondyle	2 (0-8)	-0.156	0.237	0.078	0.661

BCRL: Breast cancer related lymphedema.
*Median (minimum-maximum).
**NLR: Neutrophil/lymphocyte ratio.
***PLR: Platelet/lymphocyte ratio.
****DASH: Disabilities of the Arm, Shoulder, and Hand Questionnaire.
r: Spearman correlation test.

ments and blood samples were analyzed in patients with BCRL. There were no significant correlations of outcome measurements with NLR/PLR ($r \leq 0.3$; $p > 0.05$). Outcome measurements and correlation analysis results are shown in Table 3.

DISCUSSION

Reversible changes in the distribution of peripheral blood cells reflect immune system activation (20). A functional immune system plays an important part in diseases such as lymphedema. Lymphedema results in chronic inflammation, fibrosis, immune suppression, and an increased tendency for infections (21). It is also known that physical inactivity may be associated with both BCRL and chronic low-grade inflammation (1,2,5,22). Based on this data, we evaluated the relationship between NLR/PLR and BCRL. We found that these indicators were not higher in the BCRL group than in the control group. Also, we did not find any relationship between NLR/PLR and VAS, Q-DASH scores, or differences in upper limb size and volume. Based on this result, we believe that serum NLR and PLR were not related to the presence of lymphedema, pain, and clinical evaluations in patients with lymphedema.

Increased NLR and PLR are known to be associated with poor prognosis in a wide range of diseases such as stroke, Parkinson's, hypertension, diabetes mellitus, and pulmonary embolism (20,22-26). The hypothesis that NLR might be associated with outcomes was based mainly on the physiological association of neutrophilia and lymphopenia with systemic

inflammation and stress. Neutrophil-to-lymphocyte ratio might be indicative of a patient's response to inflammatory damage, with neutrophils boost in response to stress, producing various factors linked with chemokines, cytokines, and vascular endothelial growth factors, inducing lymphocyte apoptosis and suppressing the cytolytic activity of lymphocytes (11,27-29). Lymphocytes are essential for the regulation of proper inflammatory reaction and their loss due to apoptosis, cellular exhaustion, and downregulation may perpetuate a destructive inflammatory state. The resulting increase in NLR might identify patients who have a limited physiological reserve to survive the inflammatory damage (27). The low ratio of such a parameter might indicate a systemic background of reduced inflammation and immune system activation. The presence of a high NLR value has been recognized as a poor prognostic factor in various cancers, including breast cancer (1,7-11,30). In the present study, we found that NLR was higher in breast carcinoma patients without lymphedema. Our data support that BCRL might have more complicated mechanisms beyond our parameters. According to the literature, these mechanisms include genetic, metabolic, inflammatory, molecular, and immunologic factors.

Various studies in the literature have examined the lymphatic system and inflammatory response. Choi et al. have reported that pro-inflammatory cytokines, interleukins, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and insulin-like growth factors activate both angiogenesis and lymphangiogenesis (31). Rockson et al. have evaluated the lymphatic system and the inflammatory response and developed a bioassay utilizing proteins representing central pathogenetic modalities of the disease, lymphangiogenesis (FGF); inflammation (interleukins and tissue necrosis factor); and fibrosis [transforming growth factor-β (TGF-β)] (32). The release of TGF-β from platelets can result in a significant immunosuppressive effect with consequently impaired lymphocyte function and reduced lymphocyte counts. Platelets also contain both proinflammatory molecules and cytokines, interleukins, multiple anti-inflammatory cytokines, and large numbers of growth factors, including PDGF, as they have important functions in inflammatory and immune responses (11,32). Additionally, cytokines play a key role in modulating inflammatory responses, which might subsequently lead to fibrosis, lymphatic dysfunction, and lymphedema (33). Hence, BCRL is related to the immunologic process, cytokines, chemokines, interleukins, and tissue factors. In addition, Visser et al. have evaluated the BCRL and genetic predisposition with a systematic review. They have found that the patients with BCRL had genetic variations in 18 genes (34). These studies have shown that BCRL pathogenesis was multifactorial. Our results support that NLR and PLR were insufficient to evaluate lymphedema. In addition, these ratios are not specific and do not reflect the immune response associated with platelet, neutrophil, and lymphocyte functions.

Limitations of the present study were the small sample size and that most patients in the BCRL group had low-grade lymphedema. Furthermore, we could not evaluate cytokines, chemokines, tissue factors, and interleukins.

CONCLUSION

In conclusion, peripheral NLR/PLR values do not appear to be related to the presence or severity of BCRL. These values were not shown to affect pain, disability, physical function, or extremity size/volume in BCRL patients.

Ethics Committee Approval: This study was approved by the Adana City Training and Research Hospital Clinic Research Ethics Committee (Decision Number: 1685, Date: 16.12.2021).

Author Contributions: Concept/Design: EÇ, PDA; Analysis/Interpretation: EÇ, PDA; Data Acquisition: PDA; Writting: PDA; Critical Revision: EÇ, PDA; Final Approval: PDA.

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