RESEARCH ARTICLE / ARAŞTIRMA MAKALESI

Evaluation of the Relationship Between Breast Cancer Subtypes and Serum Inflammatory Markers

Meme Kanseri Alt Tipleri ile Serum Inflamatuar Belirteçleri Arasındaki İlişkinin Değerlendirilmesi

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Abstract

Introduction The most widespread type of cancer among women is breast cancer. Luminal A, luminal B, cerbB2 enriched type, Triple negative molecular subtypes have been defined. This study aimed to reveal the relationship between molecular subtypes and inflammatory markers.

Materials and Methods Breast cancer patients who were operated between January 2019 and April 2023 were evaluated. The study included 93 female breast cancer patients. Demographic characteristics, pathology assessments, molecular subtypes and laboratory data of the patients were collected. Systemic Inflammatory Response Index (SIRI), Platelet/Lymphocyte ratio (PLR) and Neutrophil/Lymphocyte ratio (NLR) were calculated from the hemogram. The relationship between molecular subtypes and inflammatory markers was statistically evaluated.

Results The median age of the patients included in the study was 56 years. Among the patients, 82.8% tested positive for estrogen receptor (ER+), while 61.3% tested positive for progesterone receptor (PR+). The most common molecular subtype was luminal A. When the cut-off value for Ki67 was 14, a statistically significant correlation was found between ER status (p=0.047). When Ki67 cut-off value was set to 20, a statistically significant relationship was observed with ER (p=0.002) and a statistically significant relationship with PR (p=0.025). The median of NLR was 1.9 (from a range of 0.7 to 21.3) and the median of PLR was 123 (from a range of 53.3 to 252).

Conclusion We did not find a significant relationship between breast cancer subtypes and inflammatory markers. However, the tendency to show a statistically significant difference between cerbB2 and PLR and SIRI was remarkable (p=0.08, p=0.057, respectively).

Keywords Breast cancer, Systemic Inflammatory Response Index, Neutrophil lymphocyte ratio; Platelet-lymphocyte ratio

Özet

Amaç Meme kanseri kadınlarda en sık görülen kanserdir. Meme kanserinin, luminal A, luminal B, cerbB2'den zengin tip, triple negatif moleküler subtipleri tanımlanmıştır. Bu çalışma moleküler subtipler ile enflamatuar belirteçler arasındaki ilişkiyi ortayı koymayı amaçlamıştır.

Gerec ve Yöntemler Ocak 2019 ve Nisan 2023 tarihleri arasında opere edilen meme kanseri hastaları değerlendirmeye alındı. Hastaların demografik özellikleri, patoji değerlendirmeleri, moleküler alt tipleri ve labaratuvar verileri toplandı. Hemogramdan Nötrofil/Lenfosit oranı (NLR), Trombosit/Lenfosit oranı (PLR) ve Sistemik Enflamatuvar Yanıt İndeksi (SIRI) hesaplandı. Moleküler alt tipler ile enflamatuar belirteçler arasında ilişki istatistiksel olarak değerlendirildi.

Bulgular Çalışmaya dahil edilen hastaların ortanca yaşı 56 idi. Hastaların %82,8'inde östrojen reseptörü (ER+), %61,3'ünde progesteron reseptörü (PR+) pozitif çıktı. En yaygın moleküler alt tip lümen A idi. Ki67 kesme değeri 14 olduğunda ER durumu arasında istatistiksel olarak anlamlı bir ilişki bulundu (p=0,047). Ki67 cut-off değeri 20 olarak alındığında hem ER ile (p=0,002), hem de PR ile istatistiksel olarak anlamlı ilişki (p=0,025) gözlendi. NLR ve PLR'nin ortanca değerleri sırasıyla 1,9 (aralık, 0,7:21,3) ve 123 (aralık, 53,3:252) idi.

Sonuç Meme kanseri alt tipleri ile inflamatuar belirteçler arasında anlamlı bir ilişki bulamadık. Ancak cerbB2 ile PLR ve SIRI arasında istatistiksel olarak anlamlı fark gösterme eğilimi dikkat çekiciydi (sırasıyla p=0.08, p=0.057).

Anahtar Kelimeler Meme kanseri, SIRI, Nötrofil lenfosit oranı, Trombosit lenfosit oranı

INTRODUCTION

Breast cancer incidence rates have increased over the past four decades. Between 2010 and 2019, it increased by 0.5%. It is also still the most common of cause cancer-related death (1,2). Age, disease stage, tumor subtype, histological grade, and receptor status are important factors in breast cancer prognosis. Even in patients with similar known factors, different clinical outcomes can be seen, so there is no uniform behavioral pattern for breast cancer (3). Because breast cancer is a heterogeneous systemic disease consisting of different biological subtypes (4).

When considering all subtypes, Luminal type A has the best prognosis. Many studies show that overall and disease-free survival is shorter in luminal type B (5). Again, compared to the Luminal A subtype, triple negative and HER-2 positive breast cancers have a poor prognosis (5,6). In recent years, the body's inflammatory response has been increasingly emphasized in tumor development and progression. Empirical evidence from multiple studies suggests that inflammation exerts a substantial influence as a determining factor in cancer progression (7-9). It is known that tumors are infiltrated by both inflammatory and lymphocytic cells. Studies have found that the infiltration of inflammatory and lymphocytic cells differs among different tumor types (10,11).

In the scope of our investigation, we sought to examine the associations between the distinct subtypes of breast cancer and inflammatory biomarkers NLR (Neutrophil/Lymphocyte Ratio), PLR (Platelet/Lymphocyte Ratio), and SIRI (Systemic Immune-Inflammation Index).

MATERIAL and METHODS

In this retrospective study, 93 female breast cancer patients who underwent breast cancer in Trakya University Medical Faculty Hospital were evaluated between January 2019 and April 2023. The inclusion criteria comprised patients who had undergone surgery for breast cancer, while those who received neoadjuvant chemotherapy (NACT) were excluded. Additionally, patients with active infection, chronic inflammatory or autoimmune disease, and those under steroid therapy were not included in the study.

The study encompassed the evaluation of the patient's demographic characteristics, hemogram data (including leukocytes, neutrophils, and lymphocytes) obtained one week before the surgical procedure, and post-operative pathology reports. SIRI, NLR and PLR were all derived. NLR was calculated through the dividing of the absolute neutrophil count by the absolute lymphocyte count; and PLR was computed as the quotient of the absolute platelet count divided by the absolute lymphocyte count. The formula SIRI = neutrophil count × monocyte count/lymphocyte count was employed to calculate SIRI.

ER and PR status were accepted as negative/positive according to the results of the immunohistochemical study. Patients with cerbB2 status and immunohistochemistry 3+ were considered (+). 2+ were determined according to the values obtained by fluorescence in situ hybridization (FISH). An evaluation was made with two cut-off values of 20% and 14% for Ki-67 (5,12). Breast cancer subtypes will be evaluated as Luminal A, luminal B, triple-negative, and CerbB2-enriched breast cancer (TNBC).

Statistical analysis

The distribution status of the data was checked using the Shapiro-Wilk test. In comparing two independent groups, the Student's T or Mann-Whitney U tests were preferred depending on the normal distribution. The Pearson chi-square test or Fisher's exact test investigated relationships between qualitative variables. Descriptive statistics were calculated. Mean and standard deviation were used for normally distributed quantitative variables. For those that were not normally distributed, the median and the smallest value-maximum value were used. Frequencies and percentages are given for qualitative variables. The significance level was determined as 0.05 in all statistical analyzes. Statistical analyzes were performed with JAMOVI (version 1.2).

RESULTS

The median age of the individuals enrolled in the research was 56 years old, with a range from 33 to 85 years. Among the patients, 51.6% had cancer in their left breast. The prevailing histological type was invasive ductal carcinoma, accounting for 67.7% of cases. Most breast cancer cases were classified as Grade II. Axillary lymph node involvement was identified in 12 patients, representing 12.90% of the cohort. Breast-conserving surgery (BCS) and sentinel lymph node dissection were the most performed surgical procedures. In cases with axillary lymph node involvement, axillary dissection (AD) was performed, involving 12 patients. However, patients with micrometastases did not undergo axillary dissection. For more detailed demographic features and laboratory findings of the patients, please refer to **Table**

Table 1. Demographic, Clinicopathologic Characteristics data of patients. (Breast conserving surgery: BCS, sentinel lymph node dissection: SLNB, Axillary dissection:AD)

	Median	Min:max
Age	56	33:85
Tumor size (cm)	2,0	0,4:6
NLR	1,9	0,7:6.62
PLR	123	53.3:252
SIRI	0.98	0.28:4.05
	N:93	**%**
Laterality		
Left	48	51.6
Right	44	43.4
Bilateral	1	1
Histological type		
Duktal	63	67.7
Lobuler	11	11.8
Others	19	20.5
Histological Grade		
I	21	22.6
II	49	52.7
III	23	24.7
Metastatic lymph nodes	12	12.90
Operations		
BCS+SLNB	63	67.7
Mastectomy+SLNB	8	8.6
BCS+SLNB +AD	18	19.4
Mastectomy+SLNB +AD	4	4.3

Among the patients, 82.8% tested positive for estrogen receptor (ER+), while 61.3% tested positive for progesterone receptor (PR+). Additionally, 10.8% of the patients were positive for cerbB2 (HER2/neu). The most common molecular subtype was luminal A, followed by luminal B. Detailed immunohistochemical data of the patients can be found in **Table 2.**

Significant statistical relationship were observed between cerbB2 positivity and Ki67 levels (p=0.003). Furthermore, a statistically significant correlation was found between Ki67<14 and ER positivity (p=0.047). When the Ki67 cut-off was set at 20, a statistically significant relationship was observed with ER (p=0.002) and a statistically significant relationship with PR (p=0.025).

Median values of NLR and PLR were 1.9 (range, 0.7:21.3) and 123 (range, 53.3:252), respectively.

Table 2. Immunohistochemical data

	n	%
Hormone receptor status		
ER		
(+)	77	82.8
(-)	16	17.2
PR		
(+)	57	61.3
(-)	36	38.7
CerbB2		
(+)	10	10.8
(-)	83	89.2
Ki67		
< 20	61	65.6
≥ 20	32	34.4
Ki67		
< 14	51	55.4
≥ 14	41	44.6
Moleküler alt tipler		
Lum A	57	61.3
Lum B	20	21.5
triple-negative subtype	14	15.1
CerbB2-enriched subtype	2	2.2

A statistically significant correlation was found between NLR and age (P < 0.05). There was no statistically significant relationship between NLR and size. Similarly, no statistically significant relationship existed between NLR and ER, PR, and Ki67 levels. There was no statistically significant relationship between NLR and CerbB2. We could not able to detect any significant relationship between PLR and hormone receptor status. Similarly, we did not detect a statistically significant relationship between cerbB2 expression status and PLR. A statistically significant relationship was also found between age and SIRI (p<0.05). In our study, NLR, PLR, and SIRI values according to histological subtypes are shown in detail in **Table 3.**

No statistically significant relationship was found between CerbB2 status and PLR and SIRI. However, the p values showing the relationship between both PLR and SIRI and cerbB2 were 0.08 and 0.057, respectively and tended to be significant. The relationship between hormone status (ER, PR), CerbB2 status, and Ki 67 and inflammatory markers are given in **Table 4.**

Table 3. NLR, PLR, SIRI values according to histopathological subtypes.

	NLR		PLR		SIRI	
Histopathological subtype	**Median**	**Min:max**	**Median**	**Min:max**	**Median**	**Min:max**
Luminal A	2.06	0.72:6.62	121	55:247	1.02	0.28: 4.05
Luminal B	1.93	0.91:4.9	131	53,:252	0.91	0.36:3.09
Triple-negative subtype	1.72	1.27:3.76	122	65,8:220	1.05	0.67:2.12
CerbB2-enriched subtype	1.45	1.44:1.46	127	101:154	0.72	0.57:0.9

Table 4. Relationship among hormone status, CerbB2 status, and Ki67 with inflammatory markers

	NLR			PLR			SIRI		
	Mean	**SD**	**p**	**Mean**	**SD**	**p**	**Mean**	**SD**	**p**
ER									
+	2,12	1,06	0,37	134,4	50,6	0,73	1,17	0,6	0,9
-	1,88	0,65		127	46,5		1,06	0,4	
PR									
+	2,14	1,15	0,79	128,6	45,7	0,51	1,12	0,6	0,98
-	2,01	0,8		138,4	54,4		1,18	0,7	
CerbB2									
+	1,98	1,11	0,47	161,7	58,9	**0,081**	0,98	0,78	**0,057**
-	2,093	0,9		129,8	47,9		1,17	0,62	
Ki67									
<20	2,04	0,99	0,67	131,2	50,7	0,4	1,12	0,5	0,99
≥ 20	2,16	1,05		137,1	48,7		1,23	0,8	
Ki67									
< 14	2,09	1,05	1,0	130,1	51	0,33	1,15	0,55	0,37
≥ 14	2,07	0,96		137,7	49		1,15	0,75	

DISCUSSION

There has been growing interest in studying the relationship between hematological components of the systemic inflammatory response and cancer progression in recent years. Preoperative measurements of the NLR and PLR in primary operable cancer have been reported as effective predictors of survival, independent of tumor stage. Specifically, this evidence appears particularly robust in colorectal, stomach, and kidney cancers (13). Similarly, in a separate study involving ovarian cancer patients, it was observed that preoperative mean NLR values were significantly higher (6.02) compared to healthy individuals (14). This increase in NLR has been linked to the inhibitory effect on cytolytic activity of lymphocytes, and activated T cells, thus potentially facilitating the infiltration of tumor cells into circulation and promoting tumor angiogenesis (15).

In recent years, significant advancements have been made in breast cancer research. Among the various treatment approaches, endocrine therapy is now recommended as a priority for patients with hormone receptor-positive breast cancer. Moreover, genetic testing is employed to accurately predict prognosis and identify individuals who may benefit from adjuvant chemotherapy. However, these tests have limited use due to their high cost (16). Consequently, there is an ongoing search for more affordable and accessible tools to predict prognosis and tailor treatment plans.

Studies have explored the interaction between the immune system and tumor cells in breast cancer and its association with prognosis (10,11). A meta-analysis conducted by Ethier et al. established the median cut-off value for high NLR (Neutrophil Lymphocyte Ratio) as 2.5 (range 1.9–4.0). This study also reported that NLR has a significant prognostic

impact on both Overall Survival (OS) and Disease-Free Survival (DFS) (17).

In our study, the median NLR values were 1.9 (range 0.7:21.3), and PLR (Platelet Lymphocyte Ratio) was 123 (range 53.3:252). In another investigation by Yersal et al., the median NLR and PLR values for breast cancer patients were reported as 2.01 (range 0.37–37.1) and 137.8 (range 37.1–421.3), respectively (10). Regarding the relationship between NLR and hormone receptor status, Koh et al. did not detect a statistically significant association with ER (Estrogen Receptor) status. However, they reported a significant correlation between NLR and both PR (Progesterone Receptor) and cerbB2 status (p=0.026 and p=0.002, respectively) (18).

Another study found no statistically significant relationship between NLR and HER2 expression or hormone receptor status (10). We either did not find a statistically significant correlation between NLR and ER, PR, and Ki67 levels. Similarly, NLR and CerbB2 status had no statistically significant relationship.

It has been shown that breast cancer patients with higher NLR are older and have metastases (19). In our study, NLR showed a positive correlation with age. However, we did not detect a similar relationship with PLR. It has been reported that patients with higher PLR have a worse prognosis and shorter disease-free survival. It was emphasized that 185 could be the cut-off for the PLR-value in predicting the prognosis (2). Although it was not statistically significant between PLR values and cerbB2 status in our study, we found a tendency to have a significant relationship (p=0.08) (Table 4.). However, there was no statistically significant relationship between PLR and hormone status or Ki67. Similarly, we did not find a statistically significant difference between PLR values and breast cancer subtypes.

One study created a nomogram based on grade, TNM stage, and SIRI in breast cancer patients. The overall survival (OS) of patients with a SIRI value less than 0.65 was statistically higher than that of patients with a SIRI value greater than 0.65. In the same study, it has been reported that SIRI predicts 5- and 10-year survival rates more accurately than the TNM stage alone (20). In a study conducted on postmenopausal breast cancer patients, it was found that high SIRI values were associated with progesterone receptor status (16).

We had several limitations in our study. As of the first, we had a limited number of patients. As a second limitation, we evaluated the past five years.

CONCLUSION

In conclusion, we did not find any correlation between the inflammatory markers and the hormone receptors and molecular markers of breast cancer in our limited number of cohorts. There are controversial outcomes in the literature on the prognostic value of inflammatory markers on breast cancer prognosis. However, the search for cost-effective tools to predict breast cancer prognosis and guide treatment decisions continues, with studies highlighting the potential prognostic value of immune-related markers like NLR and PLR. Studies with a larger number of patients with longer follow-ups should be conducted to thoroughly evaluate the association of inflammatory markers with the hormonal and molecular status of the patients to examine their impact on breast cancer prognosis

Ethıcal Declerations

The approval for this study was obtained from Trakya University Health Research Ethics Committee (Protocol no: TÜTF GOBAEK 2023/201).

InformedConsent:

Because the study was designed retrospectively, no written in formed consent form was obtained from patients.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

Financial Disclosure:

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Author Contributions:

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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