Are Peripheral Blood Derived Inflammation Markers Prognostic Indicators in Breast Cancer?

Periferik Kanda Ölçülen İnflamasyon Belirteçlerinin Meme Kanserli Hastalarda Prognostik Önemi var mı?

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ABSTRACT

Objective: Peripheral blood derived inflammation based scores are proposed as prognostic markers in solid tumors especially in gastrointestinal system. We aimed to investigate the association between neutrophyl/lymphocyte ratio (NLR, platelet/lymphocyte ratio (PLR) and breast cancer in means of prognostic forecast.
Methods: Of 190 patients diagnosed and operated for breast cancer. 160 patients with available pretreatment blood count were included. Ultrasound, mammography, and pathology results were also recorded.
Results: The median age was 50 years at the time of diagnosis (28-90 years). Family history was positive in 11 patients. There were 139 patients with invasive ductal carcinoma, 15 patients with invasive lobuler carcinoma. There was no association with histopathological type of the tumor and peripheral blood derived inflammation markers. The difference in PLR between T1 and T4 tumors was statistically significant. Also both NLR and PLR were significant when N0 patients compared with N1 patients ($p<0.05$). Neither estrogen nor progesterone receptor status was shown to have an association with NLR and PLR. PLR was found to be statistically significant in different pathological grade groups.
Conclusion: Both NLR and PLR were found to be correlated with advanced stage breast cancer so with prognosis. In order to use these markers in clinical practice, more clinical trials with large number of patients and long follow up period are needed.

Key Words: Breast cancer, neutrophyl/lymphocyte ratio, platelet/lymphocyte ratio

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ÖZET

Amaç: Periferik kanda saptanan inflamasyon belirteçleri gastrointestinal sistem tümörleri öncelikli olmak üzere birçok solid tümörde prognostik belirteç olarak kullanılmaktadır. Biz de bu çalışmada nötrofil/lenfosit oranı ve trombosit/ lenfosit oranları ile meme kanseri arasında prognoz belirleme bakımından ilişki olup olmadığını araştırdık.
Yöntem: Meme kanseri nedeniyle ameliyat edilen 190 hastadan preoperatif kan tetkikleri sonucuna ulaşılan 160 hasta çalışmaya dâhil edildi. Ultrasonografi, mamografi ve patoloji sonuçları da kaydedildi.
Bulgular: Hastaların yaşı 28 ile 90 arasında değişmekte olup tanı anındaki median yaş 50 idi. Aile öyküsü 11 hastada vardı. 139 hasta invaziv duktal karsinom tanısı alırken, 15 hasta invaziv lobuler karsinom tanısı almıştı. Kanserin histopatolojik tipi ile inflamasyon belirteçleri arasında istatistiksel olarak anlamlı ilişki saptanmadı. Tümör boyutları açısından bakıldığında T1 ve T4 tümörler arasında trombosit/lenfosit oranı açısından anlamlı fark saptandı. N0 ile N1 hastalar karşılaştırıldığında ise hem nötrofil/lenfosit oranı hem de trombosit /lenfosit oranı açısından fark istatistiksel olarak anlamlıydı ($p<0,05$). Östrojen ve progesteron reseptörlerinin negatif veya pozitif olmasının ise ne nötrofil/lenfosit oranı ne de trombosit/ lenfosit oranı üzerinde etkisi olmadığı görüldü. Tümör *Grade*'leri açısından karşılaştırma yapıldığında da trombosit/lenfosit oranında istatistiksel olarak anlamlı fark saptandı.
Sonuç: Hem nötrofil/lenfosit oranı hem de trombosit/lenfosit oranı'nın ileri evre meme kanseri ve dolayısıyla prognoz beklentisi ile ilişkili olduğu görülmüştür. Klinikte kullanıma girebilmesi için bu belirteçlerle ilgili daha geniş vaka serileri ve uzun takip sürelerini içeren meta analizlere ihtiyaç vardır.

Anahtar Sözcükler: Meme kanseri, nötrofil/ lenfosit oranı, trombosit/ lenfosit oranı

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INTRODUCTION

Cancer progression and prognosis are affected by the host's inflammatory response in the tumor microenvironment (1). As components of systemic inflammatory response; lymphocytes, neutrophils and platelets are increasingly being recognized to have an important role in carcinogenesis and progression of tumor (2). Peripheral blood derived inflammation based scores are proposed as prognostic markers in solid tumors commonly in gastrointestinal system especially in colorectal cancer (3). However the role of these biomarkers in breast cancer prognosis is less well known (4). We aimed to investigate the association between pre-treatment neutrophyl/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and breast cancer in means of prognosis forecast.

METHODS

Between 2012 and 2014, 190 patients diagnosed and operated for breast cancer by the same surgical team. 160 patients with available data were included in the study. Demographic data of the patients, family history and risk factors for breast cancer, physical examination, laboratory findings, ultrasound, mammography and pathology results including tumor characteristics were all recorded. In order to ascertain that the blood count results were pre-treatment values, the initial treatment dates of the patients were checked. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count and PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

After the operations, the patients were followed up in the breast unit by the same surgical team. The follow-up time was calculated from the time of diagnosis to the end of the study period. If any, date and cause of the death was recorded. Statistically categorical variables were compared by using x^2 - test and continuous variables were expressed in "median" and compared by using Kruskal-Wallis test.

RESULTS

The median age was 50 y at time of diagnosis (28 y-90 y). Family history was positive in 11 patients (7%). There were 139 patients with invasive ductal carcinoma, 15 patients with invasive lobular carcinoma, 4 patients with ductal-lobular carcinoma and 2 patients with medullary carcinoma. There was no statistically significant association between histopathological type of the tumor and peripheral blood derived inflammation markers (Table 1).

The difference in PLR between T1 and T4 tumors was statistically significant ($p<0.05$). Also both NLR and PLR were significant when N0 patients compared with N1 (Table 2). Neither estrogen nor progesterone receptor status was shown to have an association with NLR and PLR. PLR was found to be statistically significant in different pathological grade groups (Table 3).

The patients were followed up every 3 months for the first two years and then every 6 months up to 5 years. Those who were lost to follow-up were excluded. Any unexpected event related with breast cancer was documented. No death from the progression of the disease was noted.

Table 1: RDW. PDW. NLR and PLR values according to the histopathological type

Pathology	RDW	PDW	NLR	PLR
Invasive ductal ca (86%)	14.41±1.77	13.51±2.37	2.43±1.43	149.94±61.34
Invasive lobular ca (9%)	14.51±1.63	14.02±3.25	2.38±0.93	141.29±62.55
Invasive ductal +lobular ca (3%)	15.22±0.78	14.52±2.3	2.53±0.94	136.43±48.56
Medullary ca (2%)	13.4±0.28	13.65±1.2	2.16±0.45	95.67±36.30
p value	NS	NS	NS	NS

RDW: red cell distribution witdh. PDW: platelet cell distribution width

Table 2: RDW. PDW. NLR and PLR values according to the TNM's

	n	%	RDW	PDW	NLR	PLR
T						
T1	43	27	14.06 ± 1.34	13.29 ± 2.75	2.19 ± 1.01	135.68 ± 50.75
T2	92	57.5	14.4 ± 1.62	13.82 ± 2.42	2.46 ± 1.39	147.01 ± 50.66
T3	13	8	14.86 ± 2.8	13.23 ± 1.66	2.21 ± 0.97	138.69 ± 61.96
T4	12	7.5	15.47 ± 2.11	31.21 ± 2.2	3.31 ± 2.29	211.15 ± 114.81
P			a	NS	NS	a
N						
N0	66	41	14.31 ± 1.53	13.93 ± 2.62	2.2 ± 0.9	131.98 ± 43.87
N1	82	51	14.54 ± 1.9	13.23 ± 2.25	2.67 ± 1.67	160.03 ± 67.62
N2	10	6	13.88 ± 0.72	14.13 ± 2.24	2.22 ± 0.86	141.21 ± 57.64
N3	2	2	16.3 ± 4.1	14.45 ± 5.02	1.05 ± 0.27	222.59 ± 153.24
P			NS	NS	b	b
M						
0	146	91	14.36 ± 1.68	13.65 ± 2.47	2.37 ± 1.26	144.35 ± 59.1
1	14	9	15.15 ± 2.18	12.94 ± 2.1	3.08 ± 2.2	187.02 ± 67.75
P			NS	NS	NS	0.038

a: T1& T4; p=0.04 for RDW. p=0.04 for PLR
b: N0 & N1. p= 0.029 for NLR. p=0.003 for PLR

Table 3: RDW. PDW. NLR and PLR values acoording to the grade and receptor status

	n	%	RDW	PDW	NLR	PLR
GRADE						
1	14	12	14.57 ± 2.02	14.71 ± 1.62	2.49 ± 2.17	141.5 ± 73.83
2	77	65	14.49 ± 1.79	13.33 ± 2.4	2.24 ± 0.87	138.99 ± 46.47
3	27	23	14.46 ± 1.74	13.32 ± 2.35	2.62 ± 1.2	177.44 ± 77.04
P			NS	c	NS	c
ER						
Negatif	33	79	14.55 ± 1.61	13.89 ± 2.91	2.33 ± 1.1	168.01 ± 74.03
Pozitif	127	21	14.4 ± 1.77	13.51 ± 2.32	2.45 ± 1.43	143.09 ± 56.34
p			NS	NS	NS	NS
PR						
Negatif	36	22.5	14.26 ± 1.5	13.73 ± 2.59	2.28 ± 1.05	158.45 ± 74.26
Pozitif	124	77.5	14.48 ± 1.8	13.54 ± 2.41	2.47 ± 1.45	145.18 ± 56.56
p			NS	NS	NS	NS
HER reseptörü						
Negatif	99	62	14.45 ± 1.72	13.48 ± 2.41	2.6 ± 1.55	154.19 ± 60.13
Pozitif	61	38	14.39 ± 1.77	13.75 ± 2.51	2.15 ± 0.95	138.07 ± 61.31
p			NS	NS	0.028	NS

c: Grade 1 & 2. p=0.013 for PDW; Grade 1 & 3. p=0.03 for PDW; Grade 2 & 3; p=0.02 for PLR

DISCUSSION

It is now widely recognized that outcomes in patients with cancer are not determined by tumor characteristics alone but patient related factors are also playing key roles (5). Cancer associated inflammation is a key determinant of disease progression and survival in most cancers (6). The inflammatory response involves systemic alterations triggered by cytokines and chemokines like an increase in neutrophyl count or platelet count. In addition red cell distribution width (RDW) and mean platelet volume are routine and easy to measure inflammatory markers (7). A recent meta-analysis of 40559 patients with solid tumors found that an NLR greater than 4.00 was associated with a substantial increase in risk for all cause mortality (8). Although PLR is not seen to be associated with either disease-free survival or over-all survival in women with breast cancer (9), in our study both NLR and PLR were found to be correlated with advanced stage breast cancer so with prognosis.

Previous studies had found that the impact of NLR and PLR on breast cancer prognosis varies according to the cancer subtypes (10) but we did not find a significant effect. In order to use these readily available biomarkers in clinical settings and call them predictive prognostic indicators more clinical trials with large number of patients and long follow-up periods are needed.

Conflict of interest

No conflict of interest was declared by the authors.

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