Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

The effect of peripheral blood eosinophil/lymphocyte ratios on chemotherapy response and prognosis before and after neoadjuvant chemotherapy in patients with locally advanced breast cancer

Lokal ileri evre meme kanserli hastalarda neoadjuvan kemoterapi öncesi ve sonrası periferik kan eozinofil/lenfosit oranlarının kemoterapi yanıtına ve prognoza etkisi

Öykü ÜNSAL[1]
Tuğba YAVUZŞEN[2]
Işıl SOMALI[2]

[1] Department of Internal Medicine, Dokuz Eylül University, Faculty of Medicine, Izmir, Türkiye
[2] Department of Medical Oncology, Dokuz Eylül University, Faculty of Medicine, Izmir, Türkiye

Peripheral Blood Eosinophil/Lymphocyte Ratios in Patients with Locally Advanced Breast Cancer

Received: 07.01.2025
Accepted: 18.09.2025
DOI:

Corresponding author
Öykü ÜNSAL
ORCID ID: 0000-0001-7366-1158
droykuunsal@gmail.com

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

ABSTRACT

BACKGROUND

This study aims to examine the peripheral blood eosinophil/lymphocyte ratio (ELR) as a simple, affordable and easily accessible marker to predict neoadjuvant chemotherapy (NACT) response and prognosis in patients with locally advanced breast cancer (LABC).

METHODS

The study included 102 female patients over the age of 18 who were diagnosed with LABC in 2010-2019 and were treated with NACT at Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, Medical Oncology. The patients were retrospectively examined for demographic, clinical, pathological and laboratory data. Laboratory data (leukocyte count, eosinophil count and percentage, lymphocyte count and percentage, ELR and eosinophil x lymphocytes) were evaluated before chemotherapy, before surgery and before relapse. Single and multi-variable regression analyses were performed to determine risk factors important for pathological complete response (pCR) and relapse development. The Kaplan-Meier survival analysis method was used to determine the effects of these factors on PFS (progression-free survival).

RESULTS

The mean diagnostic age was 50.8±13.0 years, the follow-up time was 41.0±27.0 months, and the average time from NACT to operation was 7.9±2.5 months. Mortality rate was 10.8%, relapse rate was 14.7%, and PCR incidence rate was 27.5%. No statistically significant differences were found in the ELR and eosinophil x lymphocyte parameters before and after NACT in terms of their value in pCR and relapse prediction. The most important predictive clinical and pathological features for pCR were found to be low count of positive lymph nodes (LN) (OR = 0.342, p = 0.04) and ER negativity (OR = 2.6, p = 0.035). The risk of recurrence in patients with a positive LN count of three and above was 3.8 times greater (OR = 3.8, p = 0.008) and the duration of PFS was shorter. The risk of recurrence in patients with a pre-NACT lymphocyte percentage of 26.75 and below was 4.2 times greater (OR = 4.2, p = 0,016), and the duration of PFS was shorter.

CONCLUSION

The study suggests that if more patients are evaluated and over a long follow-up period, markers such as peripheral blood ELR or eosinophil x lymphocyte could be used as affordable, easily accessible predictive and prognostic markers for predicting NACT response.

KEYWORDS

Locally advanced breast cancer, neoadjuvant chemotherapy, pathological complete response, prognostic marker, recurrence

ÖZ

AMAÇ

Lokal ileri evre meme kanserli (LİMK) hastalarda neoadjuvan kemoterapi (NAKT) yanıtı ve prognozu öngörmek için; basit, uygun fiyatlı ve kolay ulaşılabilir bir belirteç olarak periferik kan eozinofil/lenfosit oranının (ELR) incelenmesidir.

GEREÇ YÖNTEM

Çalışmaya 18 yaş üzeri, Dokuz Eylül Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı Tıbbi Onkoloji Bilim Dalı'nda 2010-2019 yılları arasında LİMK kanseri tanısı alan ve NAKT verilen 102 kadın hasta dahil edildi. Hastaların retrospektif olarak demografik, klinik, patolojik ve laboratuvar verileri incelendi. Laboratuvar verileri (lökosit sayısı, eozinofil sayı ve yüzdesi, lenfosit sayı ve yüzdesi, ELR ve eozinofilxlenfosit) kemoterapi öncesi, operasyon öncesi ve nüks öncesinde değerlendirildi. Patolojik tam yanıt (pCR) ve nüks gelişimi açısından önemli olan risk faktörlerini belirlemek amacıyla tek ve çok değişkenli regresyon analizleri uygulandı. Bu faktörlerin PFS (progresyonsuz sağkalım) üzerine etkilerini belirlemek için Kaplan-Meier sağkalım analiz yöntemi kullanıldı.

BULGULAR

Ortalama tanı yaşı 50,8±13,0 yıl, takip süresi 41,0±27,0 ay; NAKT'den operasyona kadar geçen süre ortalama 7,9±2,5 ay olarak hesaplandı. Mortalite oranı %10,8, nüks oranı %14,7, pCR görülme oranı ise %27,5 bulundu. NAKT öncesi ve sonrası ELR ve eozinofil x lenfosit parametrelerinde; pCR ve nüksü öngörmedeki değeri açısından istatistiksel anlamlı farklılık bulunmadı. pCR için en önemli öngörü değerine sahip klinik ve patolojik özellikler; pozitif lenf nodu(LN) sayısının az olması (OR = 0,342, p = 0,04) ve ER negatifliği (OR = 2,6, p = 0,035) olarak bulundu. Pozitif LN sayısı üç ve üzeri olan hastalarda nüks gelişme riski; 3,8 kat daha fazla (OR = 3,8, p = 0,008), PFS süresi daha kısa bulundu. NAKT öncesi lenfosit yüzdesi 26,75 ve altı olan hastalarda nüks gelişme riski; 4,2 kat daha fazla (OR = 4,2, p = 0,016), PFS süresi daha kısa bulundu.

SONUÇ

Daha fazla hasta sayısı ve uzun takip süresinde değerlendirme yapıldığında; periferik kan ELR veya eozinofil x lenfosit gibi belirteçlerin, NAKT yanıtını öngörmede uygun fiyatlı, kolay erişilebilir prediktif ve prognostik belirteçler olarak kullanılabileceği düşünülmektedir.

ANAHTAR KELİMELER

Lokal ileri evre meme kanseri, neoadjuvan kemoterapi, nüks, patolojik tam yanıt, prognostik belirteç

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

Breast cancer is the most common cancer in women both globally and in Türkiye. In a healthy population, a woman has a 12.9% risk of developing breast cancer during her lifetime, with one in eight women being diagnosed with the disease. In the United States, breast cancer is the second leading cause of cancer-related death in women, after lung cancer. Among women aged 20-59, it is the leading cause of cancer-related deaths (1). In Türkiye, the age-standardized incidence of breast cancer in women is 47.7 per 100,000. Regarding the percentage distribution of the most common cancers in women of all age groups, breast cancer accounts for 25.5% of cases (2).

The definition of locally advanced stage breast cancer is heterogeneous; it includes stage IIB (T3N0) and stage IIIA, IIB, IIIC breast cancers. This group includes both slow-growing and aggressive tumors. The standard treatment approach in LABC (locally advanced breast cancer) is NACT (neoadjuvant chemotherapy) treatment (3–6). The most important factor determining treatment success and survival is pCR (pathological complete response) (3). The most widely accepted definition of pCR includes no residual invasive disease in the breast and no measurable disease in the axillary lymph nodes sampled (ypT0/ypN0) (3,7,8).

Patients who achieved a pathologic pCR after neoadjuvant chemotherapy had a higher survival rate than those who did not. Therefore, numerous studies are investigating clinical and pathological characteristics that can be used to predict whether pCR can be achieved in patients receiving NACT, as well as laboratory data that can surve as markers. However, due to their cost and limited accessibility, genetic and molecular tests are not widely used in clinical practice. Simpler, cost-effective, and easily accessible markers are needed to predict the NACT response (9,10).

The main functions of eosinophils in the immune system include the elimination of foreign substances (their role in parasitic infections) and the regulation of inflammation (they respond to cytokines secreted from lymphocytes, secrete factors that have anti-tumor effects or stimulate tumor progression, act as antigen-presenting cells and can stimulate and influence lymphocyte functioning) (11,12). Eosinophils stimulate the anti-tumor response by attracting CD8+T cells to the tumor site with various chemokines that they secrete. However, some studies suggest that they promote tumour growth by inducing angiogenesis with growth factors such as VEGF (vascular endothelial growth factor), TGF-α (transforming growth factor-alpha), TGF-β (transforming growth factor-beta), and GM-CSF (granulocyte macrophage colony stimulating factor (12–14). Although tumoral eosinophilia is considered to be associated with a poor prognosis in Hodgkin lymphoma, it has been shown to be associated with a good prognosis in colorectal, breast, and prostate cancers (12).

The purpose of our study is to analyze the use of peripheral blood eosinophil/lymphocyte ratio (ELR) before and after NACT in LABC as a marker of treatment response and prognosis. Based on studies showing that tumoral eosinophilia is associated with a good prognosis in breast cancer (12), it is thought that peripheral blood eosinophilia may also have prognostic significance.

Materials and Methods

The study began after receiving approval from the Dokuz Eylül University Ethics Board for Non-Invasive Research. Women aged 18 years and older who were diagnosed with LABC and received NACT between 2010 and 2019 at the Department of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Dokuz Eylül University were included. Participants were excluded from the study if they were under 18 years of age, if the necessary demographic and clinical information was absent from the hospital records, or if they were male. The data were obtained by scanning electronic file system records (Probel Hbys) of Dokuz Eylül University Medical Faculty Hospital and archival materials in the Department of Archives and Medical Statistics. The laboratory data were obtained retrospectively from the central laboratory of the Dokuz Eylül University Medical Faculty Hospital, which is ISO 15189 accredited. Hemogram parameters within the scope of accreditation were studied usingthe impedance method on a Beckman Coulter LH 780 analyzer (MLTR.505.105) in blood with EDTA.

The independent variables were pathological complete response, relapse, mortality, whilethe dependent variables were determined as age, histological type, tumor diameter, positive lymph node count, estrogen receptor, progesterone receptor, human epidermal growth factor

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

receptor, and peripheral blood parameters. Demographic and clinical data are shown in Table 1. Tumor histology, receptor status, and pathological response are shown in Table 2 including histological type (ductal, lobular, mixed, other), ER status and PR status, HER2 status, Ki-67 proliferation index (<20%, ≥20%, unknown), lymphocytes infiltrating the tumor, lymphovascular invasion, perineural invasion, and pathological response.

Table 1. Demographic, clinical and histopathological data

Total number of patients (n)		102
Age of diagnosis (years) (mean ± sd) (min-max)		50.8±13.0 (26.7-82.4)
Relapse rate (n, %)		15 (14.7 %)
Mortality rate (n, %)		11 (10.8%)
Follow-up time (months) (mean±sd) (min-max)		41.0±27.0 (0.3-129.8)
Tumor diameter (mm) (mean±sd) (min-max)		27.2±16.1 (3.0-80.0)
Number of lymph nodes (mean±sd) (min-max)		9.7±6.5 (1.0-32.0)
Number of positive lymph nodes (mean±sd) (min-max)		2.3±3.8 (0.0-28.0)
Chemotherapy (n, %) EC→T		76 (74.5%)
FEC→T		18 (17.6%)
Carbo→T		3 (2.9%)
Unknown		2 (2.0%)
Other		3 (2.9%)
KT type (n, %) Taxane-based		94 (92.2%)
Other		8 (7.8%)
Trastuzumab (n, %) Yes		40 (39.2%)
No		62 (60.8%)
Radiotherapy (n, %) Yes		86 (84.3%)
No		16 (15.7%)
Histological type (n, %)		69 (67.6%)
	Lobular	18 (17.6%)
	Mixed	12 (11.8%)
	Other	3 (2.9%)
Estrogen receptor (ER) (n, %)	+	4 (3.9%)
	++	12 (11.8%)
	+++	54 (52.9%)
	-	32 (31.4%)
Progesterone receptor (PR) (n, %)	+	7 (6.9%)
	++	18 (17.6%)
	+++	29 (28.4%)
	-	48 (47.1%)
HER2 (n, %)	Positive	25 (24.5%)
	Negative	77 (75.5%)
Triple negative (n, %)	Yes	17 (16.7%)
	No	85 (83.3%)
Ki-67 proliferation index (n, %)	< 20%	21 (20.6%)
	≥20%	69 (67.6%)
	Unknown	12 (11.8%)
Tumor infiltrating lymphocytes (TIL) (n, %)	Low	29 (28.4%)
	Moderate	14 (13.7%)
	High	8 (7.8%)
	Unknown	49 (48.0%)
	None	2 (2.0%)
Lymphovascular invasion (LVI) (n, %)	Yes	55 (53.9%)

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

	None	46 (45.1%)
	Unknown	1 (1.0%)
Perineural invasion (n, %) (PNI)	Yes	16 (15.7%)
	None	85 (83.3%)
	Unknown	1 (1.0%)
Pathological complete response (pCR) (n, %)	pCR	28 (27.5%)
	DCIS, LN-negative	10 (9.8%)
	DCIS, LN-positive	13 (12.7%)
	Residual invasive carcinoma, LN-negative	10 (9.8%)
	Residual invasive carcinoma, LN-positive	40 (39.2%)
	Unknown	1 (1.0%)

CT, Chemotherapy; EC→T, Epirubicin, Cyclophosfamide then docetaxel or Paclitaxel; FEC → T, Fluorouracil, Epirubicin, Cyclofosfamide then Docetaxel or Paclitaxel, Carbo→T, Carboplatin then paclitaxel

Table 2. Demographic, clinical and histopathological characteristics of patients according to pathological response

		pCR positive n=28	**No pCR n=74**	**P**
Age of diagnosis (years) (mean ± sd)		50.3±13.1	50.9±13.0	0.838
Relapse rate		1 (3.6%)	14 (18.9%)	0.051
Tumor diameter (mm) (mean ± sd)		30.4±14.4	26.1±16.6	0.229
Number of LN (median) (min-max)		6.0 (1.0-21.0)	9.5 (1.0-32.0)	**0.035**
Number of positive LN (median) (min-max)		0.0 (0.0-2.0)	2.0 (0.0-28.0)	**<0.001**
Chemotherapy (n, %)	EC→T	22 (78.6%)	54 (73.0%)	0.654
	FEC→T	5 (17.9%)	13 (17.6%)	
	Carbo→T	0 (0.0%)	3 (4.1%)	
	Unknown	1 (3.6%)	1 (1.4%)	
	Other	0 (0.0%)	3 (4.1%)	
CT type (n, %)	Taxane-based	27 (96.4%)	67 (90.5%)	0.440
	Other	1 (3.6%)	7 (9.5%)	
Transtuzumab (n, %)	Yes	14 (50.0%)	26 (35.1%)	0.170
	No	14 (50.0%)	48 (64.9%)	
Radiotherapy (n, %)	Yes	21 (75.0%)	65 (87.8%)	0.132
	No	7 (25.0%)	9 (12.2%)	
Histological type (n, %)	Ductal	24 (85.7%)	45 (60.8%)	0.083
	Lobular	2 (7.1%)	16 (21.6%)	
	Mixed	1 (3.6%)	11 (14.9%)	
	Other	1 (3.6%)	2 (2.7%)	
ER (n, %)	Positive	13 (46.4%)	57 (77.0%)	**0.003**
	Negative	15 (53.6%)	17 (23.0%)	
PR (n, %)	Positive	10 (35.7%)	44 (59.5%)	**0.032**
	Negative	18 (64.3%)	30 (40.5%)	
HER2 (n, %)	Positive	11 (39.3%)	14 (18.9%)	**0.033**
	Negative	17 (60.7%)	60 (81.1%)	
Triple negative (n, %)	Yes	9 (32.1%)	8 (10.8%)	**0.016**
	No	19 (67.9%)	66 (89.2%)	
Ki-67 (n, %)	< 20%	2 (7.1%)	19 (25.7%)	0.050
	≥20%	24 (85.7%)	45 (60.8%)	
	Unknown	2 (7.1%)	10 (13.5%)	

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

TIL (n, %)	Low	7 (25.0%)	22 (29.7%)	0.993
	Moderate	4 (14.3%)	10 (13.5%)	
	High	2 (7.1%)	6 (8.1%)	
	Unknown	14 (50.0%)	35 (47.3%)	
	None	1 (3.6%)	1 (1.4%)	
LVI (n, %)	Yes	11 (39.3%)	44 (59.5%)	0.127
	None	17 (60.7%)	29 (39.2%)	
	Unknown	0 (0.0%)	1 (1.4%)	
PNI (n, %)	Yes	3 (10.7%)	13 (17.6%)	0.671
	None	25 (89.3%)	60 (81.1%)	
	Unknown	0 (0.0%)	1 (1.4%)	

pCR, Pathological complete response; LN, Lymph node; CT, Chemotherapy; EC→T, Epirubicin, Cyclophosfamide then docetaxel or Paclitaxel; FEC → T, Fluorouracil, Epirubicin, Cyclofosfamide then Docetaxel or Paclitaxel, Carbo→T, Carboplatin then paclitaxel; ER, Estrogen receptor; PR, Progesterone receptor; HER2, Human epidermal growth factor receptor 2; TIL, Tumor infiltrating lymphocytes; LVI, Lymphovascular invasion; PNI, Perineural invasion

The presence of HER2 was evaluated using the immunohistochemical method (IHC) and fluorescent in-situ hybridization (FISH) methods. Patients with HER2 (3+) were considered positive, while patients with HER2 (0) and (1+) were considered negative. Patients with HER2 (2+) were categorized as either positive or negative following further evaluation using the FISH method. Laboratory data were classified as follows: Leukocyte count (103/ul), eosinophil percentage (%), eosinophil count (103/ul), absolute eosinophil count (103/ul), lymphocyte percentage (%), lymphocyte count (103/ul), absolute lymphocyte count (103/ul), eosinophil/lymphocyte ratio (the number of eosinophils divided by lymphocytes), and eosinophil x lymphocyte (the number of eosinophils multiplied by lymphocytes). The laboratory data were examined before NACT, before the operation (post-NACT), and before relapse.

Statistical analyses were performed with SPSS software version 22.0 (IBM, New York, USA). After making descriptive statistics, Shapiro-Wilk and Kolmogorov-Smirnov normality tests were used to determine whether the continuous data was distributed normally. The Mann-Whitney U test was used to compare variables that did not show normal distribution between groups, and the Student-T test was used to compare normal distribution variables. The results of these analyses were presented as mean ± standard deviation, median and minimum-maximum values. Categorical data between the groups was compared using Chi-Square and Fisher's exact test. The results were given in numbers and percent (%).

Single-variable regression analysis was applied to determine variables with predictive value in predicting pathological full response. In single-variable regression analysis, variables with an alpha value less than 0.2 were included in the multi-variable regression analysis. The results were presented with 95% confidence intervals. P<0.05 was taken to indicate statistical significance.

A single-variable regression analysis was performed to determine the most important risk factors for recurrence development. In single-variable regression analysis, parameters with an alpha value less than 0.2 were included in the multi-variable regression analysis (Cox regression analysis). The results were presented with 95% confidence intervals. P<0.05 was taken to indicate statistical significance. As a result of regression analyses, ROC analyses were applied for the parameters determined as risk factors. Cut-off values were determined using AUC and Youden index ratios. Sensitivity and specificity rates were determined for such cut-off values. Using cut-off values, patients were divided into high-risk and low-risk groups.

The Kaplan-Meier survival analysis method was used based on the survival analyzes to determine the effects of effective risk factors on relapse on PFS. The estimated PFS times were given with confidence intervals of 95% as an average ± standard deviation. In all statistical analyses, $p < 0.05$ was taken to indicate statistical significance.

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

Results

A total of 102 women diagnosed with LABC and treated with NACT were included in the study. The mean age at diagnosis of the patients was 50.8±13.0 years, and the mean follow-up period was 41.0±27.0 months. The mortality rate was calculated as 10.8%, while the relapse rate was 14.7%. Other demographic, clinical and histopathological characteristics are summarized in Table 1.

The NACT regimens used are listed in Table 1. Taxane based NACT regimens include EC→T (Epirubicin, Cyclophosfamide then docetaxel or Paclitaxel), FEC → T (Fluorouracil, Epirubicin, Cyclofosfamide then Docetaxel or Paclitaxel) and Carbo→T (Carboplatin then paclitaxel). Missing values in categorical variables were coded as an 'unknown' category and included in the analyses. The duration of the patients from NACT to operation was calculated as 7.9 ± 2.5 months on average. When the patients' demographics and clinical characteristics were compared with their pathological response, a higher positive LN count was observed in patients without pCR ($p < 0.001$). A comparison of the tumor histology and receptor status in patients with PCR showed that the proportion of ER- and PR-positive patients was significantly lower ($p = 0.003$ and 0.032, respectively). The percentage of HER2-positive patients was higher in the pCR group ($p = 0.033$). A higher percentage of patients were triple-negative in the pCR group ($p = 0.016$). No statistically significant differences were found when other pathological features were compared (Table 2). Additonally, no significant differences were observedbetween all peripheral blood parameters before NACT in patients with and without pCR.

The parameters that may predict whether pCR will be observed in LABC patients receiving NACT were compared using single and multi-variable analyses. According to the multivariate regression analysis, the clinical and pathological characteristics that were found to have the most important predictive value for pCR in patients receiving NACT were found to have a low number of positive LN ($p = 0.04$) and ER negativity ($p = 0.035$) (Table 3).

Table 3. Single and multi-variable regression analysis for pathological complete response

	Univariate analysis (single variable)				Multivariate analysis (multiple variable)			
Parameters	**β**	**OR**	**95% GA**	**p**	**β**	**OR**	**95% GA**	**P**
Number of LN	-0.073	0.930	0.863-1.002	0.057	0.025	1.026	0.926-1.137	0.627
Number of positive LN	-1.129	0.323	0.166-0.629	0.001	-1.073	0.342	0.165-0.708	**0.004**
ER positive vs negative	1.353	3.869	1.543-9.700	0.004	1.254	2.603	1.470-14.448	**0.035**
PR positive vs negative	0.971	2.640	1.072-6.504	0.035	-0.966	0.381	0.081-1.796	0.222
HER2 negative vs positive	1.020	2.773	1.066-7.217	0.036	1.178	3.249	0.625-16.888	0.161
Triple-negative vs non-triple-negative	1.363	3.908	1.326-11.513	0.013	1.544	4.683	0.420-52.211	0.210

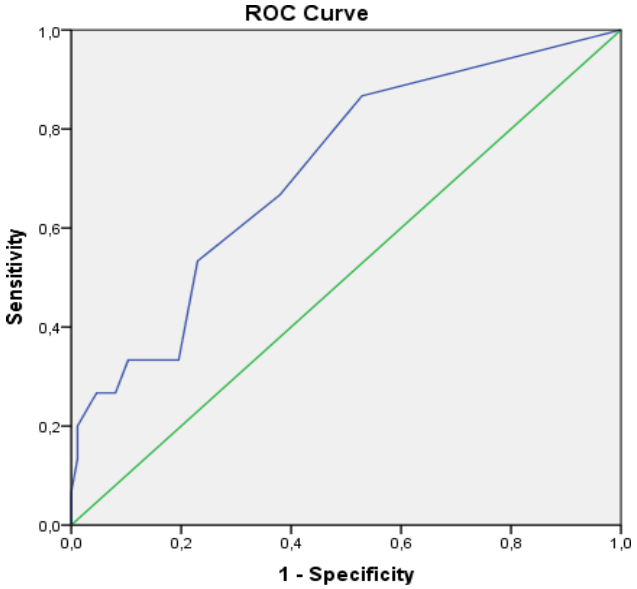
LN, Lymph node; ER, Estrogen receptor; PR, Progesterone receptor; HER2, Human epidermal growth factor receptor 2

When patients who relapsed after NACT were compared to patients who did not relapse, the number of positive LNs was found to be significantly higher in patients who relapsed ($p = 0.006$). No statistically significant difference was found in terms of tumor histology and receptor status between relapsing and non-relapsing patients.

However, relapsed patients were found to have lower percentages of lymphocytes alone in the peripheral circulation before chemotherapy than patients who did not relapse ($p = 0.016$). According to the ROC analysis conducted to evaluate the prediction of relapse development of positive LN number, cut-off value was 2.5 and the risk of relapse in patients with 3

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

or more positive lymph nodes was 3.8 times greater than in patients with less than 3 positive LNs Figure 1



	AUC	95% CI	P	Sensitivity	Specificity	Cut-off value	PPV	NPV	OR (95% CI)
Positive LN number	0.715	0.576-0.854	0.008	53.3%	77.0%	2.5	28.6%	90.5%	3.83 (1.24-11.86)

Figure 1. Relationship of positive LN to relapse in the ROC analysis curve

ROC analysis was performed to evaluate the ability of peripheral blood lymphocyte percentage to predict relapse development. The cut-off value was determined to be 26.75, and it was found that the risk of relapse was 4.2 times higher in patients with a pre-NACT lymphocyte percentage of 26.75 or below than in patients with a percentage above this value Figure 2.

The PFS of patients was found to be 92.7±4.5 months (83.7-101.6) with 95% CI Figure 3.

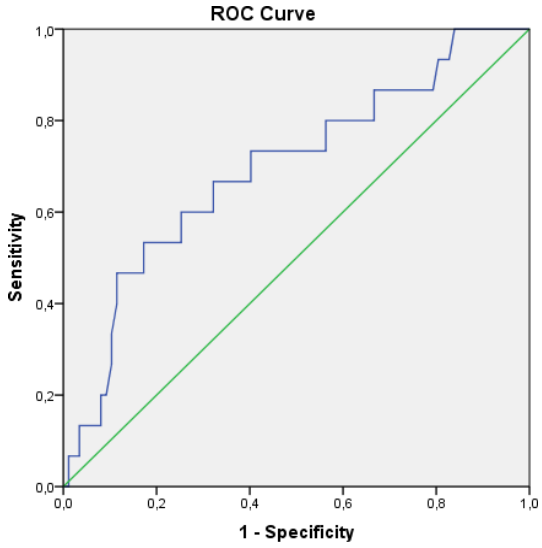
PFS was found to be shorter (p=0.013) in patients with a positive LN count of 3 and above than in patients with a count below 3 Figure 4.

PFS was found to be shorter (p=0.027) in patients with peripheral blood lymphocyte percentages of 26.75 or less than in patients with percentages above 26.75 Figure 5.

No statistically significant ELR value before or after NACT was determined to predict relapse, no cut-off value was calculated Figure 6.

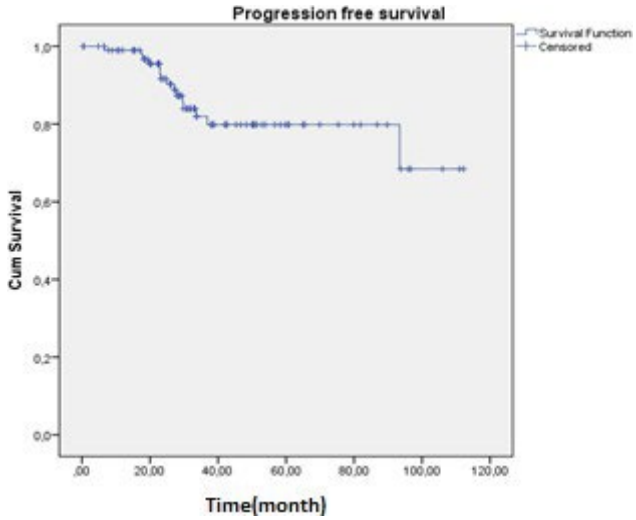
In single-variable analysis, parameters involved in relapse development in patients include age at diagnosis, positive LN count, and low lymphocyte percentage before chemotherapy. However, single-variable regression analysis of peripheral blood ELR before and after NACT found no significant results to include in the multivariate model ($p > 0.20$). In the multivariate analysis of the model created from parameters $P < 0.20$ (Cox regression), the prominent risk parameters for relapse development in this group of patients during follow-up were observed as positive LN count and low percentage of lymphocytes before chemotherapy, although no statistical significance was found ($p = 0.076$ and $p = 0.097$) (Table 4).

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64



	AUC	95% CI	P	Sensitivity	Specificity	Cut-off value	PPV	NPV	OR (95% CI)
Pre-NACT lymphocyte %	0,696	0.547-0.845	0,016	66.7%	67.8%	26.75	26.3%	92.2%	4.21 (1.32-13.50)

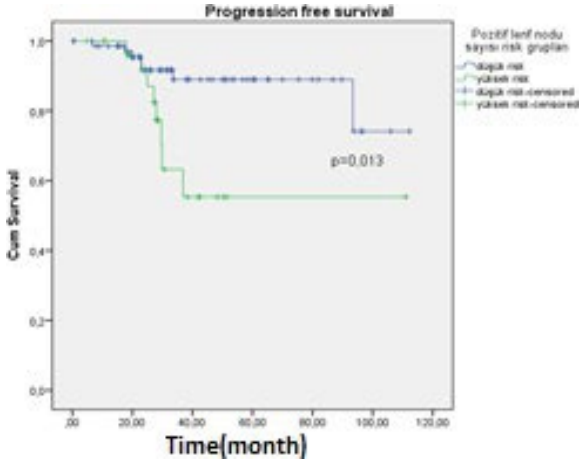
Figure 2. Relation of peripheral blood lymphocyte percentage to relapse in the ROC analysis curve



Time (months)	0	20	40	60	80	100	120
No at risk	102	79	34	17	10	3	0
No of events	4	10	0	0	1	0	0

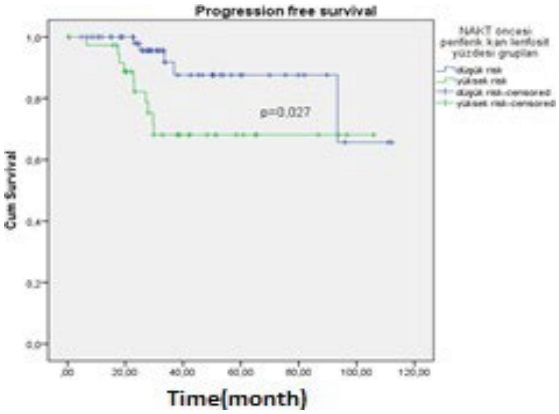
Figure 3. PFS analysis (Kaplan-Meier survival analysis)

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64



Number of positive LN	PFS (month)	95% CI	P
<3 low risk	99.5±4.5	90.6-108.4	**0.013**
≥3 high risk	74.1±10.2	54.0-94.2	

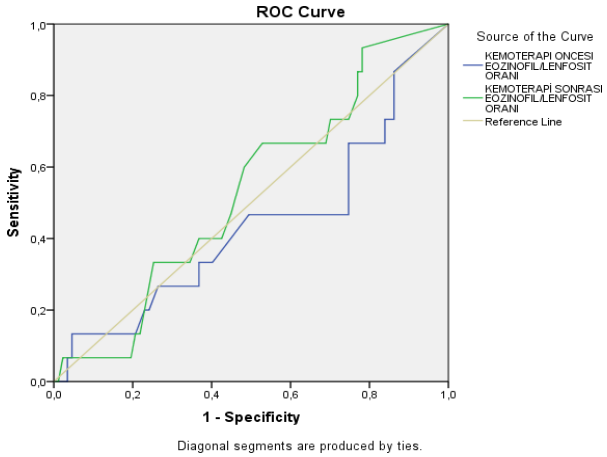
Figure 4. The effect of positive LN count on PFS (Kaplan-Meier analysis)



Pre-NACT lymphocyte percentage	PFS (month)	95% CI	P
> 26.75 low risk	**98.1±5.8**	**86.7-109.4**	**0.027**
≤ 26.75 high risk	**79.5±7.0**	**65.8-93.2**	

Figure 5. Effect of the percentage of lymphocytes in peripheral blood before NACT on PFS (Kaplan-Meier analysis)

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64



	AUC	95% CI	P	Sensitivity	Specificity	Cutoff value	PPV	NPV	OR (95% CI)
Pre-NACT ELR	0,434	0,266-0,603	0,419	-	-	-	-	-	-
Post-NACT ELR	0.530	0.384-0.676	0.713	-	-	-	-	-	-

Figure 6. Relationship of peripheral blood ELR before and after NACT in the ROC analysis curve

Table 4. Single and multi-variable regression analysis of the predictive values of the parameters for relapse

	Univariate analysis (single variable)				Multivariate analysis (multiple variable)			
Parameters	**β**	**OR**	**95% GA**	**p**	**β**	**OR**	**95% GA**	**p**
Age at diagnosis	-0.042	0.959	0.918-1.002	**0.062**	-0.036	0.964	0.924-1.007	0.099
Tumor size	0.014	1.014	0.988-1.040	0.296				
Number of positive LN Low vs High risk	1.226	3.407	1.223-9.491	**0.019**	0.975	2.652	0.903-7.792	0.076
Pre-NACT lymphocyte % Low vs High risk	1.148	3.151	1.076-9.227	**0.036**	0.935	2.547	0.844-7.691	0.097
Pre-NACT ELR	-3.738	0.024	0.000-481.015	0.460				
Post-NACT ELR	-0.824	0.439	0.000-2868.911	0.854				

LN, Lymph node; NACT, neoadjuvant chemotherapy; ELR, eosinophil/lymphocyte ratio

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

Discussion

In our study, the proportion of HER2-positive and triple-negative patients achieving pCR after NACT was significantly higher, whereas the proportion of patients with ER and/or PR receptor positive patients were statistically lower. Many other studies in the literature have reported similar findings, namely that the likelihood of pCR after NACT is highest in hormone-negative and HER2-positive tumors, followed by triple-negative tumors (15,16).

In both univariate and multivariate analyses, the two statistically significant factors with the greatest predictive value for pCR were identified as the low number of positive LN and negative ER status. A similar study conducted by Iwamoto et al., found factors predicting a high pCR rate after NACT were high-grade tumor, negative ER, and post-NACT cN0 (17). In a study by Omranipur et al., factors that predicted high pCR rates after NACT were found to be under 50 years of age, PR negativity, and high Ki-67 (15).

In our study, a positive LN count of 3 or more (3.8-fold) and a pre-NACT lymphocyte percentage of 26.75 or less (4.2-fold) were determined to be values that increase the risk of relapse. Similarly, many studies have found thata high number of axillary LNs involved in breast cancer has been found as a parameter that increases the risk of relapse (18). In the literature, it has been determined that pre-treatment lymphopenia is a parameter that predicts tumor relapse in breast cancer and is associated with poorer overall survival (19). Notably, previous studies have focused on absolute lymphocyte counts but the relationship between changes in lymphocyte percentage and relapse has not been checked.

In our study, we observed that LN positivity was elevated in patients with shorter PFS, and pre-NACT peripheral blood lymphocyte percentages were low. Similarly, Ownby et al. reported that a low pre-NACT peripheral blood lymphocyte count (<1500 cells/mm3) was associated with reduced PFS (20).

When we examined whether the ELR and eosinophil x lymphocyte parameters before and after NACT contributed to predicting CT response and prognosis, results revealed no significant associations with pCR, recurrence, or mortality. In a study conducted by Onesti et al. on 112 breast cancer patients treated with standard NACT, improvement in breast cancer-specific survival was observed in patients with high eosinophil and lymphocyte counts before treatment. Additionally, patients with high eosinophil counts before treatment had an increased rate of achieving pCR, particularly the pCR rate was higher in patients with eosinophil x lymphocytes ≥ 35.8 (21).

Peripheral blood cell-derived ratios, including lymphocyte/monocyte ratio (LMR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR), have been associated with prognosis and survival in breast cancer. Specifically, high LMR and low NLR correlated with reduced relapse risk and longer survival, whereas elevated PLR predicted shorter survival (22,23). All these studies have shown that markers containing peripheral blood cells may be associated with prognosis and survival in cancers, but studies incorporating eosinophil-based markers are limited. Endometrial cancer study have shown that higher ELR predicts poorer OS (24). In another study on endometrial cancer, higher pre-treatment ELR (≥ 0.1) and ENLR (eosinophil x neutrophil/lymphocyte ratio) (≥ 0.5) were found to be independently associated with worse overall survival (25). Low preoperative eosinophil counts and low ELR are independently associated with poorer overall survival in patients with stage II resectable pancreatic cancer (26). Additionally prostate cancer study found that higher pre-treatment ELR was associated with increased Gleason score (23). The number of studies investigating the ELR in breast cancer is limited.

The main limitations of our study are the small number of patients who have relapsed, the uneven distribution of patients across breast cancer subtypes, the short follow-up period, and the inability to exclude deaths that are not related to breast cancer or to conduct prospective monitoring.

This study's strength lies in its novel evaluation of the potential of ELR, lymphocyte count and percentage as predictive and prognostic markers for relapse and mortality in patients with LABC undergoing NACT. Our findings contribute valuable insight to the literature by addressing this gap. Other strengths include a meaningful dataset comprising 102 LABC patients, a separate assessment of parameters associated with both pCR and recurrence, and the use of ROC analyses to determine cut-off values, providing clinically applicable information. The lack of statistical significance in the ELR is also an important negative result that is worth reporting.

Although our study did not demonstrate a statistically significant association between ELR and clinical outcomes, this biomarker may still have clinical relevance. Biologically, ELR reflects the balance between eosinophils, which have been implicated in anti-tumor immunity, and lymphocytes, which are essential for adaptive immune responses. Previous studies have reported that systemic inflammatory ratios, including ELR and NLR, may serve as prognostic or predictive indicators in several malignancies, including breast cancer (7,27). Moreover, our relatively limited sample size and the heterogeneity of subgroups may have

Developments and Experiments in Health and Medicine
Year: 2026
Volume: 40
Issue: 1
RESEARCH ARTICLE
Pages:51-64

restricted statistical power, raising the possibility that a true association might be observed in larger, more homogeneous cohorts. Therefore, the prognostic and predictive significance of ELR requires further clarification in prospective studies with larger patient populations.

Conclusion

In conclusion, when larger patients and extended follow-up periods are evaluated, peripheral eosinophil and lymphocyte count, as well as combined markers such as the ELR or eosinophil x lymphocyte containing both of these cells together can be used as cost-effective, easily accessible predictive and prognostic markers for NACT response. Further comprehensive studies are needed to validate these observations. Our findings provide a foundation for such future investigations.

It was presented as a specialization thesis at Dokuz Eylül University, Department of Medical Oncology on November 18, 2021 (registered in Yöktez as thesis number 702996). Izmir Uğur Yılmaz Oncology Days, IX. Rare Tumors Symposium, Izmir, Türkiye, 25 - 27 February 2022, presented as an oral presentation.

Supporting institution and/or person
None.

Conflict of interest statement
The authors have no conflict of interest.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7–33.
2. Türkyılmaz M, Öztürk M, Dündar S. Türkiye Kanser İstatistikleri. T.C. Halk Sağlığı Kurumu Ankara. 2017. 75–77 p.
3. Güler N, Karabulut B, Koçdor MA. Lokal İleri Meme Kanseri 2010 İstanbul Konsensus Toplantısı. J Breast Heal. 2011;7(2):68–89.
4. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93–9.
5. Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA. 2019 Jan 22;321(3):288–300.
6. Barni S, Mandalà M, Williams L, Barni S. Locally advanced breast cancer. Curr Opin Obstet Gynecol. 2006;18:47–52.
7. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res. 2017 Jan 5;19(1):1–13.
8. Simon RM, Paik S HD. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009;101(21):1446–1452.
9. Eren T, Karacin C, Ucar G, Ergun Y, Yazici O, İmamoglu İ, et al. Correlation between peripheral blood inflammatory indicators and pathologic complete response to neoadjuvant chemotherapy in locally advanced breast cancer patients. Medicine (Baltimore). 2020 May 29;99(22):e20346.
10. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164–72.
11. Weller PF, Lim K. Human Eosinophil-Lymphocyte Interactions. Mem Inst Oswaldo Cruz, Rio Janeiro. 1997;92:173–82.
12. Sakkal S, Miller S, Apostolopoulos V, Nurgali K. Eosinophils in Cancer: Favourable or Unfavourable? Curr Med Chem. 2016 Jan 20;23(7):650–66.
13. Balkwill FR, Mantovani A. Cancer-related inflammation: Common themes and therapeutic opportunities. Semin Cancer Biol. 2011;22:33–40.
14. Carretero R, Sektioglu IM, Garbi N, Salgado OC, Beckhove P, Hämmerling GJ et all. Eosinophils orchestrate cancer rejection by normalizing tumor vessels and enhancing infiltration of CD8(+) T cells. Nat Immunol. 2015 May 19;16(6):609–17.
15. Omranipour R, Jalili R, Yazdankhahkenary A, Assarian A, Mirzania M, Eslami B et all. Evaluation of Pathologic Complete Response (pCR) to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients with Estrogen Receptor Positive and HER2 Negative and impact of predicting variables on pCR. Eur J breast Heal. 2020 Jun 24;16(3):213–8.
16. Simos D, Clemons M, Ginsburg OM, Jacobs C. Definition and consequences of locally advanced breast cancer. Curr Opin Support Palliat Care. 2014;8(1):33–8.
17. Iwamoto N, Aruga T, Horiguchi S, Saita C, Onishi M, Goto R, et al. Predictive factors of an axillary pathological complete response of node-positive breast cancer to neoadjuvant chemotherapy. Surg Today. 2020 Feb 1;50(2):178–84.

18. Chang JM, Leung JWT, Moy L, Ha SM, Moon WK. Axillary Nodal Evaluation in Breast Cancer: State of the Art. Radiology. 2020 Jun 1;295(3):500–15.
19. Bai YG, Gao GX, Zhang H, Zhang S, Liu Y-H, Duan X-N, et al. Prognostic value of tumor-infiltrating lymphocyte subtypes in residual tumors of patients with triple-negative breast cancer after neoadjuvant chemotherapy. Chin Med J (Engl). 2020 Mar 5;133(5):552–60.
20. Ownby HE, Roi LD, Isenberg RR, Brennan MJ. Peripheral Lymphocyte and Eosinophil Counts as Indicators of Prognosis in Primary Breast Cancer. Cancer. 1983;52:126–30.
21. Onesti CE, Josse C, Poncin A, Frères P, Poulet C, Bours V. Predictive and prognostic role of peripheral blood eosinophil count in triple-negative and hormone receptor-negative/HER2-positive breast cancer patients undergoing neoadjuvant treatment. Oncotarget. 2018 Sep 1;9(72):33719–33.
22. Losada B, Guerra JA, Malón D, Jara C, Rodriguez L, Barco S Del, et all. Pretreatment neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, and neutrophil/monocyte ratios and outcome in elderly breast cancer patients. Clin Transl Oncol. 2019 Jul 10;21(7):855–63.
23. Ferro M, Musi G, Serino A, Cozzi G, Mistretta FA, Costa B, et al. Neutrophil, Platelets, and Eosinophil to Lymphocyte Ratios Predict Gleason Score Upgrading in Low-Risk Prostate Cancer Patients. Urol Int. 2019 Jan 1;102(1):96–101.
24. Holub K, Conill C. The Impact of Inflammatory Biomarkers on Overall Survival of Patients with Pancreatic Cancer Treated with Chemoradiation. Elsevier. 2018;29(5):135.
25. Holub K, Biete A. New pre-treatment eosinophil-related ratios as prognostic biomarkers for survival outcomes in endometrial cancer. BMC Cancer. 2018;18:1280. DOI:10.1186/s12885-018-5131-x
26. Ohkuma R, Kubota Y, Horiike A, Ishiguro T, Hirasawa Y, Ariizumi H, et al. The prognostic impact of eosinophils and the eosinophil-to-lymphocyte ratio on survival outcomes in stage II resectable pancreatic cancer. Pancreas. 2021 Feb 1;50(2):167–75. DOI:10.1097/MPA.0000000000001731
27. Poncin A, Onesti CE, Josse C, Boulet D, Thiry J, Bours V, et al. Immunity and breast cancer: Focus on eosinophils. Biomedicines. 2021;9(9):1087. DOI:10.3390/biomedicines9091087.