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ORIGINAL ARTICLE

Predicting the role of the pretreatment neutrophil to lymphocyte ratio in the survival of early triple-negative breast cancer patients

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Summary

Purpose: *Increasing evidence supports an association between systemic inflammation and cancer development and progression. The neutrophil to lymphocyte ratio (NLR) is used as a basic parameter of systemic inflammation in some tumors. The aim of this study was to examine the association between the pretreatment NLR, disease-free survival (DFS), and overall survival (OS) in patients with early triple-negative breast cancer (TNBC).*

Methods: *We retrospectively studied patients diagnosed with stage I–III TNBC who had completed all phases of primary treatment from 2002 to 2013. The association between the pretreatment NLR and survival was analyzed. The difference among variables was calculated by chi-square test. OS and DFS were assessed using the Kaplan–Meier method. Multivariate Cox proportional hazards models were used to analyze the prognostic impact of clinical parameters.*

Results: *Eighty-five patients were eligible for study inclusion. There were no statistically significant differences among the pretreatment NLR and clinicopathological variables. Patients with an NLR of > 2 had significantly lower DFS (p=0.002) and OS (p=0.03) than patients with an NLR of ≤ 2. Multivariate Cox proportional hazards models showed that a higher pretreatment NLR was independently correlated with poor DFS and OS, with a hazard ratio 5.46 (95% confidence interval [CI] 1.61–18.85, p=0.006) and 2.86 (95% CI 1.04–7.86, p=0.04), respectively.*

Conclusion: *Patients with early TNBC and with elevated pretreatment NLR showed poorer DFS and OS than patients without elevated NLR. However, this finding needs to be confirmed in a large prospective study.*

Key words: *breast cancer, lymphocyte, neutrophil,ratio, survival, triple negative*

Introduction

TNBC constitutes approximately 15% of all invasive breast carcinomas [1]. It is defined by lack of estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor-2 (HER-2) amplification [1]. TNBCs are also usually larger, have a higher histological grade, show higher node involvement at the time of diagnosis, and are biologically more aggressive than other breast cancer subtypes [2]. TNBC patients are more likely to relapse within the first 3–5 years after diagnosis, and they have an increased risk of developing visceral disease [3,4]. TNBC is the most aggressive and deadly of all breast cancer subtypes because it does not respond to endocrine therapy or anti-HER-2 target agents [5-7]. As TNBC is a heterogeneous disease, many pathological and immunohistochemical subclassifications have been suggested in the past decade to describe more homogeneous subtypes. Recent advances have focused on disease

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stratification with genome-wide approaches, but gene expression analysis is not always available in clinical practice to detect more aggressive TNBCs that have a poor prognosis [8-11]. Therefore, there is an urgent need for useful markers that can predict the metastatic and recurrence potential of TNBC. Such markers should be accurate, reproducible, and easily measured.

The tumor microenvironment, particularly the inflammatory response, plays an important role in cancer development, progression, metastasis, and relapse and may be related to systemic inflammation [12-14].

Various markers in the blood that reflect the systemic inflammatory response are elevated C-reactive protein (CRP), hypoalbuminemia, increased levels of some cytokines, the NLR, and the platelet to lymphocyte ratio [15,16]. Recently, an elevated ratio of peripheral neutrophils-to-lymphocytes has been recognized as a poor prognostic indicator in various cancers, such as colorectal, gastric, pancreatic, non-small-cell lung, hepatocellular, ovarian, cervical, and renal cancers [17-24]. Previous studies have examined the role of the NLR in predicting survival and mortality, even in early breast cancer patients [25-28]. Given the absence of prognostic markers in the TNBC subgroup, the main goal of this study was to examine the association between the pretreatment NLR, DFS, and OS in patients with early TNBC.

Methods

Patients

We retrospectively evaluated patients who were diagnosed with primary TNBC and had completed all phases of their primary treatment for the disease at the Department of Medical Oncology, Erciyes University Faculty of Medicine from January 2002 to December 2013.

Demographics and clinicopathological data, such as the patient age, sex, laboratory findings, and medical history, were obtained from chart reviews of breast cancer patients in a single Oncology Department in Turkey, as well as pathological results, including tumor size, lymph node status, hormonal status, HER-2 status, and patient survival.

Patients with ductal carcinoma *in situ*, with or without microinvasion, and patients with incomplete pathological or laboratory results were excluded. We also excluded patients with stage IV breast cancer or inflammatory breast cancer and patients who were diagnosed preoperatively with systemic inflammatory or chronic diseases, such as diabetes, heart failure, hypertension, cerebrovascular disease, any hematological disorder, liver cirrhosis, end-stage renal disease, pregnancy-related breast cancer, inadequate bone marrow, and organ functions.

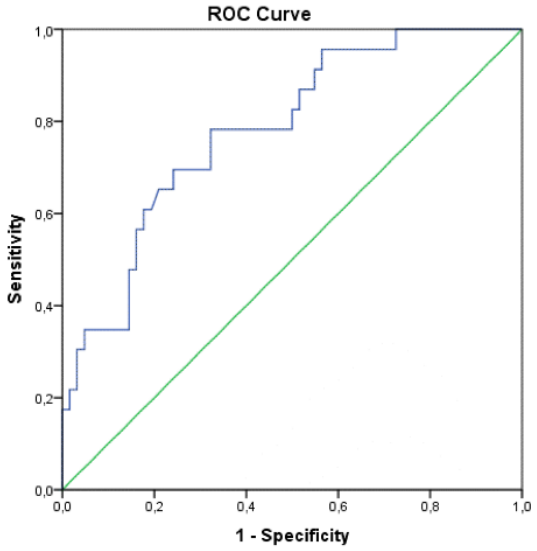

Figure 1. The predictive value of NRL for disease free survival (sensitivity 87% and specificity 51.6%, area under the ROC curve=0.782), p<0.001.

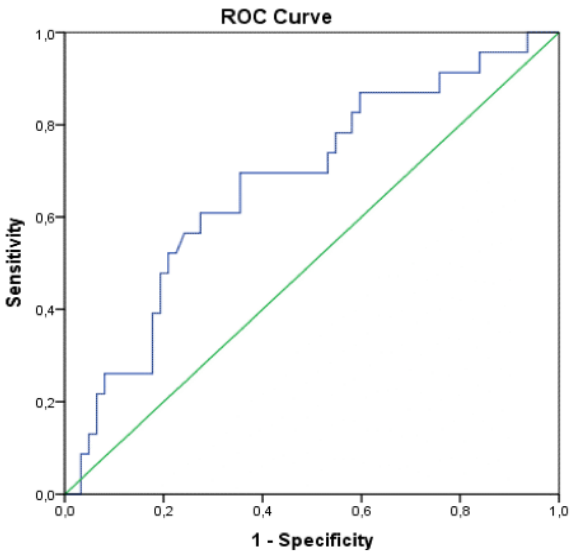

Figure 2. The predictive value of NRL for overall survival (sensitivity 78.3% and specificity 54.8%, area under the ROC curve=0.782), p=0.013.

Pathological characteristics

ERs and PRs were assessed by immunohistochemistry. ERs and PRs were considered positive when at least 1% of invasive tumor nuclei in the sample was positive. HER-2 positivity was defined as 3+ by immu-

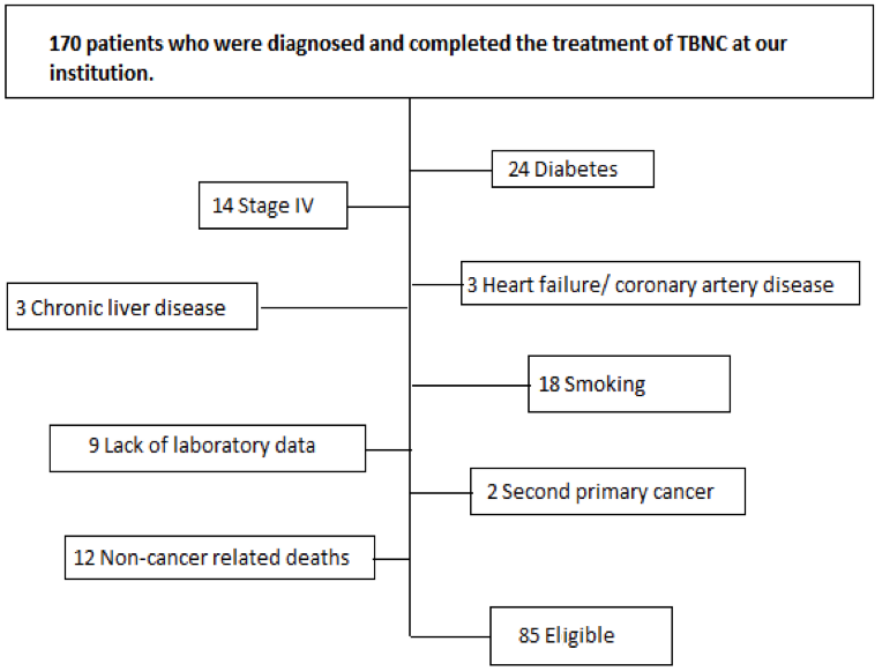

Figure 3. Flow chart of patient eligibility. We detected 170 patients who were diagnosed and completed the treatment of triple-negative breast cancer; 85 patients were eligible for analysis.

nohistochemistry or 2 + by gene amplification using fluorescence *in situ* hybridization of > 2.2-fold. The diagnosis of triple-negative status (ER negative, PR negative, and HER-2 negative) was re-reviewed by a single pathologist at our institution.

Laboratory data

The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The NLR was calculated from a full blood count routinely performed immediately after the breast cancer diagnosis and before the initiation of any treatment modality, including surgery (pretreatment NLR).

A cut-off value of 2 was determined as the maximum (sensitivity+specificity) point according to receiver operating characteristics (ROC) curves (Figures 1 and 2). The patients were further divided into two groups: A (NLR ≤ 2) and B (NLR > 2).

Statistics

For statistical analyses of the study data, SPSS 18.0 software was used (IBM Co, United States). DFS was defined as the interval between the date of the diagnosis of TNBC to the first failure (including locoregional and/or distant relapse, secondary primary, or death). OS was defined as the interval between the histological diagnosis to death or the last follow-up visit. Frequencies were compared in all patients using the chi-square test for categorical variables. All p values were two-sided, with $p<0.05$ considered as statistically significant. DFS and OS curves were calculated according to the Kaplan–Meier method with the log-rank test. Clinicolaboratory variables were investigated using univariate analysis for OS and PFS and the variables with statistical significance were further evaluated with the Cox proportional hazards model of multivariate analysis.

Results

We identified 170 patients who were diagnosed with TNBC and completed their treatment; 85 of these patients were eligible for inclusion in the analysis. Figure 3 summarizes the reasons for the exclusion of the patients. The median value of the NLR was 2.31 (range 1.02–4.25). Of 85 patients, 33 had a NLR of ≤ 2.0, and 52 had a NLR >2.0. There was no significant correlation among the pretreatment NLR and various clinicopathological factors, such as age, menopausal status, tumor size, lymph node status, grade, or Ki-67 (Table 1). The 5-year disease-specific survival rate of the patients with a NLR ≥2 was significantly lower

Table 1. Baseline characteristics of patients with TNBC by NLR

Characteristics	*Total (N = 85)* *N (%)*	*NLR ≤2 (N = 33)* *N (%)*	*NLR > 2 (N = 52)* *N (%)*	*p value*
Age, years				
>50	28 (32.9)	13 (39.4)	15 (28.8)	
≤ 50	57 (67.1)	20 (60.6)	37 (71.2,)	0,35
Menopausal status				
Pre-	59 (69.4)	23 (69.7)	36 (69.2)	
Post-	26 (30.6)	10 (30.3)	16 (30.8)	1,0
Histological subtype				
Ductal carcinoma	70 (82.4)	25 (75.8)	45 (86.5)	
Other	15 (17.6)	8 (24.2)	7 (13.5)	0,24
Histologic grade				
I-II	26 (30.6)	12 (36.4)	14 (26.9)	
III	59 (69.4)	21 (63.6)	38 (73.1)	0,46
Ki-67(%)				
≤20	13 (15.3)	6 (18.2)	7(13.5)	
>20	72 (84.7)	27 (81.8)	45 (86.5)	0,55
Tumor size (pT)				
pT1	17 (20)	7 (21.2)	10 (19.2)	
pT2	50 (58.8)	20 (60.6)	30 (57.7)	
pT3	16 (18.8)	4 (12.1)	12 (23.1)	0,21
pT4	2 (2.4)	2 (6.1)	0 (0)	
Lymph node status (pN)				
pN0	20 (23.5)	7 (21.2)	13 (25)	
pN1	41 (48.2)	18 (54.5)	23 (44.2)	
pN2	19 (22.4)	4 (12.1)	15 (28.8)	0,76
pN3	5 (5.9)	4 (12.1)	1 (1.9)	
Type of surgery				
Lumpectomy	32 (37.6)	13 (39.4)	19 (35.6)	0,82
Radical mastectomy	53 (62.4)	20 (60.6)	33 (63.5)	
Adjuvant chemotherapy				
Anthra + Tax-based	75 (88.2)	30 (90.9)	45 (86.5)	
CMF	4 (4.7)	2 (6.1)	2 (3.8)	
No	6 (7.1)	1 (3)	5 (9.6)	0,43
Adjuvant radiotherapy				
Yes	68 (80)	24 (72.7)	44 (84.6)	
No	17 (20)	9 (27.3)	8 (15.4)	0,26

Anthra: anthracyclines, Tax: taxanes, CMF: cyclophosphamide/methotrexate/5-fluorouracil, TNBC: triple negative breast cancer, NLR: neutrophil/lymphocyte ratio

than in those with a NLR <2 (5-year survival, 89 vs 59%; p=0.007) (Figure 4). The patients with a NLR of ≥ 2 showed increased breast cancer-specific mortality (5-year OS, 87 vs 68%; p=0.021; Figure 5). The Cox proportional multivariate hazard model revealed that a higher pretreatment NLR was independently correlated with poor DFS and OS, with a hazard ratio of 5.15 (95% CI 1.11–23.88, p=0.03) and 6.16 (95% CI 1.54-24.66, p=0.01), respectively (Tables 2, 3).

Discussion

The mechanisms underlying the relationship between an elevated NLR and poor outcomes in cancer patients remain unclear. One probable mechanism underlying the prognostic role of NLR is its relationship with inflammation. Neutrophilia is an inflammatory response, which restricts the immune system by suppressing the cytolytic activity of immune cells, such as activated T cells, lymphocytes, and natural killer cells [29,30]. Recent studies have emphasized the importance of lymphocytes, reporting that increased infiltration of tumors with lymphocytes was related to a better response to cytotoxic chemotherapy and a better prognosis in several tumor types [31-33]. Various cytokines and chemokines can be produced by both the tumor and associated host cells, including leukocytes, and contribute to malignant progression [34]. An elevated NLR was reported to be associated with an increase in the peritumoral infiltration of macrophages, resulting in the induction of interleukin-6 (IL-6) production [35].

Neutrophils and other cells, such as macrophages, may also secrete tumor growth-pro-

Table 2. Cox regression analysis for disease-free survival in TNBC

Variables	*Univariate*	*Multivariate*	
	p value	*HR (95% CI)*	*p value*
Age (≤50 years vs >50 years)	0.74	0.80 (0.23-2.78)	0.73
Menopausal status (Pre- vs Post-)	0.08	0.42 (0.12-1.44)	0.17
Nuclear grade (G1-G2 vs G3)	0.53	0.84 (0.29-2.41)	0.75
Ki-67 (≤20% vs >20%)	0.79	1.17 (0.32-4.26)	0.81
Tumor size (pT1 vs pT2-T3)	0.08	2.78 (0.57-13.4)	0.20
Lymph node status (pN0 vs pN+)	0.43	1.39 (0.44-4.40)	0.57
NLR (≤2 vs >2)	0.02	5.46 (1.61-18.5)	0.006

For abbreviations see footnote of Table 1

Table 3. Cox regression analysis for overall survival in TNBC

Variables	*Univariate*	*Multivariate*	
	p value	*HR (95% CI)*	*p value*
Age (≤50 years vs >50 years)	0.41	1.40 (0.38-5.15)	0.60
Menopausal status (Pre- vs Post-)	0.15	0.81 (0.23-2.84)	0.75
Nuclear grade (G1-G2 vs G3)	0.64	0.90 (0.27-2.95)	0.86
Ki-67 (≤20% vs >20%)	0.90	1.32 (0.34-5.02)	0.67
Tumor size (pT1 vs pT2-T3)	0.02	6.94 (0.82-58.2)	0.07
Lymph node status (pN0 vs pN+)	0.47	0.97 (0.29-3.19)	0.96
NLR (≤2 vs >2)	0.03	2.86 (1.04-7.86)	0.04

For abbreviations see footnote of Table 1

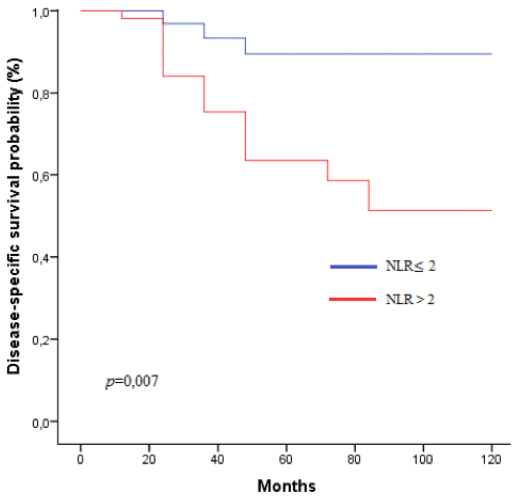

Figure 4. Disease specific survival of patients with early triple-negative breast cancer based on neutrophil/lymphocyte ratio (p=0.007).

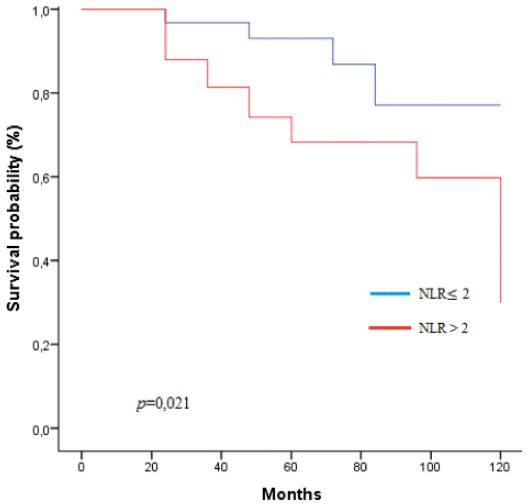

Figure 5. Overall survival of patients with early triple-negative breast cancer based on neutrophil/lymphocyte ratio (p=0.021).

moting factors, including vascular endothelial growth factor, hepatocyte growth factor, IL-6, IL-8, matrix metalloproteinases and elastases, which promote tumor cellular proliferation, angiogenesis, invasion, and metastasis [36-41]. In addition, neutrophil-derived reactive oxygen species further decrease the adhesion-promoting properties of the extracellular matrix and, via activation of nuclear factor-κB, inhibit the apoptosis of tumor cells [42,43]. Consistent with these results, studies have shown that the inhibition of neutrophil infiltration was associated with reduced tumor progression [44,45].

Several studies that examined the relation between systemic inflammation and breast cancer survival found a significant relationship between shorter survival and elevated concentrations of circulating inflammatory biomarkers, such as serum amyloid A, systemic CRP, and serum IL-6 [46,47]. Other studies demonstrated that neutrophilia predicted poor outcomes in some tumors [27,48,49]. Conversely, cytotoxic T lymphocytes were shown to stimulate apoptosis of cancer cells and suppress tumor growth, and CD8+ T lymphocyte infiltration was shown to be associated with better overall patient outcomes [50]. Different physiological, physical, and pathological factors were reported to strongly affect the lymphocyte count and neutrophil absolute count, representing the denominator and numerator, respectively [26]. The superiority of the NLR as a prognostic marker is due to the stability of the ratio compared with absolute cellular counts [26].

A few studies have evaluated the role of the NLR in predicting survival and mortality in early breast cancer patients [25-28]. A retrospective study reported that the 5-year and 10-year disease-specific survival rate of patients with a NLR ≥ 2.5 was significantly lower that that of patients with a NLR of < 2.5. In addition, patients with a higher NLR (i.e., ≥ 2.5) had an increased T stage, younger age, positive HER-2 status, and higher disease-specific mortality [26]. In another retrospective study, Azab et al. [27] divided patients into four quartiles. They reported that those in the highest NLR quartile (NLR > 3.3) had higher 1- and 5-year mortality rates compared with those in the lowest quartile (NLR < 1.8). Those in the highest NLR quartile were also statistically significantly older and had more advanced stages of cancer. In another retrospective study, Azab et al. [28] showed that the NLR continued to be a statistically significant predictor of 5-year mortality in all lymphocyte count subsets, even better than the platelet to lymphocyte ratio, in breast cancer patients.

Pistelli et al. [51] evaluated the association between the pretreatment NLR, DFS, and OS in 90 patients with early TNBC. They showed that patients with a NLR higher than 3 had significantly lower DFS and OS than those with a NLR ≤3. In addition, their Cox proportional multivariate hazard model revealed that a higher pretreatment NLR was independently correlated with poor DFS and OS. The present study detected that an increased pretreatment NLR may be associated with poor DFS and OS in patients with early TNBC, which is consistent with the results of Pistelli's study. Future studies are warranted to confirm these results in TNBC and to explore the optimal cutoff point for NLR, as well as the mechanism underlying these phenomena. Such information would support the development of more effective disease management and the clinical use of the NLR.

One limitation of the present study is that the sample was relatively small and came from a single oncology center in Turkey, which limits the generalization of the results. Despite the exclusion of most factors affecting the measurement of NRL, such as metabolic syndrome, another potential limitation of the present study is that hypercholesterolemia, the use of certain drugs, and alcohol consumption, were not ruled out, and abnormal thyroid function tests were not conducted [52].

In conclusion, patients with increased pretreatment NLR showed poorer DFS and OS than patients with early TNBC without increased NLR. We conclude that the neutrophil/lymphocyte ratio might serve as a useful biomarker for TNBC patients. However, further large prospective studies should be carried out to confirm whether NLR has predictive value in patients with TNBC.

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