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Can neutrophil lymphocyte ratio be a marker in stage 1 testicular tumor occult metastasis parameters?

Nötrofil lenfosit oranı evre 1 testis tümöründe okkült metastaz parametrelerinde belirteç olabilir mi?

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Abstract

Purpose: Neutrophile-Lymphocyte (NLR) and Platelet-Lymphocyte ratio (PLR) comparison is an easy to use and cost-effective method in diagnosis of some cancers and diseases. In this study, we aimed to investigate if NLR/PLR ratio evaluation could be utilized in diagnosis of testicular malignencies especially in early-term with occult metastasis.

Materials and methods: A total of 40 patients at stage-I, who have undergone radical inguinal orchiectomy intervention for testicular tumor between 2015 and 2019, and 43 control individuals without any testicular complaints were included in this retrospective study. The relationship between pathological risk factors for occult metastatic disease in Stage-I testicular cancer and NLR/PLR values were investigated.

Results: The average age was 30.05 years, and there was no significant difference between the groups by means of age (p=0.150). The NLR and PLR values of the tumor group were prominently higher in the patient group, when compared with the control group (p=0.001 and p=0.016, respectively). In the correlation analysis between risk-factors for occult metastatic disease in Stage-I testicular cancer and NLR/PLR, we have found that only a significant correlation was present in terms of tumor size.

Conclusion: As a result, we have concluded that NLR increases in all types of testicular tumors. We suggest that higher NLR ratio values can be used as prognostic marker in clinical practice.

Key words: Testicular tumor, occult metastasis, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio.

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Öz

Amaç: Nötrofil-Lenfosit ve Trombosit-Lenfosit oranı (NLR/PLR) karşılaştırması, bazı kanserlerin ve hastalıkların tanısında kullanımı kolay ve düşük maliyetli bir yöntemdir. Bu çalışmada, özellikle okkült metastazlı erken dönem testis malignitelerinin tanısında NLR/PLR oranı değerlendirmesinin kullanılıp kullanılamayacağını araştırmayı amaçladık.

Gereç ve yöntem: 2015-2019 yılları arasında testis tümörü için radikal inguinal orşiektomi müdahalesi yapılan hastalar retrospektif olarak incelendi. Çalışmaya testis tümör evre-I olan 40 hasta ve herhangi bir testis şikayeti olmayan 43 hasta kontrol grubu olarak çalışmaya dahil edildi. Evre-I testis kanserinde okkült metastatik hastalık için patolojik risk faktörleri ile NLR/PLR değerleri arasındaki ilişki araştırıldı.

Bulgular: Hastaların yaş ortalaması 30,05 yıl idi ve gruplar arasında yaş bakımından anlamlı fark yoktu (p=0,150). Tümör grubunun NLR ve PLR oranı değerleri testis tümörlü hastalarda kontrol grubuna göre belirgin olarak yüksekti (sırasıyla p=0,001 ve p=0,016). Evre-I testis kanseri ve NLR/PLR'de okkült metastatik hastalık için risk faktörleri arasındaki korelasyon analizinde sadece tümör boyutu açısından anlamlı bir korelasyon olduğunu bulduk.

Sonuç: Sonuç olarak, tüm testis tümörlerinde NLR'nin arttığı sonucuna vardık. Klinik uygulamada prognostik belirteç olarak daha yüksek NLR oranı değerlerinin kullanılabileceğini önermekteyiz.

Anahtar kelimeler: Testis tümörü, okkült metastaz, nötrofil-lenfosit oranı, trombosit-lenfosit oranı.

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Introduction

Testicular cancer (TC) is one of the most uncommon cancers in men aged between 15 and 44 years [1, 2]. Although the incidence of TC continue to gradually increase in developed countries, it still constitutes only 1-1.5% of the whole male cancers [3, 4]. The fact that TC is mainly encountered in younger age groups, responds well to chemotherapy, and that its 10-year survival is over 95% have increased the importance of early diagnosis and treatment of testicular cancers. The medical history, physical examination, imaging methods and laboratory tests (especially tumor markers) are used for diagnosis. Alpha-fetoprotein (AFP), human chorionic gonadotropin beta (Beta-HCG), and lactate dehydrogenase (LDH) are used as serum tumor biomarkers. These biomarkers are also used in prognostic grouping and staging, however they may not be significantly at high levels in all pathological subtypes of testicular tumors. It is also known that tumor tissues trigger an inflammatory process in the body, and thus inflammation plays a critical role in different aspects of cancer such as tumor development, progression and prognosis [5]. For this reason, inflammation has an important role in all stages of carcinogenesis [6]. Immune cells secrete cytokines that play role in tumor growth, invasion, and metastasis development [7, 8]. These cytokines also lead to changes in acute phase reactants such as blood neutrophil and lymphocyte counts [6]. Tumor-associated host inflammatory immune responses appear as hematological markers, and neutrophil/lymphocyte ratio (NLR) is the most commonly used ratio. Besides, platelet/lymphocyte ratio (PLR) is also used to predict cancer prognosis and inflammatory conditions [9]. In this study, we aimed to compare the values of NLR and PLR, which is an easy-to-apply and cost effective approach, between healthy individuals of similar age group and the patients diagnosed with testicular tumors, and to investigate the benefits they can provide in clinical practice, such as occult metastasis parameters.

Materials and methods

A total of 40 patients, who meet the inclusion criteria for Stage-I and have undergone a radical inguinal orchiectomy intervention for testicular tumor between 2015 and 2019 years, and 43 control individuals without any testicular complaints were included in this retrospective study. The relationship between NLR and PLR values in both groups and the relationship between pathological risk factors for latent metastatic disease in Stage-I testicular cancer, as well as established NLR and PLR ratio data were investigated. Informed consent was obtained for all participants of the study. The study was approved by the local Hitit University Clinical Studies Ethics Committee, and conducted in accordance with the ethical principles of the Helsinki Declaration.

Patients with testicular stromal tumors, acute infections, hematological diseases, malignancy other than testicular tumors, chronic inflammatory disease, end-stage chronic renal failure, corticosteroid use, beta blocker and / or immunomodulator drug use, patients who received hormonal therapy and blood products during the past one month, and the patients whose pre-operative tumor markers, complete blood count and pathology results could not be obtained were excluded from the study.

Complete blood cell count was measured one day prior to the surgery, and NLR was defined as dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was defined as dividing the absolute platelet count by the absolute lymphocyte count.

Although surgical practices were performed by different physicians in the same department, similar follow-up programs and adjuvant treatment protocols were applied to the patients. After inguinal orchiectomy, all patients were included in a follow-up program for physical examination and tumor marker analysis four times a year in an uro-oncology polyclinic. Furthermore, chest radiographs and abdomino-pelvic tomography were performed twice a year. The need for chemotherapy was applied in line with the oncology opinions and EAU guidelines recommendations.

Statistical analysis

IBM SPSS Statistics 22 for statistical analysis software (SPSS IBM, Chicago, USA) was used to evaluate the established data. Conformity of the parameters to the normal distribution was evaluated using Shapiro-Wilk test. Descriptive statistical values were computed (mean, standard deviation, frequency), and the comparison of quantitative data were achieved

using Kruskal-Wallis test. Mann-Whitney U test was used for the two-group comparisons of the parameters that did not show normal distribution, and Student's t test was used for the parameters with normal distribution. The cut-off point was chosen based on the ROC curve analysis. *P* values less than 0.05 were considered as statistically significant.

Results

The study was conducted with a total of 83 patients aged between 15-53 years. The average age was 30.05±7.93 years. The patients were divided into two groups as testicular tumor (n=40) and controls (n=43). When the pathologies of patients with testicular tumor were examined, Seminoma in 24 patients and Non-seminoma testicular tumors were detected in 18 patients. When age, NLR and PLR were compared between the groups, we have found that groups were similar to each other only in terms of age (p=0.150). The NLR and PLR values of the tumor group were significantly higher, when compared to the control group (p=0.001 and 0.016, respectively) (Table 1).

In our study, metastasis was detected in 10 patients during follow-up. We have performed correlation test to reveal whether there is a correlation between the prognostic risk factors identified for occult metastatic disease in testicular tumors and NLR/PLR values, and observed that only tumor size was correlated with NLR/PLR (r=0.556, p<0.001 and r=0.514, p=0.001, respectively) (Table 2).

The ROC curve was drawn for the Neutrophil/Lymphocyte ratio (NLR) in TC diagnosis. The area under the curve for NLR was 0.687 and the standard deviation was 0.06. The area under the curve was significantly higher compared to the value 0.05, which means diagnostic worthlessness (p=0.003). In TC diagnosis, the cut-off value of NLR was 2.27. It was determined that while the sensitivity of this value was 55%, the specificity was 88.5%, the positive predictive value was 81.5% and the negative predictive value was 67.9% (Figure 1).

Table 1. Comparison of age, NLR and PLR values between groups

	Testicular tumor (n=40) Mean±SD	Control (n=43) Mean±SD	*p*
Age (years)	34.33±6.84	31.79±8.84	0.150
NLR	3.45±3.19	1.73±0.51	**0.001**
PLR	157.02±120.16	109.48±39.12	**0.016**

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio

Table 2. Relationship between defined parameters for occult metastasis and NLR and PLR in testicular tumors

Occult Metastasis Parameters	NLR		PLR	
	Correlation (Rho)	p value	Correlation (Rho)	*p* value
Invasion of the rete testis	-0.052	0.750	0.073	0.653
Tumour size	0.556	**<0.001**	0.514	**0.001**
Lympho-vascular invasion in peri-tumoral tissue	-0.254	0.113	-0.298	0.061
Proliferation rate >70%	0.114	0.376	0.276	0.084
Embryonal carcinoma percentage >50%	-0.232	0.149	0.073	0.656

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio

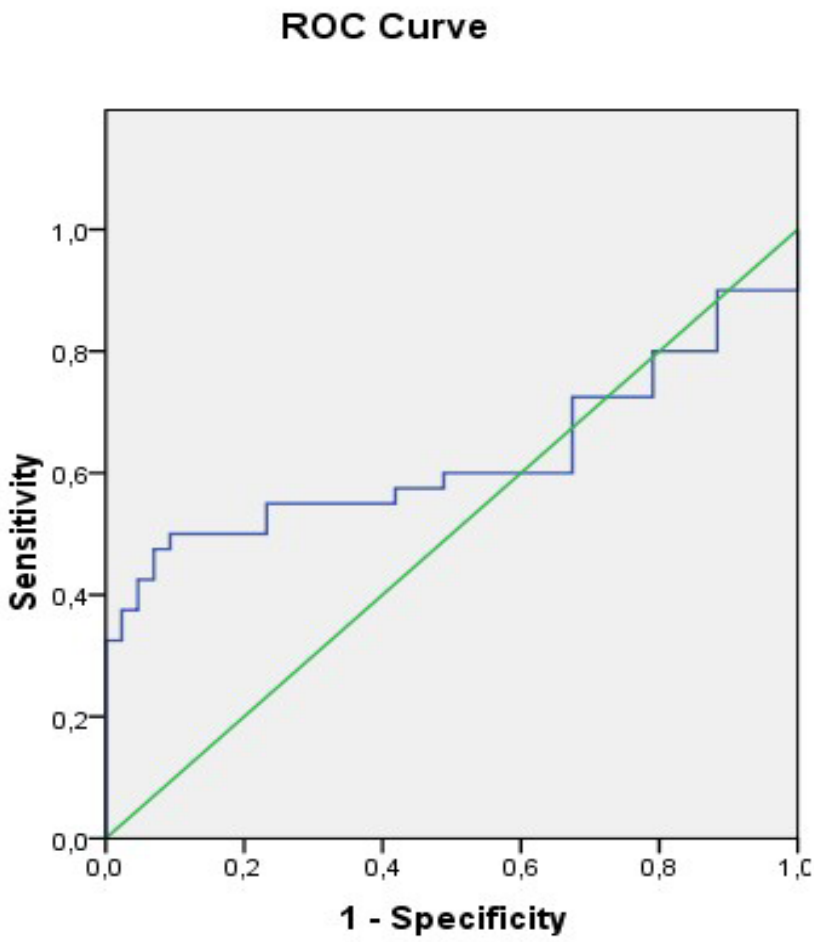

Figure 1. ROC of NLR count in testicular cancer

Discussion

In our study, we found that NLR and PLR values were significantly higher in patients with testicular tumors compared to the control group. There are pathophysiological mechanisms to explain this situation. It is postulated that carcinogenesis develops from chronic inflammation sites, and that inflammation plays an important role in every known tumoral stage [6, 10]. Total leukocyte, lymphocyte and neutrophil parameters are among important biochemical and hematological measurement items, which have been used as inflammation indicators for years. Neutrophilia may either arise from the ectopic production of myeloid growth factors as a part of paraneoplastic syndrome, or caused by a non-specific response to cancer-related tissue destruction and cytokine-mediated inflammation [11]. Increment in circulatory neutrophil number can play an important role in tumor progression and angiogenesis [12]. Thus, neutrophilia has been implied in relatively poor prognosis [8, 13]. Besides, lymphopenia is associated with cortisol-induced stress response [14]. As an increased neutrophil response to lymphopenia, high neutrophil/lymphocyte ratio (NLR) was reported to support cancer development by inhibiting antitumoral immune response [15].

In some previous studies, it has been reported that the NLR values were higher in patients with testicular tumors compared to the control group [3, 13, 16]. Neutrophil/lymphocyte ratios were found to be 3.1±1.4 by Gokcen et al. [16], 4.22±3.54 by Sahin et al. [3], and 3.18±1.76 by Yuksel et al. [13]. In our study, we found that NLR ratio was higher in patients with testicular tumors compared to the control group of similar age group, and this was in accordance with the literature. The NLR ratio was significantly higher in testicular tumor group in our study. Gokcen

et al. [16] and Sahin et al. [3] have reported that the mean PLR value was higher in testicular tumor group, when compared with the controls. Likewise, we have also found that the PLR value was prominently higher in the patient group.

It is well-known that the increase in neutrophil number plays an important role in tumor progression and angiogenesis [12]. In our study, when we examined the correlation between prognostic risk factors identified for occult metastatic disease in testicular tumors and NLR/PLR, we have found that there was a statistically significant correlation between the testicular tumor size and NLR/PLR. Thus, immune response and the neutrophil/lymphocyte ratio is expected to increase in parallel to increased tumor size, which was in accordance with the previously reported finding that the mean NLR value was directly proportional to the thyroid cancer tumor size [17]. When we look at the literature, we have observed that there is no study which mainly focus on the relationship between the testicular size and NLR. However, in a study by Bolat et al. [18] including 53 patients with testicular tumors, the neutrophil cut-off value was taken as 3.55, and they have investigated the correlation between tumor size, lymph node metastasis and invasion to rete testis. In that study, no statistically significant difference was found between NLR and tumor size in the groups with a value below and above 3.55. In our study, a positive correlation was found between NLR/PLR values and tumor size. In this case, an occult metastasis may be considered if there is no palpable mass in the physical examination of the patients with high NLR and PLR values and/or testicular tumor sizes are found to be small.

In some studies in which the NLR threshold value was investigated, it was found to be 2.25 by Gokcen et al. [16], 3.16 by Sahin et al. [3] and 2.11 by Ilktac et al. [19]. In our study, we have specified the NLR cut-off value as 2.27, which is in accordance with the literature.

Our study has some limitations. Given the fact that our study had a retrospective structure, limited study group might have affected the prognostic predictive values. Further randomized controlled trials or meta-analyses with bigger number of cases are required in this field.

As a result; NLR values can increase in testicular tumors, just as in all other cancer types. However, the current available data are not yet sufficient to clearly indicate its feasibility, cost-effectiveness, and re-applicability as a biomarker. We think that high NLR and also PLR values can be used as biomarkers which could predict cancer course and prognosis. There is a need for large-scale, prospective randomized and multicenter studies with longer follow-up periods.

Conflict of interest: No conflict of interest was declared by the authors.

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Contributions of the authors to the article

A.B. set up the main idea and hypothesis of the study. A.B, B.A. they developed the theory and edited the material method section. The evaluation of the data in the results section A.B, B.A. they did. The discussion section of the article was written by A.B. plague. written by A.B. and B.A reviewed and made necessary corrections and approved. In addition, all authors discussed the entire study and approved its final version.