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Original Article

Predictive value of preoperative neutrophil–to–lymphocyte ratio on the prognosis of germ cell testicular tumors

Preoperatif nötrofil–lenfosit oranının germ hücreli testis tümörlerinin prognozunu öngörü değeri

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ABSTRACT

Objective: We investigated the prognostic value of preoperative neutrophil-to-lymphocyte ratio (NLR) on germ cell testicular tumors (GCT).

Material and methods: The data of 53 patients who underwent inguinal orchiectomy were analyzed retrospectively. NLR was calculated from the preoperative complete blood cell counts. Receiver operating characteristic (ROC) analysis was performed to find the threshold values for NLR. Correlations between cancer-specific survival (CSS) and progression-free survival (PFS) and NLR were evaluated.

Results: The mean follow-up time was 23.55±18.06 months. The mean level of NLR was 3.08±1.81. Optimal threshold values of NLR was calculated as 3.55 for PFS (area under curve, AUC: 0.55) and 3.0 for CSS (AUC: 0.66). For patients with a NLR of <3.55 and NLR of ≥3.55, mean times-to-progression were 55.71 months (95% CI, 51.27-60.14) and 51.95 months (95% CI, 38.02-65.87, p=0.152), respectively. As well as, for patients with a NLR of <3.0 and NLR of ≥3.0, mean times -to-cancer specific death were 54.72 months (95% CI, 49.05-60.38) and 49.43 months (95% CI, 37.64-61.22, p=0.119), respectively.

Conclusion: Preoperative NLR is not a useful tool to predict the prognosis of patients with GCT.

Keywords: Inflammation; neutrophil-lymphocyte ratio; prognosis; survival; testicular cancer.

ÖZ

Amaç: Preoperatif nötrofil-lenfosit oranının (NLO) germ hücreli testis tümörleri (GHT) üzerindeki prognostik değerini araştırdık.

Gereç ve yöntemler: İngüinal orşiyektomi yapılan 53 hastanın verileri geriye dönük olarak analiz edildi. Preoperatif tam kan sayımından NLO hesaplandı. NLO için eşik değerler Alıcı işletim karakteristiği (Receiver Operating Characteristic - ROC) analizi ile hesaplandı. Kansere özgü sağkalım ve progresyonsuz sağkalım ile NLO arasındaki korelasyon değerlendirildi.

Bulgular: Ortalama takip süresi 23,55±18,06 ay idi. Ortalama NLO 3,08±1,81 idi. NLO optimal eşik değeri progresyonsuz sağkalım için 3,55 (eğri altındaki alan 0,55), kansersiz sağkalım için 3,0 (eğri altındaki alan 0,66) olarak hesaplandı. NLO <3,55 ve ≥3,55 olan hastalar için progresyona kadar geçen ortalama süre sırasıyla, 55,71 ay (%95 CI, 51,27-60,14) ve 51,95 ay (%95 CI, 38,02-65,87, p=0,152) idi. Bununla birlikte, NLO değeri <3,00 ve ≥3,0 olan hastalar için kansere özgü ölüme kadar geçen ortalama süre sırasıyla, 54,72 ay (%95 CI, 49,05-60,38) ve 49,43 ay (%95 CI, 37,64-61,22, p=0,119) idi.

Sonuç: Preoperatif NLO, GHT'li hastaların prognozunu öngörmede kullanılabilir bir yöntem değildir.

Anahtar Kelimeler: İnflamasyon; nötrofil-lenfosit oranı; prognoz; sağkalım; testis kanseri.

Introduction

Testicular cancer (TC) is a relatively rare malignancy with more than 52,000 new cases and almost 10 000 deaths estimated worldwide for the year 2008. Testicular cancer makes up approximately 1% of all male cancer cases globally. However, TC is the most common cancer form in men aged 15-44 years in many countries, and has attained high or very high scores on the Human Development Index.[1] The histological type varies, although there is a clear predominance (90-95%) of germ cell testicular

tumors (GCT) which can be subdivided into seminomatous and non-seminomatous GCT.[2]

Well-established risk factors for the development of TC include history of cryptorchidism, familial history of TC, presence of contralateral TC or testicular intraepitelial neoplasia, Klinefelter's syndrome and infertility.[2,3] Some of the other risk factors with low incidence rates are scrotal trauma, inguinal hernia, atopy, history of infectious diseases, mumps orchitis, testicular torsion, increased scrotal temperature, varicocele, and human immunodeficiency virus infection.[3]

It has been demonstrated that inflammation plays a critical role in many aspects of cancer, including tumor development, progression, clinical presentation, and prognosis.[4] Several markers of systemic inflammatuar response, such as C-reactive protein, neutrophil or platelet counts, as well as the neutrophil-to-lypmhocyte ratio (NLR), have been shown to be independent prognostic factors in various human cancers.[5] As hematological tests are routinely conducted in cancer patients, the NLR represents a simple, robust and convenient parameter of the inflammatory response.[6] In a meta-analysis it has been reported that elevated NLR is a poor predictor for survival in patients with urinary system cancers.[7]

To the best of our knowledge no prior study has evaluated the association between systemic inflammation markers and prognosis of TC. In this study we aimed to investigate the potential prognostic impact of NLR in patients with GCT.

Material and methods

Data of 53 patients who underwent inguinal orchiectomy between 2008 and 2014 were analyzed retrospectively. Informed consent was obtained from all study participants. The study has been conducted in accordance with the ethical principles of Declaration of Helsinki.

Clinicopathological data including age, preoperative alpha-fetoprotein (AFP), human chorionic gonadotrophin (HCG), lactate dehydrogenase (LDH) levels, and complete blood cell counts (CBC), tumor side, size and histopathology, tumor stage according to 2009 TNM classification for TC of the International Union Against Cancer.[8] Prognostic factors for occult metastatic disease (tumor size and invasion of rete testis for seminomas; vascular/lymphatic invasion of the primary tumor, proliferation rate and percentage of embryonal carcinoma for nonseminomatous cancer), adjuvant therapy and follow-up status were recorded.

Patients with testicular stromal tumors, infectious or inflammatory signs and conditions, hematological diseases or other malignancies, cardiovascular diseases, end-stage renal disease,

cerebrovascular disease, diabetes mellitus, smokers, corticosteroid or β-agonist users, and patients with missing data including preoperative CBC, tumor markers and pathology reports were excluded from the study.

Complete blood cell count was measured the day day prior to the surgery and the NLR was defined as absolute neutrophil count divided by the absolute lymphocyte count.

Different physicians in the same department performed similar follow-up schedule and adjuvant therapy protocols. After inguinal orchiectomy, all patients were included in a follow-up programme for physical examination and tumor marker analysis 4 times a year at an urooncology outpatient clinic. Also, chest X-ray and abdominopelvic tomography were performed twice a year. Cancer-specific survival (CSS) was defined as the time (in months) interval between the dates of surgery and cancer- related death. Progression-free survival (PFS) was defined as the time (in months) elapsed from the date of surgery to the recurrence of biochemically or radiologically confirmed distant metastases.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at a p value of <0.05. Receiver operating characteristic (ROC) curve analysis was performed to find the cut-off levels for NLR as a predictor of CSS and PFS, respectively. Youden's index method was used to find the optimal cut-off value for NLR. Patients who were alive and progression-free were censored at the last follow-up date. Patients were grouped according to the cut-off levels of NLR. *Chi*-square, Fisher's exact and two sample t-tests were used for intergroup comparisons. Kaplan-Meier method was used to evaluate the correlation between NLR and the time-to-event for CSS and PFS, respectively. Log-rank test was used to assess the statistically significant intergroup difference in NLR with respect to CSS and PFS.

Results

Demographic characteristics of patients were summarized in Table 1. Mean age of study population (n=53) was 38.85±15.70 years (range 16-81years). Of the Twenty-seven (50.9%) patients had seminomas and 14 (26.4%) mixed GCTs. Positive nodes were detected in 24 patients (45.3%) and lung metastasis was detected in 6 patients (11.3%). Mean follow-up time was 23.55±18.06 months (range 2-66 months). During the follow-up period, 5 patients (9.4%) showed disease progression and 7 (13.2%) died because of TC. No patient died because of other reasons except TC.

As shown in Figure 1, optimal cut-off value of NLR was 3.55 for PFS (AUC; 0.55) and 3.0 for CSS (AUC; 0.66). The pa-

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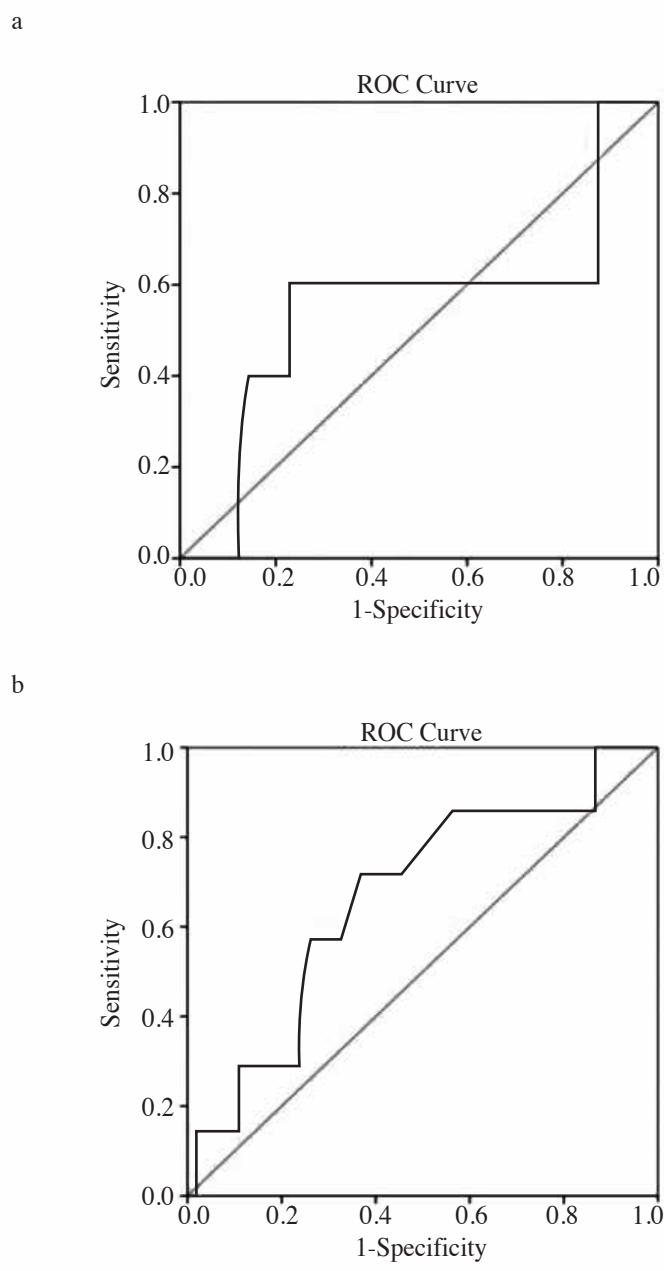| Table 1. Demographic characteristics of the patients	
	Mean±SD (range)
Age, years	38.85±15.70 (16-81)
Tumor size, cm	4.48±2.22 (1-10)
Preoperative lymphocyte count, 10^3/uL	2.02±0.78 (0.60-5.30)
Preoperative neutrophil count, 10^3/uL	5.67±3.35 (2.3-25)
Neutrophil-to-lymphocyte ratio	3.08±1.81 (3-48)
Follow-up time, months	23.55±18.06 (2-66)
Total number of the patients, n (%)	53 (100)
Seminoma	27 (50.9)
Mixed germ cell tumor	14 (26.4)
Embryonal carcinoma	4 (7.5)
Teratoma	3 (5.7)
Spermatocytic seminoma	2 (3.8)
Yolk sac tumor	2 (3.8)
Choriocarcinoma	1 (1.9)
Tumor stage	n (%)
1	28 (52.8)
2A	11 (20.8)
2B	5 (9.4)
2C	6 (11.3)
3	0
4	3 (5.7)
Rete testis invasion	2 (3.8)
Lymphovascular invasion	3 (5.7)
Preoperative pathological lymph node metastasis	24 (45.3)
Preoperative lung metastasis	6 (11.3)
Preoperative non-pulmonary solid organ metastasis	-

Figure 1. a, b. Receiver operating characteristic curves used to find the optimal cut-off value of neutrophil-to-lymphocyte ratio for progression- free survival (a) and cancer-specific survival (b)

tients were divided into two groups according to their NLR of <or≥3.55, a NLR of 3.55 was chosen as the threshold as it had the best sensitivity and specificity values for PFS in this study. There were no statistically significant differences between the groups in terms of any clinical or pathological variables except the lymph node metastasis at the time of diagnosis (Table 2).

Neutrophil-to-lypmhocyte ratio was inversely related with lymph node involvement at the time of diagnosis (p=0.045).

As shown in Figure 2A, patients with a NLR of <3.55 revealed a mean time-to-progression (TTP) of 55.71 months (95% CI, 51.27-60.14) and patients with a NLR of ≥ 3.55 revealed a mean TTP of 51.95 months (95% CI, 38.02-65.87) (p=0.152).

Further the patients were divided into two groups according to a NLR of <or≥3.0, and a NLR of 3.0 was chosen as the threshold value as it had the best sensitivity and specificity values

Table 2. Comparison of clinical parameters between the patients with a NLR of <3.55 and ≥3.55 (PFS cut-off)

	NLR <3.55 (n=39)	NLR ≥3.55 (n=14)	p
Age, years, Mean±SD	38.05±16.05	41.07±15.08	0.542
Tumor size, cm, Mean±SD	4.27±2.17	5.04±2.36	0.275
Follow-up time, months, Mean±SD	21.97±17.98	27.93±18.21	0.294
Rete testis invasion, n (%)	1 (2.6)	1 (7.1)	0.462
Lymphovascular invasion, n (%)	3 (7.7)	-	
Stage, n (%)			0.10
1	20 (51.3)	8 (44.4)	
2A	10 (25.6)	1 (7.1)	
2B	5 (12.8)	0	
2C	3 (7.7)	3 (21.4)	
3	0	0	
4	1 (2.6)	2 (14.3)	
Lymph node metastasis at the time of diagnosis, n (%)	18 (46.2)	6 (42.9)	0.045
Lung metastasis at the time of diagnosis, n (%)	4 (10.3)	2 (14.3)	0.649
Progression, n (%)	3 (7.7)	2 (21.4)	0.599
Time to progression, months, Mean±SD	26.0±22.52	9.0±1.73	0.386
Cancer- specific death, n (%)	4 (10.3)	3 (21.4)	0.364

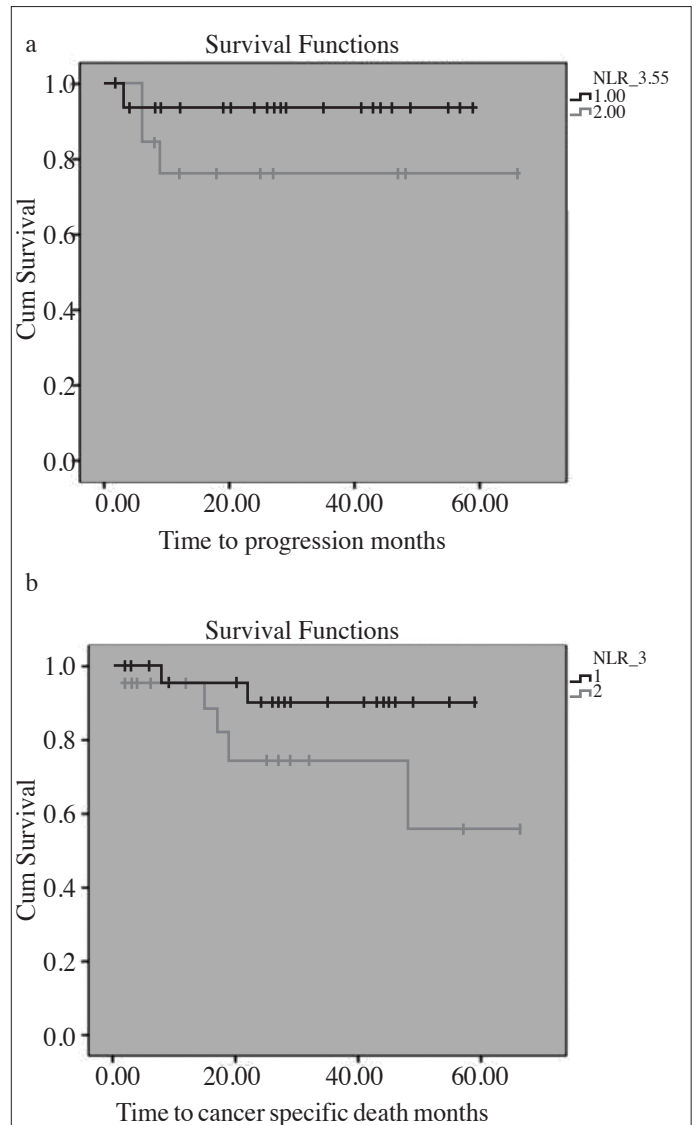PFS: progression- free survival; NLR: neutrophil-to-lymphocyte ratio; SD: standard deviation

Figure 2. a, b. Kaplan-Meier curves used to evaluate the correlation between neutrophil-to-lymphocyte ratio and the time-to-event for progression- free survival (a) and cancer-specific survival (b)

for CSS. There were no statistically significant differences between the groups in terms of any clinical or pathological variables (Table 3).

As shown in Figure 2B, patients with a NLR of <3.0 revealed a mean time-to-cancer specific death (TTD) of 54.72 months (95% CI, 49.05-60.38) and patients with a NLR of ≥3.0 revealed a mean TTD of 49.43 months (95% CI, 37.64-61.22) (p=0.119).

Discussion

In the present study, we sought to investigate the potential association between the preoperative NLR and prognosis of GCT in patients treated with inguinal orchiectomy. Wei et al.[7] reported that elevated NLR indeed predicted a worse clinical outcome in a meta-analysis including 17 studies involving 3159 cases with urinary system cancers. In this study subgroup analyses revealed that poor OS with high NLR could be found in RCC and worse PFS/CSS in RCC, bladder cancer and urothelial carcinoma. To the best of our knowledge, our study represents the first trial determining the prognostic effect of preoperative NLR on GCT. In this study we found that the preoperative NLR is not significantly associated with PFS and CSS in the patients with GCT. By determining the optimal NLR cut-off levels of 3.55 and 3.0, patients with increased level of NLR did not show significantly lower rates of PFS and CSS, respectively.

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Table 3. Comparison of clinical parameters between the patients with a NLR of <3.0 and ≥3.0 (CSS cut-off)			
	NLR <3.0 (n=31)	NLR ≥3.0 (n=22)	p
Age, years, Mean±SD	37.97±15.5	40.1±16.2	0.632
Tumor size, cm, Mean±SD	4.38±2.37	4.60±2.03	0.734
Follow-up time, months, Mean±SD	23.42±17.76	23.73±18.89	0.952
Rete testis invasion, n (%)	1 (3.2)	1 (4.5)	0.062
Lymphovascular invasion, n (%)	3 (9.7)	-	
Stage, n (%)			0.753
1	16 (51.6)	12 (54.5)	
2A	8 (25.8)	3 (13.6)	
2B	3 (9.7)	2 (9.1)	
2C	3 (9.7)	3 (13.6)	
3	0	0	
4	1 (3.2)	2 (9.1)	
Lymph node metastasis at the time of diagnosis, n (%)	14 (45.2)	10 (45.5)	0.983
Lung metastasis at the time of diagnosis, n (%)	3 (9.7)	3 (13.6)	0.683
Progression, n (%)	2 (6.5)	3 (13.6)	0.638
Time to progression, months, mean±SD	15.0±6.97	22.0±12.51	0.737
Cancer specific death, n (%)	2 (6.5)	5 (22.7)	0.113

CSS: cancer specific survival; NLR: neutrophil-to-lymphocyte ratio; SD: standard deviation

Several studies reported the relationship between increased NLR and worse prognostic outcomes in various cancers including breast, colorectal and hepatocellular carcinomas, as well as, several urinary malignancies including prostate, bladder and renal cell carcinomas (RCC).[9-14] Proctor et al.[15] performed a Scottish Cancer Registry review across 11 different malignancies, including 8759 patients, and noted a significantly increased risk of cancer-specific (HR=1.76) and overall mortality (HR=1.77) in patients with a preoperative NLR>5. Our results could not demonstrate the presence of any significant relationship between the NLR and PFS or CSS.

Although chronic inflammation has a negative impact on cancer progression, various studies have shown that carcinogenesis itself activates chronic inflammation, which leads to the evaluation of inflammation markers as possible predictors of survival and cancer-related complications.[16] This inflammatory response reflects a non-specific response to tumor hypoxia, tissue injury and necrosis.[15-17] Suggested mechanisms to explain neutrophilia include release of granulocyte-colony stimulating factor (G-CSF) by tumor cells, and cancer inflammation through release of interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha (TNF-α).[18,19] Neutrophils are recruited by (G-CSF), which is associated with tumor progression. In addition, IL-6 also mobilizes neutrophils into a circulating pool and can be measured to predict cancer stage and oncological outcome.[20,21] Relative neutrophilia increases the number of inflammatory markers including pro-angiogenic factors, growth factors, proteases and anti-apoptotic markers that support tumor growth and progression.[22,23] Furthermore, a relative lymphocytopenia may reflect a lower count of CD4+ T-helper lymphocytes, resulting in a suboptimal lymphocyte-mediated immune response to malignancy.[13] Both of these factors may contribute to aggressive tumor biology, cancer progression, and poor prognosis. On the other hand, we did not find any significant association between the NLR and prognosis of TC. This situation creates a doubt about the relationship between the chronic inflammation and development of TC. In our opinion, further studies are needed in order to reveal the underlying inflammatory response in testicular carcinogenesis.

Every patient with a suspect testicular mass must undergo inguinal exploration with exteriorization of the testis within its tunics. For seminoma stage I, tumor size (>4 cm) and invasion of the rete testis have been identified as predictors for relapse in a pooled analysis.[24,25] For non-seminoma stage I, vascular or lymphatic invasion of the primary tumour, higher proliferation rate (>70%) and higher percentage of embrional carcinoma (>40%) are the most important predictors of occult metastatic disease.[26,27] Our study we evaluated the possible relationship between NLR and risk factors for metastatic disease. According to our results, there was no significant association between the increased NLR and risk factors for occult metastatic disease such as higher tumor size, rete testis invasion and lymphovascular invasion.

Risk factors for metastatic disease are primary location of TC, elevation of tumor marker levels and presence of non-pulmonary visceral metastasis.[28] In our study, we found a negative correlation between the NLR (for PFS cut-off value of 3.55) and lymph node metastasis at the time of diagnosis.

There are some limitations of our study. Due to the retrospective design of the recent study, some of the patients with missing data were excluded. Second limitation is the relatively small number of patients recruited from a single center. Small sample size may also be responsible from lower prevalence of TC and the wide range of our exclusion criteria. Lastly, we had data only about medium-term follow-up outcomes of our patients.

In conclusion, in contrast to other urological cancers, preoperative NLR is not useful in order to predict survival rates of the patients with GCT. However, further large-scale, prospective randomized and multi-center studies with longer follow-up time are required to investigate the possible association between NLR and prognosis of GCTs.

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