Can Neutrophil-Lymphocyte Ratio Be Used to Predict Recurrence and Progression in Non-Muscle Invasive Bladder Cancer?

Nötrofil-Lenfosit Oranı Kasa İnvaze Olmayan Mesane Kanserinde Nüks ve Progresyonu Tahmin Etmek İçin Kullanılabilir mi?

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Abstract

Objective: In this study, we aimed to investigate the predictive value of neutrophil-lymphocyte ratio (NLR) in determining progression and recurrence in non-muscle invasive bladder tumors (NMIBC).

Materials and Methods: The files of patients who underwent transurethral bladder tumor resection (TUR-BT) in our urology clinic between 2015 and 2020 were reviewed retrospectively. A total of 405 patients were included in the study. The patients were evaluated, and grouped in terms of disease progression, and recurrence observed during follow-up. Elevation of T stage of the disease, low grade tumor progressing to a high grade, and carcinoma in situ (CIS) negative cases advancing into CIS-positive stage were considered as evidence of disease progression.

Results: Fifty female, and 355 male patients were included in the study. The mean age of the study population was 64.9 ± 12.75 years. Disease recurrence was detected in 134, and disease progression in 136 out of 405 patients. The mean NLR value of the patients with relapse was 2.45 ± 2.75 ($p=0.009$). The mean NLRs of patients with, and without progression were 1.94 ± 1.67, and 2.04 ± 2.3, respectively ($p=0.645$).

Conclusion: High NLR value can predict recurrence in the follow-up of NMIBC patients. The preoperatively detected higher NLR value is a warning for the physician and draws attention to the need for more invasive and regular follow-up of the patient.

Keywords: non-muscle invasive bladder cancer, bladder carcinoma, neutrophil-lymphocyte ratio, recurrence, progression

Öz

Amaç: Bu çalışmada kas invaze olmayan mesane tümörlerinde (KİOMK) nötrofil-lenfosit oranının (NLO) progresyon ve rekürrensi belirlemedeki prediktif değerini araştırmayı amaçladık.

Gereçler ve Yöntemler: 2015 ve 2020 yılları arasında üroloji kliniğimizde transüretral mesane tümörü rezeksiyonu (TUR-MT) operasyonu uygulanmış hastaların dosyaları retrospektif olarak incelendi. Çalışmaya toplam 405 hasta dahil edildi. Hastalar, takiplerinde progresyon ve nüks durumlarına göre gruplara ayrılıp değerlendirildi. Hastalığın T evresinde yükselme, düşük dereceli tümörün yüksek dereceli hale geçmesi ve karsinoma in situ (CIS) negatif iken pozitif hale gelmesi progresyon olarak kabul edildi.

Bulgular: Çalışmaya 50 kadın ve 355 erkek hasta dahil edildi. Çalışma popülasyonunun ortalama yaşı $64,9 \pm 12,75$ idi. 405 hastanın 134'ünde hastalık nüksü, 136'sında hastalık progresyonu saptandı. Nüks görülen hastaların ortalama NLO değeri $2,45 \pm 2,75$ olarak bulundu ($p=0.009$). Progresyon gösteren hastaların ortalama NLO: 1.94 ± 1.67 iken progresyon göstermeyen hastaların ortalama NLO: 2.04 ± 2.3 olarak bulundu ($p=0.645$).

Sonuç: Yüksek NLO değeri, KİOMK hastalarının takibinde nüksü öngörebilir. Ameliyat öncesi tespit edilen yüksek NLO değeri hekim için bir uyarı niteliğinde olup, hastanın daha invaziv ve düzenli takibine dikkat çekmektedir.

Anahtar kelimeler: kasa invaze olmayan mesane kanseri, mesane karsinomu, nötrofil-lenfosit oranı, nüks, progresyon

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Introduction

Bladder cancer is the second most common cancer of the genitourinary system. It ranks 7th in the male population worldwide and 11th in both genders. The average age at diagnosis is 65 years. By this age, 75% of bladder cancers are localized, while 25% of them metastasize to lymph nodes or distant organs [1].

Non-muscle invasive bladder cancer (NMIBC) consists of the majority of urothelial carcinomas, and it is the most expensive group receiving cancer treatment [2]. Cystoscopy is the gold standard diagnostic procedure used during diagnostic process and follow-up of these patients [3]. Urine cytology was expected to replace cystoscopy due to its low false-positive rates and high specificity, but it could not give the desired result due to its low sensitivity and its inability to recognize low-grade tumors [4-6]. Furthermore, NMIBCs are tumors with a high potential for progression and recurrence. Therefore, control and follow-up of the patients are essential. Various studies have been conducted on the factors affecting the recurrence and progression of bladder cancers [5]. However, any biomarker has not been used routinely in daily practice.

An ideal tumor marker should be specific for the tumor being screened, should not yield positive results in other diseases or conditions, should demonstrate diagnostic sensitivity in the early stage of the disease and screening of small tumors, and should be able to identify all tumors in question. Since cystoscopy is the gold standard method for detecting bladder tumors the cystoscopic findings reported up to date in all studies have been evaluated and some sensitivity and specificity rates have been retrieved [7,8]. Considering that cystoscopy is practitioner-dependent, using an additional diagnostic method and urologist's prior knowledge about the NIMBC before application of the cystoscopy procedure may increase the detection rate of the tumor during cystoscopy [8].

As an actively used up-to-date parameter in the treatment and follow-up of many diseases, NLR suggestively predicts disease recurrence and progression in oncological patients [9]. Therefore, in this study, we aimed to investigate the predictive value of NLR in determining disease progression and recurrence in patients with NMIBC.

Material and Methods

The protocol of the present study was reviewed and approved by the Institutional Review Board of University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital (approval date and no: 2022-1806). Informed consent was obtained from all subjects when they were enrolled in the study. The files of the patients who underwent transurethral bladder tumor resection (TUR-BT) in our clinic between 2015 and 2020 were reviewed retrospectively. A total of 405 patients were included in the study. Nineteen parameters were investigated in the preoperatively obtained blood samples using Cell-Dyn/Rubby (Abbott) hematology analyzer. The NLR value was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count.

The histopathology results of the patients who underwent TUR-BT were retrieved from the pathology records of our hospital. Demographic and clinical data such as age, gender, complete blood count obtained before the cystoscopic procedure, histopathology results, and cystoscopic follow-up records were scanned retrospectively from the patient registry system and clinical records. According to the pathology results, the patients were divided into groups with or without disease progression or recurrence observed during the follow-up period. Elevated T stage of the disease, a low-grade tumor progressing to a high grade, and carcinoma in situ (CIS)-negative cases advancing to a CIS-positive stage were considered as evidence of disease progression.

Patients having WBC counts below 4.2 x 10^3/ml and above 10.2 x 10^3/ml, an active infection at the time of admission, any hematologic, rheumatologic, and acute coronary artery disease, and those with a history of other cancer were excluded from the study.

Statistical Analysis

Data were analyzed using software (SPSS, Version 23.0; IBM Corp, Armonk, NY). The Kolmogorov-Smirnov test was performed to determine the normality of the distribution. Afterward, the Mann-Whitney U test was used to evaluate the group association. The results were reported as the mean and the standard deviation (±SD). ROC analysis was performed to determine the cut-off point of preoperative TUR-BT. The statistical significance was set at $p<0.05$.

Results

Fifty female, and 355 male patients were enrolled in the study. The median age of the patients was 64.9 ± 12.75 years. Hundred and fifty patients had tumors less than 3 cm, and 255 patients had tumors greater than 3 cm in their greatest diameter (**Table 1**).

Table 1. Demographic and clinical data of the patients (n=405)

Age ± SD		64,9±12.75
Sex (%)	Male	355 (87.7)
	Female	50 (12.3)
Tumor size (%)	<3cm	150 (37)
	>3m	255 (63)
Tumor stage (%)	Ta	250 (61.7)
	T1	155 (38.3)
CIS (%)	Yes	52 (12.8)
	No	353 (87.2)
Recurrence (%)	Yes	134 (33.1)
	No	271 (66.9)
Progression (%)	Yes	136 (66.4)
	No	269 (33.6)

Table 2. Comperation of recurrence, tumor characteristics, and NLR

		No Recurrence	Recurrence	p
TM size n (%)	<3m	128 (31.6)	22 (5.4)	**0.001**
	>3cm	143 (35.3)	112 (27.7)	
TM stage n (%)	Ta	190 (46.9)	60 (14.8)	**0.001**
	T1	81 (20)	74 (18.3)	
TM grade n (%)	LG	154 (38)	117 (28.9)	**0.001**
	HG	50 (12.3)	84 (20.7)	
CIS n (%)	Yes	27 (6.7)	25 6.2)	**0.018**
	No	244 (60.2)	109 (26.9)	
NLR mean (±SD)		1.79 (±1.68)	2.45 (±2.75)	**0.009**

Table 3. Comperation of progression, tumor characteristics, and NRL

		No Progression	Progression	p
TM size n (%)	<3cm	97 (20)	53 (13.1)	0.587
	>3cm	172 (42.5)	83 (20.5)	
TM stage n (%)	Ta	160 (39.5)	109 (26.9)	0.196
	T1	90 (22.2)	46 (11.4)	
TM grade n (%)	LG	128 (31.6)	76 (18.8)	0.141
	HG	141 (34.8)	60 (14.8)	
CIS n (%)	Yes	236 (58.3)	33 (8.1)	0.639
	No	117 (28.9)	19 (4.7)	
NLR mean (±SD)		2.04 (±2.3)	1.94 (±1.67)	0.645

Mean preoperative neutrophil (3.79 ± 2.57 10^3/ml), and lymphocyte (2.77 ± 9.28 10^3/ml) counts were as indicated. Recurrence was detected in 134 (18.9%) patients, and disease recurrence was not observed in 271 (38.3%) patients. In the preoperative evaluation, the mean NLRs of the patients with and without recurrence were 2.45 ± 2.75 (p=0.009), and 1.79 ± 1.68, respectively (**Table 2**). Tumor size, stage, grade, and CIS were compared with recurrence rates using a chi-square test. All results were statistically significant (p=0.001, p=0.001, p=0.001 and p=0.018, respectively).

The sensitivity of NLR in predicting recurrence was evaluated on the ROC curve. The AUC value was determined as 0.586 (CI:0.527-0.646) (p=0.005) (**Figure 1**). Moreover, the cut-off value was determined as 1.22 (sensitivity: 71%, specificity: 39%). Furthermore, disease progression was detected in 136 (19.2%) patients, while in 269 (38%) patients disease progression was not noted. The mean NLRs of the patients with and without progression were 1.94 ± 1.67, and 2.04 ± 2.3, respectively (p=0.645) (**Table 3**). The sensitivity of NLR in predicting progression was also evaluated on the ROC curve. The AUC value was determined as 0.488 (Cl:0.428-0.549) (p=0.704).

Discussion

Our study found a statistically significant difference between NMIBC patients with and without recurrence in the follow-ups in terms of NLR values. This finding suggests that the high NLRs detected before cystoscopy is a parameter that may prompt the urologist to perform cystoscopy more carefully.

Since a relationship exists between a high NLR value which is an indicator of inflammatory response in different cancer types, and high-risk disease, disease recurrence, and survival, NLR may be used as a prognostic predictive parameter for patients with high-risk, aggressive tumors [10,11].

When the literature is evaluated, it is seen that the NLR value is mainly used preoperatively to evaluate the prognosis of carcinomas including urinary system malignancies. A meta-analysis published in March 2014 determined that NLR was effective in the prognostic evaluation of urinary system cancers, and its high level predicted poor clinical course [12]. In addition, high NLR values were associated with lower overall survival in renal cell cancer patients. High NLR values are associated with low recurrence-free or cancer-specific survival rates in patients with urothelial, renal cell, and bladder cancers. Although this meta-analysis emphasized that an easily calculated NLR is a poor predictor of survival in patients with urinary cancer, it was concluded that it could provide appropriate prognostic information for patients undergoing treatment for urinary cancers
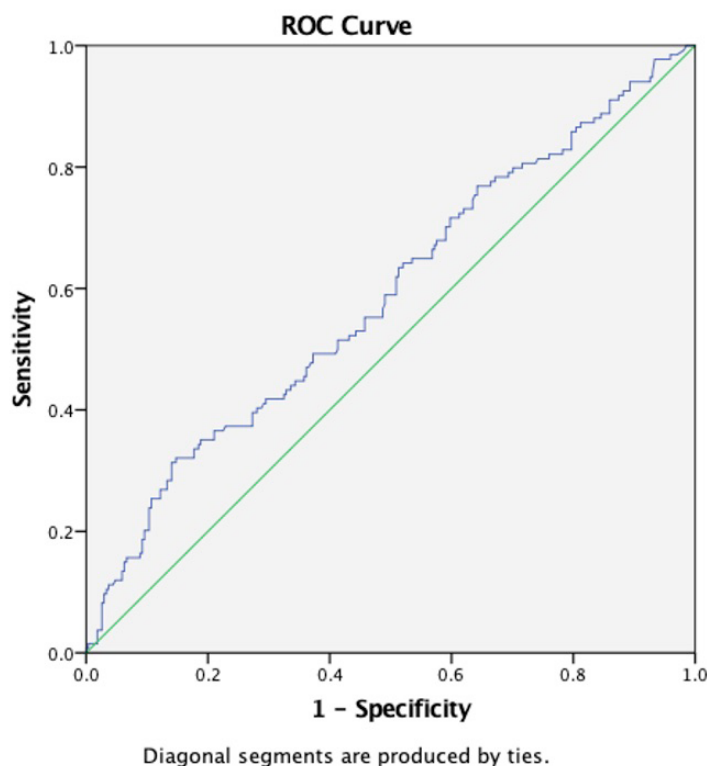
Figure 1. ROC curve of NLR for tumor recurrence

[12]. Moreover, Mano et al. examined 122 non-muscle invasive patients who underwent TUR-BT due to bladder tumors and found that a high NLR value was significantly associated with the recurrence and progression of the disease [13]. Ozyalvacli et al. confirmed the relationship of NLR with the recurrence and progression of the disease in their study of patients with T1 bladder tumors [14].

Our study found a statistically significant difference between patients who did, and did not develop recurrence during their follow-up in terms of NLR values. In line with the results of similarly designed studies, our study findings suggested that patients with high NLR values will develop a disease recurrence in their prospective follow-up. However, we did not find any correlation between disease progression and NLR values. Presumably, our small-scale patient population was insufficient to evaluate recurrence properly.

Çelen et al. divided the patients into two groups according to the preoperative NLR values of ≥2.5 and <2.5 to evaluate whether the preoperative measurement of NLR would predict a recurrence in the follow-up of NMIBC patients who underwent TUR-BT. After one year follow-up period, they found that patients with NLR ≥2.5 (55.6%) had statistically significantly higher recurrence rates compared to patients with NLR <2.5 [15]. Our study evaluated the sensitivity of NLR in predicting recurrence on the ROC curve. We found that an NLR of over 1.52 could predict recurrence.

However, our study has a limitation that needs to be addressed. We did not compare the groups according to the treatment they had. Indeed, some patients received immunotherapy, and some chemotherapy.

Conclusion

NLR seems to be a promising predictor of recurrence in NMIBC patients and may be used as a helpful parameter in predictive nomograms. However, it apparently fails to predict progression. Furthermore, prospective studies with greater number of patients are needed to fully define its use in clinical setting.

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