

ORIGINAL ARTICLE

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Clinical significance of preoperative neutrophil to lymphocyte ratio in organ-confined urothelial bladder cancer

Engin Kolukcu¹, Velid Unsal², Latif Mustafa Ozbek³, Osman Demir⁴¹Gaziosmanpasa University, Faculty of Medicine, Department of Urology, Tokat, Turkey²Artuklu University, Faculty of Health Sciences and Central Research Laboratory, Mardin, Turkey³Private Atasam Hospital, Faculty of Medicine, Department of Urology, Samsun, Turkey⁴Tokat Gaziosmanpasa University, Faculty of Medicine, Department of Biostatistics, Tokat, Turkey

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Abstract

We aimed to investigate the relationship between the preoperative neutrophil to lymphocyte ratio (NLR) and the postoperative tumor stage and grade in patients with organ-confined urothelial bladder cancer. We examined 308 patients who underwent transurethral resection in our clinic. Our study only included patients whose pathology results were organ-confined urothelial bladder cancer. The patients were classified according to tumor stage (Ta, T1, and T2) and tumor grade (Grade 1 and 2, indicating a low-grade; Grade 3, referring to a high-grade). Then each group was compared within itself based on the NLR evaluated before the surgery. A total of 279 cases (90.6%) were male. The mean age, tumor size, neutrophil and lymphocyte counts of the patients were 69.33 ± 10.92 years, 2.99 ± 2.35 cm, 5.36 ± 1.99 K/uL, and 2.23 ± 0.78 K/uL, respectively. Inflammation parameters regarding the cancer stage were as follows: NLR was 2.08, 2.36, and 3.07, for Ta, T1, and T2 tumors respectively. The relationship between T1 and T2 tumors and Ta and T2 tumors was significant ($p < 0.001$, $p < 0.001$). But there was no significant difference between the Ta and T1 tumors ($p: 0.142$). NLR was 2.07 and 2.78 for low- and high-grade tumors, respectively. These values were statistically significant ($p < 0.001$). We could not statistically correlate between Ta and T1 tumors. However, based on the other positive correlations we have obtained, we think that NLR evaluated before transurethral resection may be a valuable parameter in predicting the operative pathology result.

Keywords: Lymphocyte, neutrophil, bladder, cancer

Introduction

Bladder cancer has an important place among other urogenital malignant diseases considering its clinical course and oncological results. It ranks ninth for cancer incidence worldwide. Its incidence is reported higher in geographies with developed socioeconomic conditions [1]. It is predicted that 81,400 new cases related to this malignancy will have been diagnosed and 17,980 deaths will have occurred in the United States by 2020 [2]. More than 90% of bladder cancer consists of urothelial carcinoma. However, various pathologies can also be encountered such as squamous cell carcinoma, small cell carcinoma, and adenocarcinoma, though rarely [3]. Consumption of tobacco products is among the most important etiological factor.

In connection with this situation, men are four times more likely to develop them than do women. Bladder cancer is most commonly observed in the elderly as many clinical studies report that 90% of newly diagnosed patients are over 60 years of age [4]. Approximately 75% of patients with bladder cancer present with a disease that is confined to the submucosa or mucosa [5]. The world of science has been working meticulously on many markers for many years to predict the clinical course of cancer cases. In this century, many studies began to establish the links between cancer and inflammation on more robust foundations. Clinical analyses examining the clinical course of cancer cells with inflammatory parameters have become extremely important. The main pathophysiology of this condition lies in the ongoing inflammatory reactions leading to an increase in tumor proliferation and angiogenesis, but also inhibiting apoptosis [6,7]. Systemic inflammatory reactions lead to changes in complete blood count parameters at various levels. One of these parameters is preoperative neutrophil to lymphocyte ratio (NLR), a simple, reproducible, and low-cost indicator. The increase in neutrophil

*Corresponding Author: Engin Kolukcu, Gaziosmanpasa University, Faculty of Medicine, Department of Urology, Tokat, Turkey.
E-mail: drenginkolukcu@gmail.com

counts and decrease in lymphocyte counts during systemic inflammation are expected to lead to an increase in NLR. Based on this connection, our study aimed to evaluate the role of NLR that was examined before the transurethral resection in organ-confined urothelial bladder cancer in predicting the tumor stage and grade after surgery.

Materials and Methods

We retrospectively analyzed the data of the patients who had a preliminary diagnosis of bladder cancer and underwent transurethral resection in the urology clinic of the Medical Faculty at Tokat Gaziosmanpaşa University between 2011 and 2019. The study included patients who had a single tumor, underwent transurethral resection for the first time, and were diagnosed with organ-confined urothelial bladder cancer after pathological evaluation. The patients' ages, genders, presenting complaints, uroflowmetric examination results, body mass indexes, radiological image records, and preoperative hemogram parameters were noted. Tumor size, locations, grade, and cancer stage were analyzed after the pathological examination of the samples. Hemogram parameters were examined in a biochemistry device that is maintained regularly (Mindray BC-6800, China). These parameters were based on the routine blood analysis results taken preoperatively by the anesthesiology clinic. NLR was calculated by dividing the neutrophil number obtained in the complete blood count by the lymphocyte count. All specimens were analyzed by an experienced and dedicated pathologist. The cases were divided into three groups according to the tumor stage: those invading the muscle layer (T2), those invading only the lamina propria layer (T1), and those that did not reach the lamina propria (Ta). In terms of the tumor grade, Grade 3 patients were considered high grade, and the others were considered low grade [8]. All patients underwent contrast-enhanced abdominal computed tomography or magnetic resonance imaging to confirm the organ-confined disease. Patients with clinical conditions that would change NLR, such as active infection, hematological malignancy, severe endocrinological disorder, and antiaggregant or anticoagulant use were not included in the study. Besides, we excluded the cases whose pathology results indicated carcinoma in-situ, multiple tumors, and when the tissue samples were not obtained at sufficient depth during transurethral resection. The study was carried out following the principles of the Helsinki Declaration and with the approval of the local ethics committee (Tokat Gaziosmanpaşa University, Ethics Committee, Confirmation number and date: 20-KAEK-110 and 10.7.2020).

Statistical Analysis

Data are expressed as mean±standard deviation or frequency and percent distribution. The independent sample t-test or the one-way analysis of variance was used to compare the continuous normal data between/among the groups. The Kruskal-Wallis test or the Mann-Whitney U test was used to compare the continuous non-normal data among the groups. For multiple comparisons between the pair-wise groups, the Bonferroni-Correction and the Mann-Whitney U test were used. A Chi-Square test was used to compare the categorical data between/among the groups. Categorical variables were presented as a count and percentage. Receiver operating characteristic (ROC) analysis was applied to determine the power of NLR in predicting significant TNM classification and

grading system. Pearson correlation coefficient was used for the correlation between variables. A p-value <0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Results

A total of 308 patients were included in the study. Two hundred and seventy-nine (90.6%) of them were male. The mean age, tumor size, neutrophil and lymphocyte counts of the patients were 69.33 ± 10.92 years, 2.99 ± 2.35 cm, 5.36 ± 1.99 K/uL, and 2.23 ± 0.78 K/uL, respectively. The symptoms of 273 patients (88.6%) indicated hematuria. Twenty-three patients (7.5%) applied to our clinic with lower urinary tract symptoms such as dysuria, frequency, and urgency. Twelve patients (3.9%) were referred to our clinic by other departments due to incidentally detected bladder mass. The mean prostate volume of our male patients was 57.33 ± 26.21 cc and 87.4% of our cases underwent uroflowmetric analysis. The mean maximum flow rate of our patients was 14.74 ± 4.45 mL/s. The average body mass index of our patients was calculated as 27.44 ± 4.25 kg/m². However, a total of 50 (16.23%) were rated as obese. The tumor was localized on the lateral walls in 123 patients (39.9%), on the back wall in 55 patients (17.9%), and in the dome in 30 patients (9.7%). The remaining tumors were in other localizations such as the trigon and bladder neck. Pathology specimens revealed that 190 patients (61.7%) were low grade. However, 40 patients (13%) had tumor cells invading the muscle layer, while 140 (45.5%) patients had invasion only to the lamina propria layer.

Inflammation parameters were evaluated according to the tumor stage: NLR was 2.08, 2.36, and 3.07 for Ta, T1, and T2 tumors, respectively. When the relationship between Ta and T1 tumors was evaluated by ROC analysis, the NLR cut-off value was 1.75 and there was no significant difference between the two groups ($p: 0.142$) (Figure 1). The relationship between Ta and T2 tumors was similarly analyzed using ROC analysis and the cut-off value was the same. The difference was statistically significant between them ($p < 0.001$) (Figure 2). The NLR cut-off value between T1 and T2 tumors was 3.05, and the difference between the two groups was significant ($p < 0.001$) (Figure 3). A detailed analysis of the tumor stage and other variables is given in Table 1. The inflammation parameters were evaluated according to tumor grade: NLR was 2.07 and 2.78, for the low and high-grade tumors, respectively. According to the ROC analysis of both groups, the cut-off value was 2.09 which was statistically significant ($p < 0.001$) (Figure 4). Similarly, all parameters related to tumor grade are presented in detail in Table 2.

Discussion

Cancer remains a major public health problem worldwide. Its incidence varies directly in connection with many different conditions such as the geography where the individual maintains their life, their genetic family tree, and personal lifestyle. However, the number of cancer cases is increasing worldwide. It is predicted that 1,806,590 cancer cases will be diagnosed and an extremely high number of cancer-related deaths such as 606,520 will occur in the United States in 2020 [2]. Cancer cases have high mortality rates and pose a great burden to national economies. In this context, it is important to provide primary protection by avoiding

Table 1. The distribution of age, tumor size and inflammatory markers by stage

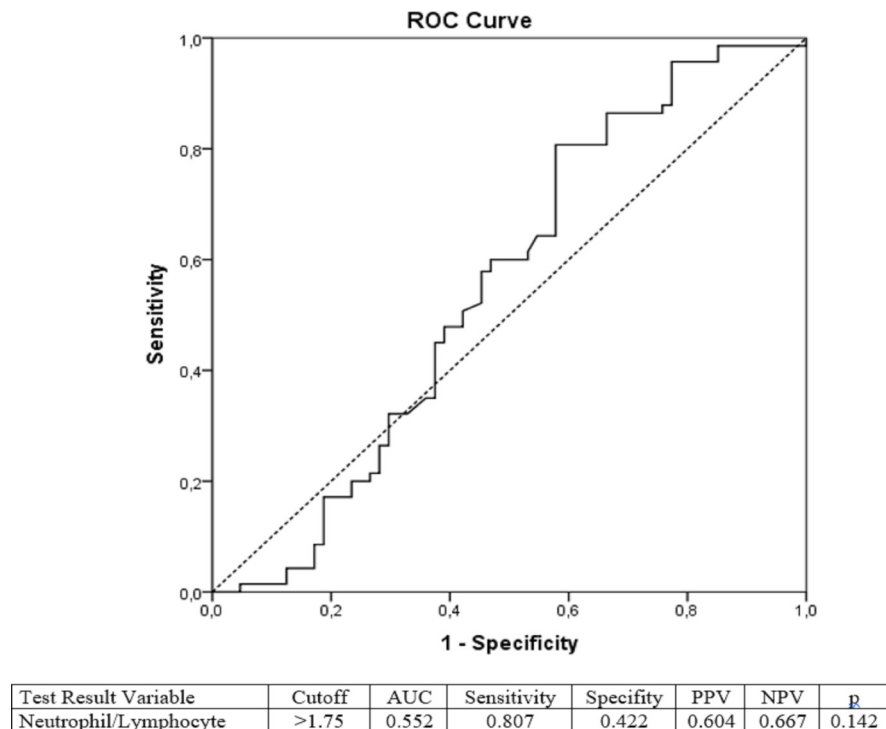
Variables	Stage			p
	Ta	T1	T2	
	Ort±SS	Ort±SS	Ort±SS	
Age	67.98±9.92	69.67±11.68	72.5±10.74	0.064
Size	2.07±1.92 (a)	3.39±2.29 (b)	4.52±2.61 (c)	<0.001
Neutrophil count	5.33±2.12 (a)	5.07±1.63 (b)	6.5±2.31 (a)	<0.001
Lymphocyte count	2.36±0.94 (a)	2.16±0.65 (b)	2.07±0.57 (b)	0.041
Neutrophil / Lymphocyte	2.08[1.59-3.2] (a)	2.36[1.78-3.03] (a)	3.07[2.22-3.88] (b)	<0.001*

Data are shown as mean±SD or median[IQR]. One-way ANOVA or *Kruskal Wallis test were used. (abc): Common letters in a row indicate statistically insignificance.

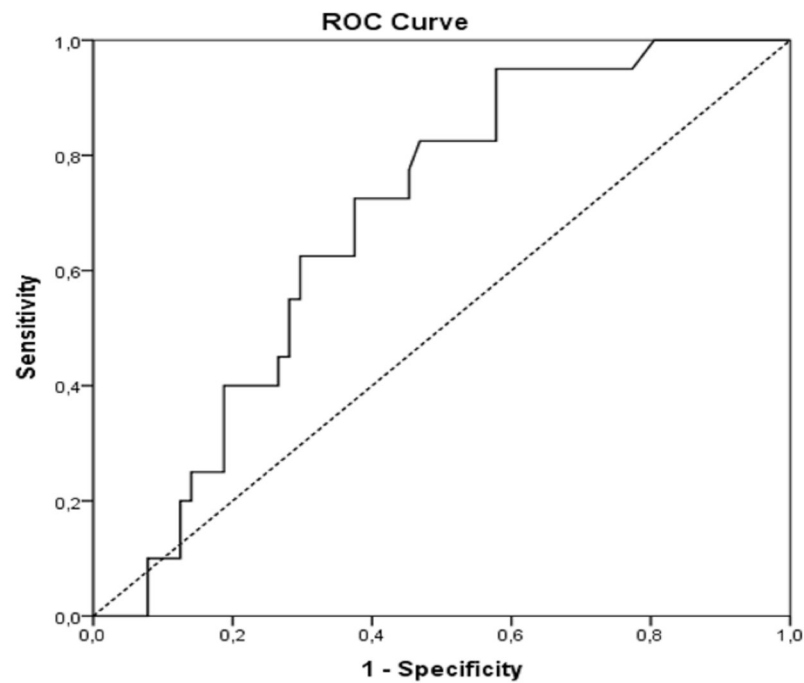
Table 2. The distribution of age, tumor size and inflammatory markers by grade

Variables	Grade		p
	Low	High	
	Ort±SS	Ort±SS	
Age	68.34±10.72	70.94±11.1	0.042
Tumor size	2.56±2.21	3.68±2.41	<0.001
Neutrophil count	5.02±1.92	5.92±1.97	<0.001
Lymphocyte count	2.27±0.8	2.16±0.76	0.222
Neutrophil / Lymphocyte	2.07[1.62-2.98]	2.78[2.05-3.36]	<0.001*

Data are shown as mean±SD or median[IQR]. Independent samples t test or *Mann Whitney U test were used.

**Figure 1.** The result of ROC analysis for Ta versus T1 for stages

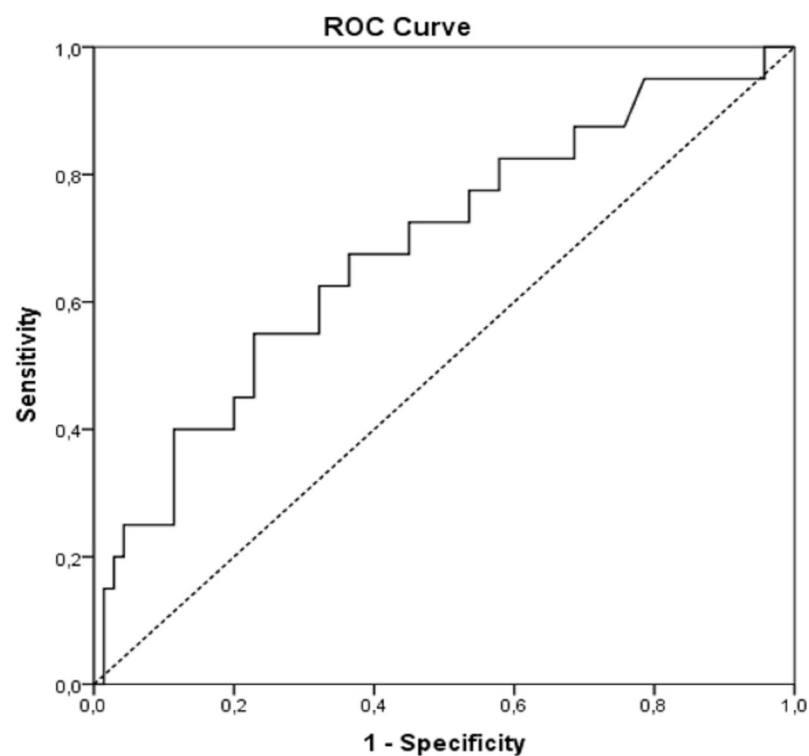
AUC:Area under curve PPV:Positive predictive value NPV: Negative predictive value



Test Result Variable	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	p
Neutrophil/Lymphocyte	>1.75	0.686	0.950	0.422	0.339	0.964	<0.001

Figure 2. The result of ROC analysis for Ta versus T2 for stages

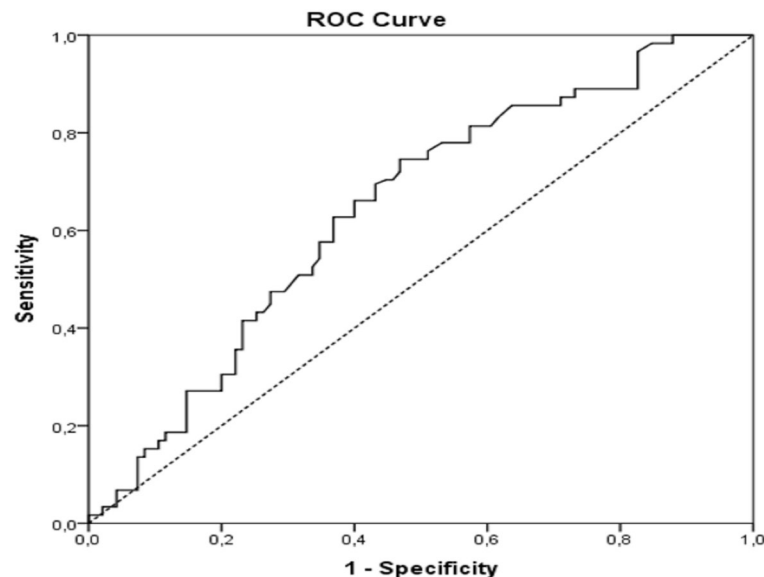
AUC:Area under curve PPV:Positive predictive value NPV: Negative predictive value



Test Result Variable(s)	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	p
Neutrophil/Lymphocyte	>3.05	0.684	0.550	0.771	0.407	0.857	<0.001

Figure 3. The result of ROC analysis for T1 versus T2 for stages

AUC:Area under curve PPV:Positive predictive value NPV: Negative predictive value



Test Result Variable(s)	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	p
Neutrophil/Lymphocyte	>2.09	0.644	0.746	0.532	0.497	0.771	<0.001

Figure 4. The result of ROC analysis for the low group versus high group for stages

AUC:Area under curve PPV:Positive predictive value NPV: Negative predictive value

external factors such as tobacco use, radiation, and environmental chemicals, which are accepted as common etiological factors in almost all cancers, and to diagnose cancer cases early [9]. Many authors suggest that it is extremely valuable to predict the clinical stages of cancer cases preoperatively in determining targeted treatment strategies and establishing follow-up protocols. Scientific publications from the last decade support the common view that this will contribute to both the health economy and the clinical course of the disease [10,11]. However, in direct connection with the aging world population and increasing life expectancy, it is predicted that cancer cases will be encountered at a higher level in the near future. This prediction increases the importance of all these concepts. Similarly, the elderly population was predominant in our study with an average age of 69.33 ± 10.92 years. Several clinical studies in our century have developed models for predicting the course of cancer cells.

In this context, the scientific world has taken an interest in the relationship between inflammation and cancer for many years. The first step of this relationship was the examination of the physiological and pathological processes in wound healing and inflammation. In this process, multifactorial pathways are activated against tissue damage and recovery begins in the body. Neutrophils are the first activated cells. Then monocytes turn into macrophages in tissue and come to the damaged tissue with chemotactic agents. Once macrophages are activated, they become the main source of growth factors and cytokines. Thus, extremely critical changes are observed in the epithelium and mesenchymal cells locally [12]. In local inflammation, cytokines, transcription factors, chemokines, and other inflammatory proteins provide intercellular communication and spread tumors. Cells with high division rates are generally predicted to induce hypoxia or activate

cytokines/chemokines and cause necrosis. For this reason, tumor necrosis with inflammation is often thought to be associated with poor prognosis [13,14]. Cytokines are also involved in very important steps in the relationship of the inflammatory response and cancer such as chemokine activation, its direct effects on the cell, mesenchymal change process from epithelium, and acceleration of metastasis. Chemokines are chemotactic cytokines that are highly effective in tumor progression produced in the tumor microenvironment. They stimulate tumor development, angiogenesis, and activation of leukocytes. They also account for metastatic activation in invasive tumors [15,16].

Various studies have analyzed the inflammation parameters and urogenital system cancers in the past decade. Luo et al. [17] examined 34 retrospective cohort studies in their meta-analysis, where they evaluated the relationship between NLR, one of the widely used inflammation parameters, with urologic tumors. They reported that high NLR can be used as a poor prognostic marker for these cancers. Another meta-analysis addressed 43 studies with 7,490 cases with renal cell carcinoma, upper tract urothelial cancer, bladder cancer, or prostate cancer. It showed that a high level of C-reactive protein, another inflammatory marker, suggests a poor prognosis for patients with urological cancer [18]. In a similar meta-analysis, Wei et al. [10] reported that elevated NLR was a poor predictor for survival in patients with urinary cancers. On the other hand, Su et al. [11] examined 12 studies including 6585 patients with prostate cancer, urothelial cancer, or transitional cell carcinoma. Their meta-analysis reported that a higher-derived level was negatively associated with NLR, cancer-specific survival, disease-free survival, overall survival, and biochemical recurrence-free survival. In their meta-analysis of 85 studies involving 3171 patients, Wu et al. [19] analyzed another inflammatory marker, the

platelet-to-lymphocyte ratio, and reported that the elevation of this rate did not correlate with pathological data such as tumor stage, tumor grade, and necrosis in urogenital cancers.

Studies evaluating the clinical significance of inflammatory markers in cases with bladder cancer have shown similar results. In their study of 226 cases, Lee et al. [20] concluded that NLR, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio are significant predictors of muscle-invasive disease. Çelik et al. [21] evaluated 222 patients with a mass greater than three cm in the bladder and reported that NLR was statistically significantly higher in muscle-invasive patients. The mean tumor size of the patients included in our study was 2.99 ± 2.35 cm. Our analysis similarly revealed that NLR in muscle-invasive patients was significantly higher than in other cases. Çelen et al. [22] reported that high NLR was associated with increased recurrence in their series of 178 cases where they evaluated the clinical course of superficial bladder cancer after curative transurethral resection. The clinical course of our patients could not be presented. However, the relationship between NLR and tumor grade that directly correlates with the prognosis of bladder cancer has been discussed. Our analyses revealed that cases with high tumor grade had a statistically significant increase in NLR. Şefik et al. [23] stated that NLR may be a marker in predicting locally advanced disease in organ-confined muscle-invasive bladder cancer in their study consisting of 126 cases who underwent radical cystectomy. Racioppi et al. [24] evaluated the response to BCG therapy in 100 high-risk patients with non-muscle-invasive bladder cancer. They showed a positive correlation between the preoperative NLR values and the recurrence and progression. In the study evaluating another inflammatory marker, lymphocyte-to-monocyte ratio, Temraz et al. [25] evaluated 68 patients with transitional cell carcinoma of the bladder. They reported a relationship between this inflammatory marker and the overall survival and prolonged treatment recurrence. Guo et al. [26] analyzed the C-reactive protein/albumin ratio that is often used as a preoperative inflammatory marker in patients undergoing radical cystectomy. They reported a positive correlation between the inflammatory marker and the postoperative overall survival and progression-free survival. Tang et al. [27] evaluated 302 patients with bladder cancer and stated that, although there was a statistically significant relationship between NLR and tumor grade, there was no correlation with the pathological stage of the tumor. Ojerholm et al. [28] failed to establish a relationship between NLR and overall survival in patients with muscle-invasive bladder cancer in their study from a large patient series.

The main limitation of our study is that it was conducted retrospectively and our clinical follow-up results could not be documented. In this context, we could not present patient groups with recurrence and progression rates. An important advantage of our study is that it dealt with cases with a single tumor and had a transurethral resection for the first time. For this reason, it has clearly demonstrated the link between NLR and tumor stage and grade, unlike many previous studies.

Conclusion

In our study, a positive link was established between tumor grade and NLR. However, when evaluated in terms of tumor stage, different results appeared for Ta, T1, and T2 tumors. Accordingly,

when NLR was evaluated separately for each cancer stage, there was no statistically significant difference between Ta and T1 tumors. However, a positive correlation was observed between Ta and T2 tumors as well as between T1 and T2 tumors. According to the data we obtained, we think that NLR, a hematological parameter that is routinely evaluated preoperatively, is a marker that should be considered in predicting tumor stage and grade after transurethral resection. We also believe that our results should be supported with large series, multicentered, randomized studies.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Tokat Gaziosmanpasa University, Ethics Committee, Confirmation number and date: 20-KAEK-110 and 10.7.2020).

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