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ORIGINAL ARTICLE

Can the neutrophil-to-lymphocyte ratio be used to predict recurrence and progression of non-muscle-invasive bladder cancer?

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Abstract The aim of our study was to evaluate whether neutrophil-to-lymphocyte ratio (NLR) is a predictor of disease progression and recurrence in patients with primary non-muscle-invasive bladder cancer (NMIBC). This was a prospective study of 86 patients with newly diagnosed NMIBC. The patients were classified by the number of points assigned by the European Organization for Research and Treatment of Cancer risk tables. The correlation between progression score, recurrence score, age, mean platelet volume, red blood cell distribution width and NLR was assessed statistically. The same parameters were compared between the risk groups. A significant difference in NLR and age values was observed between recurrence and progression risk score groups. The relationships between NLR and recurrence and progression risk scores were no longer significant after correcting for the statistical effect of age on scores. Age was significantly different between groups after adjusting for NLR. Our study revealed that NLR and age were associated with patient age and bladder tumor progression and recurrence risk scores. After correcting for age, the significant relationship with NLR was lost, in contrast to some previous studies. We recommend that patient age should be corrected to avoid misleading results in NLR studies.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

The overall incidence of urinary bladder cancer (BC) was about 429,200 cases in 2012. Most (75%) BC is non-muscle invasive (NMI) at the first diagnosis [Ta, T1, and carcinoma *in situ* (CIS)] and usually has a good prognosis. Between 30% and 80% of cases will relapse as NMI tumors and 1–45% will progress to muscle invasion (MI) within 5 years [1–3]. The difficulty of treating non-muscle-invasive bladder cancer (NMIBC) is to protect the bladder and its function for as long as possible, accepting the risk of recurrence while minimizing the possibility of progression to muscle-invasive disease. The European Organization for Research and Treatment of Cancer (EORTC) risk stratification can be used to measure these risks [1,3]. The aim has been to divide patients into risk groups of good, intermediate, and poor prognosis. After transurethral resection of bladder tumor (TURBT) and one immediate instillation of chemotherapy, treatment can be modified according to the patient's prognosis. Patients with a good prognosis receive either no more instillations or intravesical chemotherapy. The treatment of choice for poor prognosis patients is Bacillus Calmette–Guérin with maintenance. Treatments for intermediate-risk patients are controversial [4].

According to recent theories, the systemic inflammatory response induced by cancer causes relative neutrophilia and lymphocytopenia, producing a protumor inflammatory state [5]. The neutrophil-to-lymphocyte ratio (NLR), as a marker of the systemic inflammatory response, has been studied as a valuable prognostic biomarker in various types of tumors including BC [6–8]. Among patients with BC, a high NLR is related to muscle-invasive disease, extravesical disease, and poorer cancer-specific and overall survival [8–12]. Nonsteroidal anti-inflammatory drugs have been suggested to decrease the risk of evolving BC by 19%, suggesting a critical correlation between BC and inflammation [13]. Mean platelet volume (MPV) is also related with the pathophysiological characteristics of various types of cancer and inflammation [14,15]. Red blood cell distribution width (RDW) is a strong predictor of all-cause mortality, including cancer-related death and cancer progression [16,17].

The aim of our study was to evaluate whether NLR is a predictor of disease progression and recurrence in patients with primary NMIBC.

Methods

Study population

This was a prospective study of 86 patients with newly diagnosed NMIBC (72 men and 14 women) who presented consecutively at the Urology Clinic of Bozok University Research Hospital, Yozgat, Turkey. We selected patients using our laboratory information system database to retrieve data regarding NLR, RDW, hemoglobin, MPV, and age. Clinical and pathological data were recorded. The NLR ratio was calculated using the neutrophil and lymphocyte values obtained from the complete blood counts. Patients with newly diagnosed urothelial carcinoma underwent TURBT at a single institute between 2010 and 2014. These patients were followed up until September 2015. The study data were collected from 2010 to 2015. All specimens were reviewed by a pathologist, and the urothelial carcinoma of the bladder diagnosis was confirmed. Tumors were staged according to the 2002 American Joint Committee on Cancer TNM (tumor–node–metastasis) staging system [18], and graded according to the 1973 World Health Organization grading system [19].

The patients were classified by the number of points assigned by the EORTC risk tables. Patients with a progression risk score of 0, 2–6, 7–13, and $>$ 13 were categorized as Group 1, 2, 3, and 4, respectively. Furthermore, scores of 0, 2–6, and $>$ 6 were considered low, intermediate, and high risk for progression, respectively, according to the European Association of Urology (EAU) guidelines. Patients with a recurrence risk score of 0, 1–4, 5–9, and $>$ 9 were Groups 1, 2, 3, and 4, respectively. Similarly, 0, 1–9, and $>$ 9 were low, intermediate, and high risk of recurrence, respectively according to the EAU guidelines [20].

A second TURBT was routinely performed in patients who had a T1 tumor or the important risk of residual tumor after the first TURBT of Ta or G3 tumor in initial TURBT. Patients received postoperative intravesical instillations based on tumor characteristics, and according to the choice of the treating urologist. Maintenance chemotherapy or immunotherapy was administered to medium- and high-risk patients according to the selection of treating urologist. Postoperative follow-up was designed according to EAU guidelines and the selection of the treating urologist, for instance, high-risk patients underwent cystoscopy every 3 months for 2 years, and every 6 months in the following years. Low-risk patients were monitored after 3 months, and if the result was negative, the next cystoscopy was planned for 9 months and subsequently once yearly [3]. Recurrence of bladder tumor was defined as the first histologically confirmed tumor relapse in the bladder, regardless of its stage. Progression of bladder tumor was defined as an advance in T category from CIS or Ta to T1 (invasion), development of T2 or an increase in grade of tumor from low to high [21]. The study endpoints were defined as immunotherapy requirement or T2 disease. The follow-up average was 29 months.

This study was approved by the Institutional Ethics Committee of Bozok University. The correlation between progression score, recurrence score, patient age, MPV, RDW, and NLR was assessed statistically. Similar parameters were compared between the recurrence and progression risk groups.

Statistical analysis

Shapiro–Wilk's and Levene's tests were used to test for normality and homogeneity of the data. Values are expressed as frequencies and percentages, mean ± standard deviation, or median and 25–75th percentiles. Student *t* test and one way analysis of variance were used to compare parametric continuous variables, and the Mann–Whitney *U* test was used to compare nonparametric continuous variables. Categorical data were compared using the χ^2 distribution. Pearson's test was used for the correlation analysis. A multiple linear regression model was

used to identify independent predictors of recurrence and progression scores. Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered to indicate significance.

Results

The baseline characteristics and follow-up data of the patients are summarized in Table 1. The mean age of the patients was 65.8 ± 12 years. NLR was positively correlated with patient age ($p = 0.018$, $r = 0.315$), recurrence risk score ($p = 0.001$, $r = 0.421$), and progression risk score ($p = 0.004$, $r = 0.375$; Figure 1A–C, respectively). Patient age was positively correlated with recurrence risk score ($p = 0.018$, $r = 0.313$), and progression risk score ($p = 0.001$, $r = 0.443$; Figure 1D and 1E, respectively). No other significant correlations were detected. We showed that NLR increased relative to the increase in risk score in the comparison of NLR and recurrence risk scores of patients. Similarly, a significant difference in NLR values was observed between recurrence risk score groups ($p = 0.041$). Risk score increased significantly with the increase in age ($p = 0.003$). No significant differences were detected between the other variables (Table 2). NLR values increased with the increase in progression risk scores. In addition, a significant difference in NLR values was observed between the groups ($p = 0.042$). Progression risk score increased with the increase in patient age ($p = 0.001$). No significant differences were found between any other variables (Table 3). The relationships between NLR and progression and recurrence risk scores were no longer significant after correcting for the statistical effect of age on the progression and recurrence risk scores. NLR did not differ statistically between the recurrence or progression risk score groups after adjusting for age ($p = 0.229$ and $p = 0.146$, respectively). Age was significantly different between the recurrence risk score and progression risk score groups after adjusting for NLR ($p < 0.001$ and $p < 0.003$, respectively). The results of performed multiple linear regression also were similar (Tables 4 and 5).

Table 1 Characteristics and follow-up data of patients with bladder cancer.

Variables of 86 patients	Mean ± SD or *n* (%)
Age (y)	65.8 ± 12
Sex	
Male	72 (84)
Female	14 (16)
NLR	2.64 ± 0.51
MPV (fL)	8.12 ± 1.2
Hemoglobin (g/dL)	14 ± 1.4
RDW (%)	15.8 ± 1.9
Recurrence risk score	5.1 ± 1.3
Progression risk score	7.68 ± 1.9
Pathological stage	
Ta	50 (58)
T1	36 (42)
Grading	
G1	11 (13)
G2	48 (56)
G3	27 (31)
Concomitant CIS	13 (15)
No. of tumors	
1	59 (69)
2–7	18 (21)
≥ 8	9 (10)
Tumor size (mm)	
≤ 10	29 (34)
10–30	36 (42)
≥ 30	21 (24)
Tumor morphology	
Papillary	68 (79)
Nonpapillary	18 (21)
EORTC recurrence risk	
Low	10 (12)
Medium	55 (64)
High	21 (24)
EORTC progression risk	
Low	14 (16)
Medium	21 (25)
High	51 (59)
Recurrence	
No	50 (58.2)
1st year	25 (29)
After 1 year	11 (12.8)
Progression	
No	67 (77.9)
1st year	10 (11.6)
After 1 year	9 (10.5)

EORTC = European Organization for Research and Treatment of Cancer; MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; RDW = red blood cell distribution width; SD = standard deviation.

Discussion

We found that NLR was significantly associated with recurrence risk score, progression risk score, and patient age. However, the significant differences were lost after adjusting for age.

NLR has been recommended as a simple systemic inflammatory response marker in patients with a variety of diseases and can be easily obtained from the differential white blood cell count [22,23]. BC is often related to chronic or recurrent inflammation, and a high number of inflammatory cells are found in the tumor field [24]. The numbers of T lymphocytes and natural killer cells are significantly lower in patients with invasive bladder carcinoma than those in patients with superficial carcinoma [25]. Several inflammatory parameters obtained from blood tests, including C-reactive protein, NLR, platelet–lymphocyte ratio, and albumin level are related to treatment outcomes from primary operable malignancies [26]. A higher NLR during the preoperative period has been linked to a poor prognosis in certain cancers, including that of the bladder [10,27,28]. Furthermore, several studies have reported that a high NLR is associated with worse recurrence-free, disease-specific, and overall survival in patients with BC and upper urinary tract cancers [12,29]. NLR level is significantly associated with disease

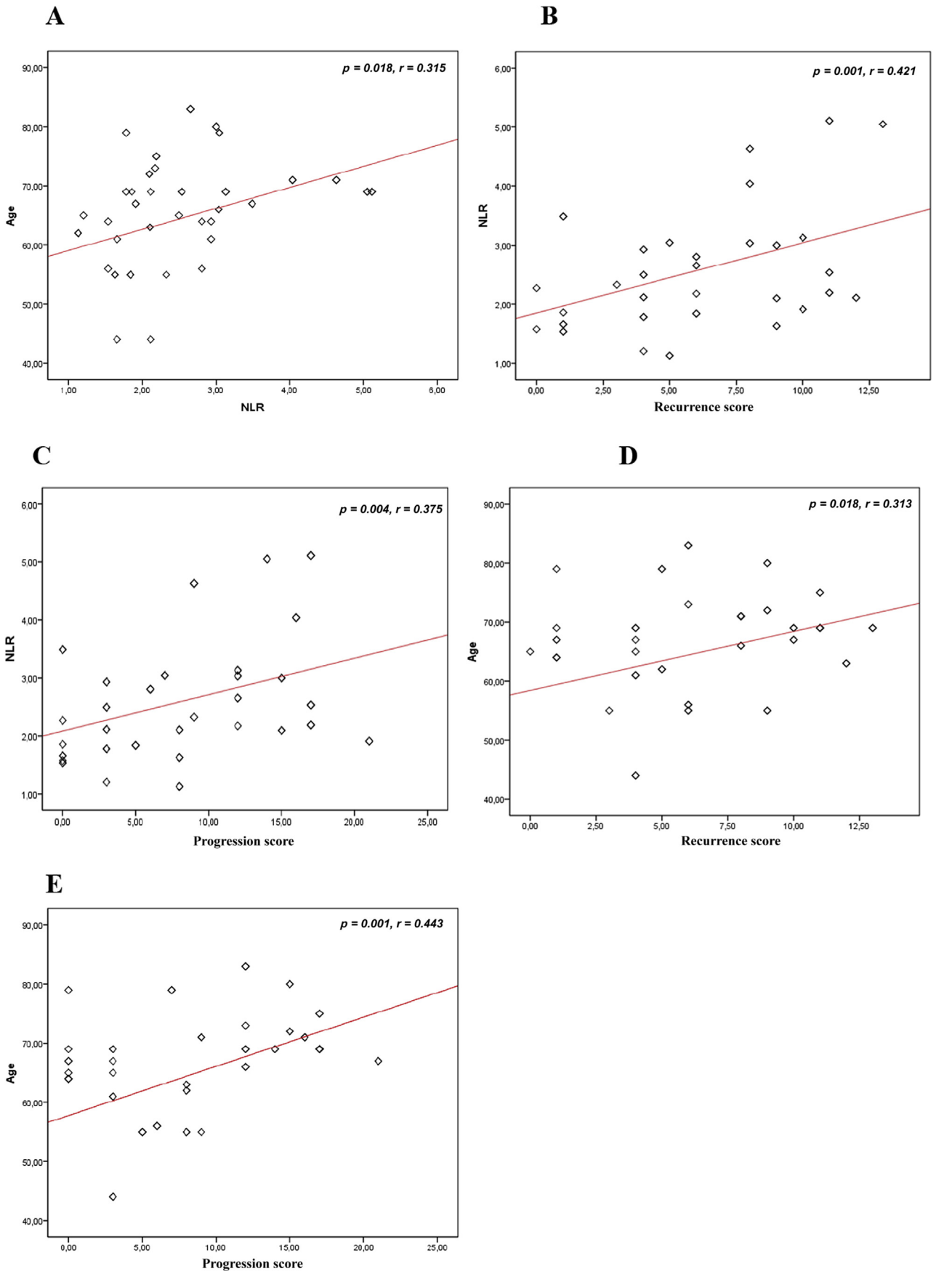

Figure 1. (A) Correlation between age and NLR. (B) Correlation between NLR and recurrence score. (C) Correlation between NLR and progression score. (D) Correlation between age and recurrence score. (E) Correlation between age and progression score. NLR = neutrophil-to-lymphocyte ratio.

Table 2 Comparison of NLR, MPV and RDW between groups of recurrence risk.

Variables	Group 1 (Low risk; Score 0; $n = 10$)	Group 2 (Intermediate risk; Score 1–4; $n = 24$)	Group 3 (Intermediate risk; Score 5–9; $n = 31$)	Group 4 (High risk; Score > 9; $n = 21$)	p^*
NLR	1.93 ± 0.3^a	2.18 ± 0.4^b	2.68 ± 0.5^{bc}	3.17 ± 0.5^c	**0.041**
MPV (fL)	7.88 ± 1.6^a	7.97 ± 1.6^a	8.38 ± 1^a	8.56 ± 1.17^a	0.607
RDW (%)	15.6 ± 1^a	16.2 ± 1.7^a	15.5 ± 1.7^a	16.3 ± 2.4^a	0.517
Age (y)	45.2 ± 8^a	59.9 ± 11^{ab}	68.8 ± 13^b	69.9 ± 15^b	**0.003**

Values are expressed as mean ± standard deviation.
* Different subscripts letters in a row indicate statistically significant difference. Bold values indicate statistically significant ($p < 0.05$).
MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; RDW = red blood cell distribution width.

Table 3 Comparison of NLR, MPV and RDW between groups of progression risk.

Variables	Group 1 (Low risk; Score 0; $n = 14$)	Group 2 (Intermediate risk; Score 2–6; $n = 21$)	Group 3 (High risk; Score 7–13; $n = 27$)	Group 4 (High risk; Score > 13; $n = 24$)	p^*
NLR	2.12 ± 0.4^a	2.23 ± 0.4^a	2.63 ± 0.5^{ab}	3.25 ± 0.6^b	**0.019**
MPV (fL)	7.68 ± 0.7^a	7.95 ± 0.9^a	8.24 ± 1.3^a	8.67 ± 1.7^a	0.186
RDW (%)	17.1 ± 1.8^a	15.3 ± 1^a	15.8 ± 1.6^a	15.7 ± 2.5^a	0.171
Age (y)	55.8 ± 9^a	$62.9 \pm 12^{a,b}$	68.6 ± 13^b	71.7 ± 15^b	**0.001**

Values are expressed as mean ± standard deviation.
*Different subscripts letters in a row indicate statistically significant difference. Bold value indicates statistically significant ($p < 0.05$).
MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; RDW = red blood cell distribution width.

Table 4 Independent predictors of recurrence risk scores by multiple linear regression analysis.

Factors	B	S.E.	β	t	p^*
NLR	0.094	0.039	0.301	2.413	0.064
MPV (fL)	0.057	0.393	0.020	0.144	0.886
RDW (%)	−0.400	0.293	−0.208	1.366	0.178
Age (y)	1.544	0.510	0.439	3.029	**0.004**

* Bold value indicates statistically significant ($p < 0.05$).
B = unstandardized coefficients; β = standardized coefficients; MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; RDW = red blood cell distribution width; SE = standard error.

Table 5 Independent predictors of progression risk scores by multiple linear regression analysis.

Factors	B	S.E.	β	t	p^*
NLR	2.366	0.821	0.396	2.883	0.064
MPV (fL)	0.697	0.633	0.141	1.100	0.276
RDW (%)	−0.663	0.471	−0.204	−1.407	0.166
Age (y)	0.204	0.063	0.386	3.268	**0.002**

* Bold value indicates statistically significant ($p < 0.05$).
B = unstandardized coefficients; β = standardized coefficients; MPV = mean platelet volume; NLR = neutrophil-to-lymphocyte ratio; RDW = red blood cell distribution width; SE = standard error.

progression and recurrence in patients with NMIBC [30]. Elevated preoperative NLR is associated with increased risks of extravesical tumor extension and disease recurrence. Furthermore, a higher preoperative NLR among patients undergoing radical cystectomy is associated with cancer-specific and all-cause mortality [12]. Higher pre-NLR is an independent risk factor of disease recurrence and cancer-specific mortality in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. In addition, an elevated pre-NLR is significantly associated with worse pathological features and patient age [31]. According to Li et al [32], the eldest age group has the highest NLR, and the youngest age group possesses the lowest NLR. Healthy elderly people have a high NLR [32]. In our study, we evaluated patient age, NLR, RDW, and MPV according to the EORTC risk score. Patient age and NLR were correlated with recurrence risk score and each other. Patient age and NLR may be related to the recurrence risk score. Additionally, NLR and age increased significantly according to recurrence risk group. NLR was no different between the risk score groups after adjusting for age. However, age was significantly different in the recurrence risk score groups after adjusting for NLR. Our results show that recurrence risk was affected by age, in contrast to NLR in other studies [12,30,31]. Studies that evaluate recurrence risk in patients with BC should consider age as a factor.

Tumor size, hydronephrosis, and hemoglobin levels in patients with BC are the most important preoperative prognostic factors [33]. Hilmy et al [34] advised that the preoperative systemic inflammatory response is more nearly related to outcome in patients with BC treated with radical cystectomy and reported the usefulness of CRP as an important prognostic factor for disease-specific survival. A previous study reported that patients with a higher NLR display relative lymphocytopenia and may show a poorer lymphocyte-mediated immune response to malignancy; thus, deteriorating their prognosis and

increasing the potential for tumor progression [35]. The association between increased preoperative NLR and cancer-specific mortality outcomes is complex and yet to be elucidated. A high NLR reflects both a heightened neutrophil-dependent inflammatory reaction and a decreased, lymphocyte-mediated, anti-tumor immune response. Both of these factors may contribute to aggressive tumor biology, cancer progression, and poor prognosis [28,36]. Most studies that have evaluated the relationship between NLR and outcomes after radical cystectomy reported that a high NLR is related to worse recurrence-free, disease-specific, and overall survival rates [8,10,12]. Although Mano et al [30] recommended that NLR may add prognostic knowledge to presently used risk stratification tools for recurrence and progression, more studies are needed to assess whether the NLR forecasts disease-specific and overall survival in patients with NMIBC. Nevertheless, within the limitations of an early-phase study to evaluate markers, our findings suggest that NLR is a potential prognostic marker for predicting disease recurrence and progression in patients with NMIBC [37]. Kaynar et al [38] found a significant relationship between patient age and tumor invasiveness. Moreover, a correlation analysis revealed a positive correlation between age, tumor invasiveness, and tumor size NLR [38]. NLR is an important predictor of disease progression and recurrence. These findings suggest that pretreatment NLR might potentially serve as a prognostic marker in patients with NMIBC. Additional prospective studies with larger cohorts are needed to validate these findings [30]. Can et al [9] and Ceylan et al [11] reported that high NLR levels are significantly related with cancer muscle invasiveness. An elevated NLR is significantly associated with extravesical disease and worse overall and cancer-specific survival in a multivariate analysis [8]. Age, female sex, and NLR are predictors of invasiveness by urothelial carcinoma [9]. Furthermore, high NLR levels are associated with patient age. Similarly, a higher NLR level and patient age is associated with worse pathological features [9,12,31,32]. In the current study, patient age and NLR were correlated with progression risk score and with each other. Patient age and NLR may be associated with the progression risk score. Furthermore, NLR and age were significantly different between to progression risk groups, and NLR was no different between progression risk score groups after adjusting for age. By contrast, age was significantly different between the progression risk score groups after adjusting for NLR. These results show that progression risk is affected by age but not NLR, as in other studies [8,11,30]. Studies that assess progression risk in patients with BC should consider age and adjust for its effect.

In conclusion, our study revealed that NLR was associated with patient age and bladder tumor progression and recurrence risk scores. Similarly, age was associated with the same scores. After correcting for age, the significant relationship with NLR was lost in contrast to some previous studies. However, age was significantly different between the progression risk score groups after adjusting for NLR. We recommend that patient age should be corrected to avoid misleading results in NLR studies.

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