Prognostic Value of Preoperative Inflammation Markers in Non-Muscle Invasıve Bladder Cancer

ABSTRACT:

Purpose: To investigate the prediction values of the preoperative NLR, LMR, PLR, MPV, RDW for recurrence and progression of patients with non-muscle invasive bladder cancer (NMIBC).

Methods: In this prospective study, 94 consecutive patients, newly diagnosed with NMIBC between July 2017 - August 2018 were included. The blood samples were collected from patients before transurethral resection of bladder tumor (TURB) and NLR, LMR, PLR, RDW, MPV values were calculated. The effect of these preoperative inflammatory parameters and other clinicopathological parameters on recurrence and progression rates were evaluated. Kaplan-Meier and multivariate Cox regression analyses were performed to identify significant prognostic variables.

Results: The mean follow-up was 11 ± 6.4 months. Recurrence was observed in 35.1% and progression was detected in 7.4% of the patients. Neutrophil-lymphocyte ratio was statistically significantly associated with both recurrence (p = 0.01) and progression (p = 0.035) whereas lymphocyte-monocyte ratio was only associated with recurrence (p = 0.038). In the survival analyses, the relationship between recurrence and LMR was confirmed in both univariate (p = 0.021) and multivariate (p = 0.022) analyses. The relationship between NLR and recurrence was confirmed in univariate analysis (p = 0.019), however in multivariate analysis was found to be statistically insignificant (p = 0.051).

Conclusions: Lymphocyte-monocyte ratio might be an easy obtainable, non-invasive and cost-effective method for predicting recurrence of disease in patients with non-muscle invasive bladder cancer.

What's known: Inflammation markers such as neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, red cell distribution width, mean platelet volume are emerging markers of host inflammation and have been shown to be an independent prognostic factor for various malignancies. Treatment of non-muscle invasive bladder cancer is determined by the risk stratifications that predict recurrence and progression of the disease, and there is no biomarker currently in use.

What's new: In our study, we demonstrated that lymphocyte-monocyte ratio may be used as a biomarker to further improve the accuracy of risk classifications for non-muscle invasive bladder cancer.

Keywords: Bladder cancer, inflammatory markers, prognosis, survival

INTRODUCTION:

Bladder cancer is the 7th most frequently diagnosed cancer in the male population in the world and its incidence decreases to 11th when both sexes are considered [1]. Most bladder cancers (75%) are not muscle-invasive at first diagnosis and usually have a good prognosis [2]. The difficulty in treating non-muscle invasive bladder cancer (NMIBC) is to minimize the risk of progression to muscle-invasive disease and recurrence while preserving the bladder and its function as long as possible. The European Cancer Research and Treatment Organization (EORTC) risk classification is used to measure these risks [3]. While intravesical chemotherapy or any additional treatment may not be required after resection in patients with a good prognosis, intravesical BCG is the preferred treatment for patients with poor prognosis. There has been several studies to find a biomarker that predicts the prognosis of bladder cancer and improve the accuracy of risk tables especcialy for intermediate and high risk groups. The role of inflammation on cancer development and progression gains in importance as we learn more about immune response [4]. Parameters such as neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), red cell distrubition width (RDW), mean platelet volume (MPV), which can be easily calculated in routine whole blood tests, are emerging markers of host inflammation and have been shown to be an independent prognostic factor for various malignancies [5–7]. In our study, we aimed to investigate the relationship of preoperative hematological inflammatory markers with recurrence and progression of the tumor in patients with non-muscular invasive bladder cancer.

MATERIALS AND METHODS:

After approval of the Dokuz Eylül University Ethics Committee was obtained (approval number: 2017/19-31), patients who admitted to the urology clinic between July 2017 and August 2018 and diagnosed with a mass lesion in bladder are included in our study. An informed consent was obtained from all patients who participated in this study. Patients who had muscle-invasive cancer and previously diagnosed with bladder cancer were excluded. Our exclusion criteria were another known malignancy, metastatic disease at the time of diagnosis, presence of an active clinical infection, a hematological or rheumatological disease or any medication that may affect blood count and blood transfusion in the last 2 weeks. Patients who have been recently diagnosed with systemic or local infections or who have suspected symptoms, such as fever, were excluded from the study. All patients went through physical examination preoperatively by an anesthesiologist routinely and patients who are suspected to have a pulmonary or upper respiratory tract infections are consulted to a pulmonologist. Patients with asymtomatic bacteriuria are also excluded. Ninety-four patients who met the criteria were included in the study and evaluated prospectively.

Blood samples were collected in EDTA containing tubes before transurethral resection of bladder tumor (TURB). All blood samples were analyzed using LH 780 analyzer (Beckman Coulter Inc., Miami, FL, USA). NLR, LMR, PLR, RDW and MPV values were calculated. If the patient had tests performed in last one month, this test was included in the study. If there are more than one test results in the last month, the result closest to the operation date was used. Neutrophil-lymphocyte ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Lymphocyte-monocyte ratio was calculated by dividing the absolute lymphocyte count by the absolute monocyte count. Platelet-lymphocyte ratio was calculated by dividing the platelet count by the absolute lymphocyte count. All patients underwent cystoscopy, and TURB was performed on tumoral formations observed during cystoscopy.

Patients were divided into risk groups according to EAU NMIBC guidelines and followed up [8]. Intravesical BCG treatment was applied to all intermediate and high-risk patients according to EAU recommendations [8].

The study endpoints were determined as progression-free survival and recurrence-free survival. Recurrence was defined as pathologically confirmed malignant tumor in the control cystoscopy after the first TURB [9]. Progression was defined as an increase in stage or grade of the tumor detected during follow-up, emerging lymph node, or distant metastasis [9,10].

Statistical Analysis

All statistical analyses were performed with SPSS version 24.0 (SSPS Inc, Armonk, NY). Mann-Whitney U test was used for the analysis of non-parametric data. For the parameters with a significant difference in the Mann-Whitney U test, a ROC curve was applied and cut-off points were determined. The recurrence-free survival and progression-free survival curves were created using the Kaplan-Meier method, and log-rank test was performed to compare survival between patient groups. Univariate and multivariate (backward Wald) Cox regression models were used to evaluate the relationship between clinicopathological features and recurrence and progression. A p-value <0.05 was considered statistically significant.

RESULTS:

The age of the patients ranged between 30 and 90, and the mean age was 67.7 ± 11.6. 90.4% of the patients were male and 9.6% were female. The mean follow-up was 11 ± 6.4 months. Recurrence was observed in 35.1% of patients during follow-ups. The mean recurrence time was 4.7 ± 4.3 months. The earliest recurrence occurred at 1 month and the latest recurrence occurred at 20 months. Patients with recurrence at 1 month were those who underwent full resection during the first TUR-B and new papillary tumors were detected during reTUR performed due to their high grade tumors or T1 stage. Progression was detected in 7.4% of the patients. The mean progression time was 8.7 ± 7.8 months. The earliest progression occurred at 1 month and at the 23rd month at the latest. Clinicopathological features of the patients are shown in table 1.

Mann-Whitney U test was performed to determine whether there is a relationship between hematological parameters and disease recurrence and progression (Table 2a, Table 2b). A statistically significant relationship was found between NLR (p = 0.01) and LMR (p = 0.038) values and recurrence . There was no significant relationship with other parameters. A statistically significant relationship was detected between progression and NLR only (p = 0.035).

Further analyzes were performed for the parameters that were found to be significant in non-parametric tests. By drawing the ROC curve for NLR and LMR, cut-off values were determined for the highest sensitivity and specificity values (shown in Fig. 1). The cut-off value for recurrence-free survival was 2.54 for NLR and 3.63 for LMR. A meaningful survival analysis model for progression could not be created due to the low number of patients progressed.

According to the determined cut-off points, patients divided into 2 groups and by Kaplan-Meier method, recurrence-free survival curves were generated (shown in Fig. 2a, Fig. 2b). One-year recurrence-free survival for NLR <2.54 and NLR> 2.54 was 74% and 41%, respectively (log-rank p = 0.013) . One-year recurrence-free survival for LMR>3.63 and LMR<3.63 was 77% and 48%, respectively (log-rank p = 0.014).

In univariate Cox reggression analysis NLR (p = 0.019) , LMR (p = 0.021) , tumor stage (p = 0.010) , tumor degree (p = 0.015) and single or multiple being (p = 0.020) were found to be statistically significant relationship with recurrence (Table 3).

In the multivariate Cox regression analysis, including age, gender, stage, grade, presence of CIS, lesion size, number and structure of lesions, NLR was observed to lose statistical significance with recurrence (p = 0.051). Whereas stage (p = 0.020) and LMR (p = 0.022) were shown to be independent predictors in recurrence-free survival (Table 3).

DISCUSSION:

Most bladder cancers (75%) are not muscle-invasive in the initial diagnosis and generally have a good prognosis. Between 30% and 80% of NMIBC cases will recur, and 1 to 45% will progress to muscle-invasive disease within 5 years [2]. Risk classifications such as European Organisation for Research and Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment (CUETO) models are widely used to predict these risks and to decide on appropriate treatment [3,11]. Risk classifications are performed according to clinical and pathological factors and there is no biochemical marker currently in use. In this regard, the role of inflammation in the neoplastic process has become evident.

Neutrophils are the first cells to respond in acute inflammation. Then, monocytes migrate to the tissue injury site under the guidance of chemotactic factors and differentiate into macrophages in the tissues [4]. After activation, macrophages are the main source of growth factors and cytokines affecting endothelial, epithelial and mesenchymal cells in the local microenvironment [4,12]. In particular, lymphocytes have strong antitumor immune function that can prevent the progression of tumors. Some lymphocyte subtypes, especially CD8 + T cells and memory T cells, have been shown to play an important role in tumor response [13]. Although the inflammatory response has an antitumor effect, this response has changed in people who develop cancer. Cells exposed to DNA damage and / or mutagenic attack continue to proliferate in a microenvironment rich in inflammatory cells and growth factors, in which case inflammation plays a role in stimulating tumor growth for these cells [14]. Major infammatory pathways which are involved in infammation-induced carcinogenesis mainly action through the transcription factors signal transducer and activator of transcription 3 (STAT3) and nuclear factor-κB (NF-κB) [15].

Parameters such as neutrophil-lymphocyte ratio, lymphocyte monocyte ratio, platelet lymphocyte ratio, MPV, RDW, which can be easily calculated in routine complete blood counts, are indicators of host inflammation and have been reported to be independent prognostic factors for various malignancies. High pre-treatment neutrophil-lymphocyte ratio have been shown to be associated with worse cancer-specific mortality in patients with upper urinary tract urothelial carcinoma (UTUC) which is particularly important for our subject due to its close relationship with bladder tumours [6,7]. Also, in EAU UTUC guidelines, NLR is mentioned as a preoperative prognostic factor [16]. As for NMIBC, in EAU guidelines it is stated that preoperative NLR may have prognostic value, however, this data needs further validation [8]. In a prospective study conducted by Albayrak et al, it was shown that NLR in NMIBC patients was successful in predicting recurrence and progression, but this significant difference disappeared when the age factor was added to the analysis [17].

In another prospective study of 178 patients, NLR has been shown to be a useful parameter in predicting recurrence in NMIBC patients and not in predicting progression [18]. Likewise in a similar study conducted in patients with T1 bladder tumor, it was reported that NLR was successful in predicting recurrence but was not related to progression [19]. According to Mano et al, high NLR is associated with both recurrence and progression [20]. In another study performed on patients with tumors larger than 3 cm, a significant difference was reported between the NLR mean values of MIBC and NMIBC patients [21]. In addition to these contradictory results in the literature, in our study, NLR is found as a parameter related to recurrence and progression in the non-parametric analysis. However, statistical significance was lost when evaluated with other factors that may affect recurrence ($p = 0.051$). In a meta-analysis of six studies, high preoperative NLR was found to be associated with an increased risk of recurrence and progression in NMIBC patients [22].

In a study comparing patients with bladder urothelial carcinoma with the normal population, NLR and PLR have been shown to be independent predictive factors for urothelial carcinoma, conversely, there was no relationship with urothelial carcinoma and RDW and LMR [23]. In all of our univariate and multivariate analyzes, LMR was found to be successful in predicting NMIBC recurrence, whereas no statistically significant relationship was found between progression and LMR. There was no significant relationship between PLR and any parameters.

Thrombocytosis is associated with decreased survival in various cancers such as lung cancer, ovarian cancer, endometrial cancer, rectal cancer, kidney cancer, stomach cancer, pancreatic cancer, and breast cancer [24–26]. Increased platelets facilitate the progression and metastasis of cancer by promoting angiogenesis and tumor cell formation in remote areas [27]. For bladder cancer, high expression of platelet-derived endothelial cell growth factor is clearly associated with tumor progression of bladder cancer [28]. In addition, platelet-derived growth factor receptor beta has been found as a biomarker to predict NMIBC recurrence [29]. However, these indices that reflect activated platelets are expensive and have not been widely evaluated in the clinical setting. Therefore, it is thought that MPV can be used as a marker of platelet activation [30]. It was reported in the literature that, decreased MPV has been shown to be associated with poor prognosis in invasive bladder cancer patients [30]. In our study, no statistically significant relationship was found between MPV and any prognostic parameters.

Previous studies suggest that there is a relationship between RDW and overall-survival and cancer-specific survival of some cancers [31,32]. In our patient group, no significant relationship was found between RDW and recurrence-free survival or progression-free survival.

The major limitation of our study is a relatively low number of patients from a single institution. We acknowledge that recurrence and progression in NMIBC are a complex matter; so is the impact of inflammation and any markers of inflammation on such events; this is hardly reflected in a rather small series. Another one is that, due to the low number of patients with tumor progression, a meaningful model could not be established and a progression-free survival analysis could not be performed. Besides, biomarkers themselves has some limitations. Laboratory values do not allow any statements about molecular pathological or histological properties of the tumor. Furthermore, laboratory values are dependent on pretreatment factors such as nutritional deficiencies, comorbidities, medication, lifestyle.

CONCLUSION:

Management of non-muscle invasive bladder cancer is carried out in a balance between protecting the patient from the side effects of radical surgical treatment and intravesical treatments and preventing progression and recurrence of the disease. We believe that the lymphocyte/monocyte ratio is a promising marker as an easy-to-obtain, non-invasive and cost-effective method in predicting the recurrence of the disease and deciding the appropriate treatment option. Due to contradictory results in the literature, randomized, prospective studies are needed on larger cohorts.

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Tables:

Table 1- Baseline characteristics of the patients

Characteristic	n (%)

Number of patiens	94 (100)
Gender	
Male	85 (90,4)
Female	9 (9,6)
Age	
>65	58 (61,7)
<65	36 (38,3)
Tumor stage	
pTa	45 (47,9)
pT1	49 (52,1)
Tumor grade	
Low grade	47 (50)
High grade	47 (50)
Concurrent CIS	
Yes	15 (16)
No	79 (84)
Number of tumors	
Single	52 (55,3)
Multiple	42 (44.7)
Tumor pattern	
Papillary	83 (88,3)
Solid	11 (11,7)
Tumor size	
<3cm	34 (36,1)
>3cm	60 (63,9)
Recurrence	
Yes	33 (35,1)
No	61 (64,9)
Progression	
Yes	7 (7,4)
No	87 (92,6)
EAU risk group	
Low	26 (27,7)
Intermediate	14 (14,9)
High	54 (57,4)

CIS: carcinoma in situ

EAU: European Associaton of Urology

Table 2a- Comparison of hematological parameters between groups of recurrence

Recurrence	**Yes**	**No**	**p**
n	33	61	
NLR *median* *(min-max)*	2,6 (1-4,7)	2,0 (0,8-4,6)	0,010*

LMR *median* *(min-max)*	3,1 (1,5-5,5)	4,0 (1,5-7,7)	0,038*
PLR *median* *(min-max)*	120,5 (64,1-215,2)	116,6 (40-235,3)	0,447
RDW *median* *(min-max)*	14,1 (12,1-33,1)	14,4 (12,5-25,3)	0,463
MPV *median* *(min-max)*	8,9 (6,6-12)	8,6 (6,7-11,9)	0,595

**p<0.05, statistically significant difference.*

NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, PLR: platelet-lymphocyte ratio, RDW: red cell distribution width, MPV: mean platelet volume, min: minimum, max: maximum

Table 2b- Comparison of hematological parameters between groups of progression

Progression	**Yes**	**No**	**p**
n	7	87	
NLR *median* *(min-max)*	2,8 (2,2-4,1)	2,1 (0,8-4,7)	0,035*

LMR *median* *(min-max)*	3,6 (2,7-5,6)	3,7 (1,5-7,7)	0,713
PLR *median* *(min-max)*	123,5 (81-197,1)	117,8 (40-235,3)	0,823
RDW *median* *(min-max)*	13,7 (13,6-15,5)	14,4 (12,1-33,1)	0,589
MPV *median* *(min-max)*	9,5 (8,3-10,4)	8,7 (6,6-12)	0,246

**p<0.05, statistically significant difference.*

NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, PLR: platelet-lymphocyte ratio, RDW: red cell distribution width, MPV: mean platelet volume, min: minimum, max: maximum

Table 3- Univariate and multivariate Cox Regression analyses for recurrence-free survival

Variable (Reference)	**Univariate analysis**			**Multivariate analysis**		
	OR	**%95 CI**	**P**	**OR**	**%95 CI**	**p**

NLR (>2,54)	2,26	1,14-4,50	0,019*	1,99	0,99-3,98	0,051
LMR (<3,63)	2,39	1,14-5,03	0,021*	2,41	1,14-5,07	0,022*
Age (Continous variabl)	1,02	0,99-1,06	0,082			
Gender (Male)	1,46	0,34-6,13	0,605			
Stage (T1)	2,74	1,27-5,90	0,010*	2,47	1,13-5,36	0,020*
Grade (High grade)	2,52	1,20-5,31	0,015*			
Concurrent CIS (Yes)	1,62	0,72-3,61	0,238			
Tumor size (Continous variabl)	1,00	0,99-1,01	0,296			
Number of tumors (Multipl)	2,32	1,14-4,75	0,020*			
Tumor pattern (Solid)	1,19	0,42-3,42	0,734			

**p<0.05, statistically significant difference.*

OR: odds ratio, CI: confidence interval, NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte-monocyte ratio, CIS: carcinoma in situ

Figure legends:

Figure 1- Receiver operator characteristics (ROC) curves of neutrophil-lymphocyte ratio and leukocytemonocyte ratio for predicting recurrence

Figure 2a- Kaplan-Meier curves for recurrence-free survival of the patients and neutrophil-lymphocyte ratio values.

Figure 2b- Kaplan-Meier curves for recurrence-free survival of the patients and leukocyte-monocyte ratio values.