ORIGINAL RESEARCH

Neutrophil-lymphocyte ratio as a predictor of recurrence and progression in patients with high-grade pT1 bladder cancer

Mehmet Emin Ozyalvacli, MD;* Gulzade Ozyalvacli, MD;† Ramazan Kocaaslan MD;§ Kursat Cecen, MD;§ Ugur Uyeturk, MD;* Eray Kemahlı, MD;* Adnan Gucuk, MD*

*Department of Urology, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey; †Department of Pathology, Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey; §Department of Urology, Faculty of Medicine, Kafkas University, Kars, Turkey

Abstract

Introduction: We investigated the value of the preoperative neutrophil-lymphocyte ratio (NLR) in predicting recurrence and progression of high-grade pT1 non-muscle-invasive tumour in patients with bladder cancer during a 5-year follow-up period.
Methods: We retrospectively reviewed data of 1100 patients with bladder cancer; these patients underwent transurethral resection and were monitored at multiple centres from 2008 to 2013. In total, 166 consecutive and newly diagnosed patients with high-grade pT1 tumours were included in this study. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.
Results: Of the 166 patients, 152 were male. The patients were evaluated as two separate groups in terms of recurrence and progression. The mean follow-up period was 24.2 months (interquartile range 13.8–36.6 months). A statistically significant difference was found between recurrence and tumour size ($p = 0.001$), number of tumours ($p < 0.001$), NLR ($p < 0.001$), and smoking ($p = 0.007$). No statistically significant correlation was found between NLR and progression. According to receiver operating characteristic (ROC) analysis, the optimum cut-off value for the NLR was ≥2.43 (74% sensitivity, 60% specificity, $p < 0.001$; area under the curve [AUC] 0.687, 95% confidence interval [CI] 0.607–0.767). Multivariate logistic regression analysis determined that the following factors were independent predictors of recurrence in patients with high-grade pT1 non-muscle-invasive bladder cancer: tumour number (OR 5.32, 95% CI 2.10–12.90), NLR of ≥2.43 (OR 2.587; 95% CI 1.156–5.789), and smoking (OR 4.17, 95% CI 1.31–13.21).
Conclusion: A high preoperative NLR may play an important role in predicting recurrence of superficial transitional cell type high-grade pT1 bladder tumours. Prospective studies are required to validate the role of NLR as a prognostic marker in high-grade pT1 bladder tumours.

Introduction

At diagnosis, about 75% of bladder cancers are non-muscle-invasive tumours (Ta, T1, and carcinoma in situ).[1] Of these, 20% are pT1 tumours, with 5-year recurrence and progression rates of 30% to 80% and 1% to 50%, respectively.[2-4] Recurrence and progression of these tumours are predicted based on the scores and risk tables of the European Organization for Research and Treatment of Cancer (EORTC); no biochemical indicators are currently used for this purpose. It is particularly difficult to predict the behaviour of high-grade pT1 superficial bladder tumours over time. Such tumours either do not show recurrence or progress to muscle-invasive and metastatic stages. This complicates the clinician's decision-making process regarding follow-up and treatment.[5]

Many studies have shown that inflammation plays a role in tumour response to systemic treatment, tumour metastasis, and angiogenesis in the formation and progression stages of most cancer types.[6] The neutrophil-lymphocyte ratio (NLR) is an indicator of systemic inflammation and is convenient and inexpensive to measure. Recent studies have demonstrated that a high NLR is an important marker of recurrence and poor prognosis in colorectal, gastric, ovarian, and thyroid cancers, as well as in renal and hepatocellular carcinoma and malignant mesothelioma.[7-13]

Our aim in this study was to determine the value of the preoperative NLR in predicting recurrence and progression of high-grade pT1 non-muscle-invasive bladder tumours during a 5-year follow-up period.

Methods

Patient selection

We retrospectively evaluated the data of 1100 patients with bladder cancer who underwent transurethral resection and

were monitored at 4 medical centres from 2008 to 2013. Approval for this study was obtained from the ethics committee at our university. The tumours were graded according to the World Health Organization-International Society of Urologic Pathology 2004 guidelines and the TNM 2002 staging system. All pertinent laboratory and pathology results (tumour size and number, presence of carcinoma in situ, re-transurethral resection [TUR], postoperative immunotherapy and chemotherapy), and medical data were obtained from the hospital databases. The recurrence and progression status was determined for each patient based on these data. Recurrence was defined as the relapse of transitional cell carcinoma of the bladder at any pathological stage after initial surgery. Re-TUR was defined as the TUR which was performed 2 to 6 weeks after the initial transurethral resection. Patients with non-transitional cell bladder cancers, carcinoma in situ, acute inflammatory disease, bleeding disorders, hematological disorders, autoimmune diseases, any malignancies other than bladder tumour, preoperative active infection, or a history of splenectomy as well as patients on maintenance intravesical chemotherapy after transurethral resection were excluded from the study. Of the 1100 examined patients, we consecutively selected 166 patients with pathologically newly diagnosed high-grade pT1 tumours after initial surgery. When we were designing our study, we thought that the systemic inflammatory effects of pTa and low-grade superficial bladder tumors would be very low. Among these tumours, pT1 G3 tumours would be at a greater risk of recurrence and progression; therefore, we included only patients with pT1 G3 tumours. The follow-up period was calculated from the date of surgery, to either the last follow-up or death.

Blood tests

Data obtained from the patients' routine preoperative test results included the neutrophil count, lymphocyte count, red cell distribution width, and mean platelet volume. The NLR was determined by dividing the absolute neutrophil count by the absolute lymphocyte count.

Statistical methods

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY). Continuous variables were tested for normality by the Kolmogorov–Smirnov test. Normally distributed data were presented as means ± standard deviation. The rates and proportions of discrete variables were determined using the chi-squared test. The median with data range (minimum to maximum) was used for non-normally distributed data. The independent samples t-test and Mann–Whitney U test were used for parametric and nonparametric groups, respectively. Correlations between tumour size and recurrence were evaluated using Spearman's rank correlation coefficient. Potential predictors of recurrence and progression in individual patients with superficial transitional cell cancer of the bladder were initially compared, and variables that showed a p value of <0.05 were included in a logistic regression model. Results were expressed as odds ratio (OR) and 95% confidence interval (CI). The two-sided p value of <0.05 was considered statistically significant.

Results

In total, 166 patients were enrolled in the study (152 male, 14 female). The patients were evaluated as two separate groups in terms of recurrence and progression. The mean follow-up period was 24.2 months (interquartile range 13.8–36.6 months).

Spearman's correlation test showed a statistically significant positive correlation between tumour size and recurrence ($r = 0.368$, $p < 0.001$). In the recurrence group, the tumour size was ≤3 cm in 20 patients (31.2%) and >3 cm in 45 patients (69.2%). A statistically significant difference was found between recurrence and tumour size ($p < 0.001$). A statistically significant positive correlation was also found between tumour size and progression ($r = 0.171$, $p = 0.028$). In the progression group, the tumour size was ≤3 cm in 6 patients (31.6%) and >3 cm in 13 patients (68.4%). However, there was no statistically significant difference between progression and tumour size ($p = 0.097$) (Table 1).

After Spearman's correlation analysis there was positive correlation between tumour number and recurrence ($r = 0.361$, $p < 0.001$). Recurrence rates were significantly higher in patients with multiple tumours than in patients with a single tumour (59.4% vs. 40.6%, respectively, $p < 0.001$). There was also a positive correlation between tumour numbers and progression ($r = 0.211$, $p = 0.006$). Progression rates were significantly higher in patients with multiple tumours than in patients with a single tumour (66.7% vs. 33.3%, respectively, $p = 0.006$) (Table 1). Similarly, there was a positive correlation between re-TUR and recurrence ($r = 0.25$, $p = 0.001$); recurrence rates were significantly higher in patients with re-TUR than in patients who were treated once (41.3% vs. 18.4%, respectively, $p = 0.001$). There was no statistically significant relation between progression rates and re-TUR ($p = 0.080$).

The Spearman's correlation test revealed a statistically significant relation between smoking and reccurence ($r = 0.246$ $p = 0.007$). Among the patients in the smoking group, 48 (64%) had reccurence, while 36 (86.7%) did not. Consequently, there was a statistically significant relation between smoking and reccurence ($p = 0.007$).

The NLR was 2.8 ± 2.7 (range: 1.4–16.8) in the recurrence group and 2.2 ± 1.2 (range: 0.7–8.2) in the non-recurrence group. A significant correlation was found between recur-

rence and the NLR. According to receiver operating characteristic (ROC) analysis, the optimum cut-off value for the NLR was ≥2.43 (74% sensitivity, 60% specificity, $p < 0.001$; area under the curve [AUC] 0.687, 95% CI, 0.607–0.767) (Fig. 1). The NLR was 2.6 ± 3.4 (range: 1.9–16.8) in the progression group and 2.5 ± 1.7 (range: 0.7–16.3) in the non-progression group. No significant correlation was found between progression and the NLR ($p = 0.34$) (Table 1).

In univariate analyses, tumour size greater than 3 cm, multiple tumors, and NLR of ≥2.43 were risk factors for recurrence. Multivariate logistic regression analysis determined that the following factors were independent predictors of recurrence in patients with high-grade pT1 non-muscle-invasive bladder cancer: tumour number (OR 5.32, 95% CI 2.10–12.90), NLR of ≥2.43 (OR 2.587; 95% CI 1.156–5.789), and smoking (OR 4.17, 95% CI 1.31–13.21) (Table 2). Since there was a significant correlation between tumour size and number, only tumour number was used in the multivariate analysis.

Multivariate logistic regression analysis determined only tumour number as an independent predictive factor to determine progression in patients with high-grade pT1 non-muscle-invasive bladder cancer (OR 3.29; 95% CI 1.08–10.06) (Table 3).

Discussion

Many studies have demonstrated a link between systemic inflammation and cancer development and prognosis.[6,14-16] The NLR indicates the presence of systemic inflammation. The correlation between a high NLR and poor prognosis and recurrence in patients with cancer has been confirmed.[9,13,17-22] In the present study, the optimal cut-off value of the NLR as an indicator of recurrence and progression in patients with bladder cancer was ≥2.43. Patients with an NLR above this value exhibited significantly higher recurrence, but no progression, highlighting the potential role of the NLR in pT1 superficial bladder tumours. There is limited information on this topic in the literature. To our knowledge, this is the first clinical study investigating the correlation between the NLR and recurrence in patients with only high-grade pT1 bladder tumours.

The neutrophil and lymphocyte counts play important roles in systemic inflammation. The neutrophil count is increased by anti-apoptotic markers that affect tumour growth and progression (NF-κB), growth factors, and pro-angiogenic factors (VEGF).[23-25] The lymphocytic response is the main component in the control of cancer progression. Lymphocytopaenia leads to a decrease in the cellular immune response. While some studies have reported that
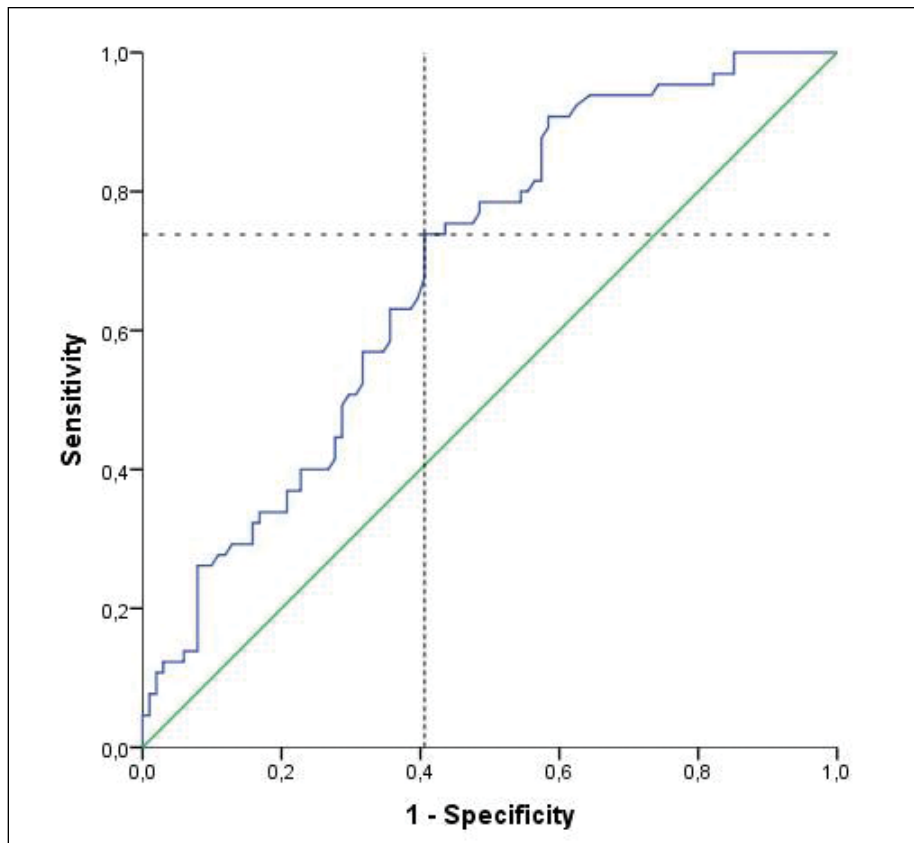

Fig. 1. Assesment of cut off value of neutrophil-to-lymphocyte ratio to predict recurrence.

Table 1. Comparison of patients according to the presence of recurrence and progression

		Recurrence			Progression		
		Absent N = 101	Present N = 65	*p* value	Absent N = 147	Present N = 19	*p* value
Sex (F/M)		6/95	8/57	0.15	11/136	3/16	0.22
Age (year)*		67.3 ± 11	67.7 ± 9.4	0.84	67.5 ± 10.5	67.5 ± 10.2	1
MPV*		8.2 ± 1.2	8.5 ± 1.3	0.09	8.4 ± 1.3	8.2 ± 1.2	0.57
RDW*		15.6 ± 1.6	15.5 ± 1.3	0.67	15.6 ± 1.5	15.4 ± 1.3	0.46
NLR¥		2.2 (0.7–8.2)	2.8 (1.4–16.8)	<0.001	2.5 (0.7–16.3)	2.6 (1.9–16.8)	0.34
BCG usage		36 (35.6%)	17 (26.2%)	0.2	50 (34.0%)	3 (15.8%)	0.11
Single dose mitomicyn		20 (19.6%)	14 (21.9%)	0.725	30 (20.3%)	4 (22.2%)	0.846
Tumour size (cm)	≤3	65 (64.4%)	20 (30.8%)	0.001	79 (53.7%)	6 (31.6%)	0.047
	>3	36 (35.6%)	45 (69.2%)		68 (46.3%)	13 (68.4%)	
No. tumours	Single	78 (76.5%)	26 (40.6%)	<0.001	98 (66.2%)	6 (33.3%)	0.006
	Multiple	24 (23.5%)	38 (59.4%)		50 (33.8%)	12 (66.7%)	
Smoking		48 (64%)	39 (86.7%)	0.007	77 (70.6%)	10 (90.9%)	0.15

*mean ± standard deviation; ¥median(minimum-maximum); BCG: Bacillus Calmette-Guerin; MPV: mean platelet volume; NLR: neutrophil-lymphocyte ratio; RDW: red cell distribution.

decreased T-cell activity inside the tumour speeds up primary tumour progression, other studies have shown a link between lymphocytes and the cell-mediated response with respect to tumour infiltration;. Additionally, a low level of lymphocytic infiltration at tumour margins indicates a poor prognosis.[17,26,27] The fact that the NLR indicates only part of the inflammatory response somewhat limits its value as a marker. However, the NLR is still a convenient, inexpensive, and reproducible parameter that demonstrates the link between inflammation and tumour development.

Few studies have examined the link between an increased NLR and muscle-invasive bladder cancers. Some of these studies have shown that the risk of invasion significantly increases beyond a certain cut-off NLR value and that a high NLR is significantly correlated with the pathologic stage.[28-30] In a recent study that evaluates the NRL in terms of reccurence and progression in non-invasive bladder cancer, the NLR cut-off point for reccurence and progression was 2.43 and 2.41, respectively. A statistically significant increase in terms of reccurence and progression has been found among individuals with NLR levels over the cut-off limit. A positive correlation between tumour grade and higher levels of NRL has been found as well.[31] In our study, while the cut-off limit

for NLR was able to establish a significant difference in reccurence, we could not find a significant difference regarding progression. In the study mentioned above patients with pTa and pT1 tumours were evaluated;[31] in our study, however, we evaluated only high-grade pT1 tumours. Therefore we considered our study more significant regarding case homogenity and number.

Several recent studies also examined the link between the preoperative NLR and recurrence of other types of cancer. Motomura and colleagues determined a NLR cut-off value of ≥4 for recurrence of hepatocellular carcinoma.[19] Mallappa and colleagues found that the stage of colorectal cancer and a preoperative NLR of >5 were important independent risk factors for recurrence.[21] In a study of recurrence of clear-cell renal carcinoma, Ohno and colleagues reported a significant difference in the 10-year survival rate between patients with an NLR of ≥2.7 and those with an NLR of <2.7.[22] All of these findings are consistent with the results obtained in our present study regarding the NLR cut-off value beyond which recurrence significantly increased.

In a study carried out with patients on sunitinib for metastatic renal cell carcinoma, Keizman and colleagues found that NLR values lower than 3 prior to treatment correlated

Table 2. Univariate and multivariate logistic regression analysis of independent predictive factors for recurrence in high–grade pT1 bladder cancer

		Univariate analysis			Multivariate analysis		
	Reference	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	≥65	0.95	0.50–1.81	0.87	1.09	0.42–2.85	0.84
Sex	Female	2.29	0.75–6.93	0.13	2.58	0.40–16.64	0.31
BCG Usage		0.66	0.33–1.32	0.24	0.75	0.33–2.23	0.75
No. tumours	Multiple	4.75	2.41–9.35	<0.001	5.32	2.1–12.9	<0001
NLR	≥2.43	4.29	2.15–8.54	<0.001	3.81	1.50–9.67	0.005
Smoking		3.66	1.37–9.74	0.007	4.17	1.31–13.210	0.015

OR: odds ratio; CI: confidence interval; BCG: Bacillus Calmette–Guerin; NLR: neutrophil–lymphocyte ratio.

Table 3. Univariate and multivariate logistic regression analysis of independent predictive factors for progression in high-grade pT1 bladder cancer

	Reference	Univariate analysis			Multivariate analysis		
		OR	95% CI	*p value*	OR	95% CI	*p value*
Age	≥65	0.9	0.33¬–2.47	0.842	0.73	0.25–2.15	0.570
Sex	Female	2.5	0.62–9.93	0.183	1.97	0.43–9.03	0.383
BCG Usage		0.39	0.11–1.42	0.141	0.47	0.13–1.77	0.265
No. tumours	Multiple	3.92	1.4–11.06	0.006	3.29	1.08–10.06	0.036
NLR	≥2.43	1.79	0.64–5.04	0.262	1.47	0.49–4.38	0.490
Smoking		1.52	0.57–4.1	0.403	1.08	0.37–3.18	0.891

OR: odds ratio; CI: confidence interval; BCG: Bacillus Calmette-Guerin; NLR: neutrophil-lymphocyte ratio.

with overall survival and progression-free survival.[32] In a recent meta-analysis evaluating the role of NLR in solid tumours, overall survival, progression-free survival and recurrence-free survival negatively correlated with NRL values over the cut-off point.[33] Contrary to previous studies, in our study, no statistically correlation was found between NLR and progression.

Conclusion

Our results indicate that a high preoperative NLR can play an important role in determining recurrence of superficial transitional cell type high-grade pT1 bladder tumours. However, it did not accurately predict progression in this study, possibly because of the short follow-up period and small sample size. Prospective studies are required to validate the role of NLR as a prognostic marker in high-grade pT1 bladder cancers.

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Correspondence: Dr. Mehmet Emin Ozyalvacli, Abant İzzet Baysal Üniversitesi Tıp Fakültesi, Gölköy 14280 Bolu/Turkey; dreminoz@gmail.com