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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

The Preoperative Neutrophil-to-lymphocyte Ratio is a Novel Biomarker for Predicting Worse Clinical Outcomes in Non-muscle Invasive Bladder Cancer Patients with a Previous History of Smoking

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ABSTRACT

Purpose. We speculated that a heterogeneous population of non-muscle invasive bladder cancer (NMIBC) patients with a previous history of smoking may be more precisely stratified by a biomarker associated with tumor aggressiveness and then focused on the preoperative neutrophil-to-lymphocyte ratio (pre-NLR), which is a simple index of systemic inflammation.

Methods. Our study population comprised 605 patients initially diagnosed with NMIBC at our 3 institutions between 1995 and 2013. We analyzed the relationships between pre-NLR levels and clinical outcomes in NMIBC. A pre-NLR level of ≥2.2 was defined as elevated according to a calculation by a receiver-operating curve analysis.

Results. In overall, a total of 296 patients (48.9 %) had pre-NLR ≥ 2.2, and the pre-NLR level was one of independent risk factors for tumor recurrence and stage progression. Among 344 patients with a previous history of smoking, 184 (53.5 %) had pre-NLR ≥ 2.2 and the pre-NLR level was one of independent risk factors for tumor recurrence and stage progression. The 5-year recurrence-free survival and progression-free survival rates in patients with pre-NLR < 2.2 were 66.3 and 97.5 %, respectively, which were significantly higher than those in their counterparts (31.7 and 90.4 %, $p < 0.001$). In either subgroup of patients who were current smokers ($N = 175$) or former smokers ($N = 169$), the pre-NLR level was the only independent risk factor for tumor recurrence. The pre-NLR level was not associated with tumor recurrence or stage progression in 261 nonsmoking patients.

Conclusions. Pre-NLR levels may be a useful marker for identifying worse clinical outcomes in NMIBC patients, particularly those with a previous history of smoking.

Bladder cancer is the most common cancer of the urinary tract, with approximately 75 % of cases being non-muscle invasive bladder cancer (NMIBC).[1] Although the prognosis of NMIBC is good, the 5-year recurrence and progression rates are 30–80 and 1–45 %, respectively.[2]

Smoking is the most important risk factor for the occurrence of bladder cancer.[3,4] Furthermore, we previously revealed that NMIBC patients who smoked had a significantly higher incidence of tumor recurrence and that refraining from smoking for more than 15 years may affect the prevention of subsequent tumor recurrence.[5] However, some patients with a previous smoking history had good clinical outcomes, whereas others had worse clinical outcomes. Therefore, we speculated that the heterogeneous population of NMIBC patients with a previous history of smoking may be more precisely stratified and a biomarker may be used to identify a subgroup of patients with a smoking history and worse clinical outcomes. We focused on the neutrophil-to-lymphocyte ratio (NLR), which is a simple index of systemic inflammation and a biomarker associated with tumor aggressiveness. Many studies have demonstrated that an elevated NLR is associated with worse clinical outcomes in a number of malignancies, including NMIBC.[6–13] In addition, a recent study showed that smoking

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is associated with altered systemic immune and inflammation marker levels, particularly in heavy smokers.[14]

Therefore, we determined whether preoperative NLR (pre-NLR) levels have a prognostic impact on clinical outcomes, particularly in NMIBC patients with a previous history of smoking.

MATERIALS AND METHODS

Patient Selection

We retrospectively reviewed medical records between 1995 and 2013 archived at Keio University Hospital, Saiseikai Central Hospital, and Saitama Medical University Hospital. During this period, 1328 patients underwent transurethral resection of bladder tumors (TUR-BT) at these 3 institutions. A total of 1136 patients were initially diagnosed with NMIBC. We excluded 38 patients who died or were lost to the follow-up within 3 months from TUR-BT and 443 for whom detailed data on the smoking status were not obtained. After excluding patients without a full set of blood data, those with active infection accompanied by fever, and those with chronic inflammatory or autoimmune diseases at the time of TUR-BT, the remaining 605 patients were assessed in the present analysis.

Patients were followed-up postoperatively with cystoscopy and urinary cytology every 3 months for 2 years, every 6 months for the next 3 years, and then annually thereafter. Excretory urograms and/or computed tomography were used to evaluate the upper urinary tract every year for 5 years after the treatment.

Patients Stratified by Smoking Statuses

Data on self-reported cigarette smoking statuses including the number of cigarettes per day (CPD), number of years of smoking, age at smoking initiation, and the smoking cessation period were obtained by an interview with attending physicians as part of the patient history at the initial consultation. These data were confirmed by a resident or fellow in a secondary interview at TUR-BT. In the present study, smoking statuses were classified into two groups: nonsmokers and patients with a positive smoking history. Patients were classified as non-smokers, those who had never smoked during their lifetime, patients with a previous smoking history including former smokers ($N = 169$), and current smokers ($N = 175$).

Calculation for NLR

The laboratory data assessed including white blood cells, neutrophils, and lymphocytes in the analyses were obtained just before TUR-BT for initially diagnosed NMIBC. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The ideal cutoff value of NLR was calculated by applying a receiver-operating curve analysis. As a result, the ideal cutoff values of NLR for tumor recurrence and stage progression were 2.2 and 2.38, respectively. In the present study, we stratified patients into two groups using a cutoff value for NLR of 2.2.

Statistical Analysis

The relationships between clinicopathological features and pre-NLR were analyzed by the χ^2 test or Mann–Whitney *U* test. Tumor recurrence was defined as first relapse in the bladder after first TUR-BT, regardless of the tumor stage. Tumor progression was defined as the tumor recurrence of equal or more than pT2 and/or metastasis to the lymph nodes and/or other organs. The recurrence-free survival (RFS) and progression-free survival (PFS) rates were estimated using the Kaplan–Meier curves and compared using the log-rank test. Independent variables included in the present study were patient age (<70 vs. ≥ 70 years), sex, tumor grade (low vs. high), tumor stage (Ta vs. T1), multifocality (solitary vs. multiple), tumor size (<3 vs. ≥ 3 cm), presence or absence of concomitant CIS, whether intravesical BCG therapy was performed, smoking status, and pre-NLR. Differences among groups were considered significant at $p < 0.05$. These analyses were performed with the SPSS v. 22.0 statistical software package (IBM Corp., Somers, NY).

RESULTS

Relationship Between Pre-NLR and Clinicopathological Features in the Overall Patient Population

Overall, 491 patients (81.2 %) were male and 114 (18.8 %) were female. The mean age at initial TUR-BT was 68 years (range 21–94). The median time from initial TUR-BT until the date of the last follow-up was 68.8 months (range 4.5–237). A total of 296 patients (48.9 %) had pre-NLR $\geq$ 2.2 and 309 (51.1 %) had pre-NLR $<$ 2.2. The relationships between pre-NLR and clinicopathological characteristics in all patients are shown in Table 1. Significant differences were observed in sex and previous smoking history between patients with pre-NLR $\geq$ 2.2 and pre-NLR $<$ 2.2.

Prognostic Significance of Pre-NLR on Tumor Recurrence and Stage Progression in the Overall Patient Population

Tumor recurrence developed in 255 patients (42.1 %), consisting of 160 patients with pre-NLR $\geq$ 2.2 and 95

TABLE 1 Association between pre-NLR and clinicopathological features in all patients

	Pre-NLR ≥ 2.2 ($n = 296$)	Pre-NLR < 2.2 ($n = 309$)	p value
Sex			0.001
Male	257 (86.8 %)	234 (75.7 %)	
Female	39 (13.2 %)	75 (24.3 %)	
Age at diagnosis (years)			0.133
Mean ± SD (range)	69 ± 12 (29–94)	68 ± 12 (21–90)	
Smoking history			0.011
Yes	184 (62.2 %)	160 (51.8 %)	
No	112 (37.8 %)	149 (48.2 %)	
Tumor grade			0.134
Low	189 (63.9 %)	178 (57.6 %)	
High	107 (36.1 %)	131 (42.4 %)	
Tumor stage			0.117
Ta	193 (65.2 %)	220 (71.2 %)	
T1	103 (34.8 %)	89 (28.8 %)	
Tumor multiplicity			0.33
Solitary	150 (50.7 %)	144 (46.6 %)	
Multiple	146 (49.3 %)	165 (53.4 %)	
Tumor size (cm)			0.102
<3	153 (83.2 %)	172 (89.1 %)	
≥3	31 (16.8 %)	21 (10.9 %)	
Unknown	112	116	
Concomitant CIS			0.291
Yes	27 (9.1 %)	37 (12.0 %)	
No	269 (90.9 %)	272 (88.0 %)	
BCG therapy			0.167
Performed	128 (43.2 %)	151 (48.9 %)	
Not performed	168 (56.8 %)	158 (51.1 %)	

NLR neutrophil-to-lymphocyte ratio, *SD* standard deviation, *CIS* carcinoma in situ, *BCG* bacillus Calmette–Guérin

patients with pre-NLR < 2.2. A Kaplan–Meier curve revealed that the rate of tumor recurrence was significantly lower for patients with pre-NLR < 2.2 than for their counterparts ($p < 0.001$, Fig. 1a). The 5- and 10-year RFS rates were 68.4 and 59.3 % for patients with pre-NLR < 2.2 and 46.0 and 32.1 % for patients with pre-NLR ≥ 2.2, respectively. Table 2 shows the results of uni- and multivariate analysis for tumor recurrence in overall NMIBC patients. The multivariate analysis revealed that pre-NLR ≥ 2.2 (hazard ratio: HR 2.08, $p < 0.001$) was an independent risk factor for tumor recurrence in addition to a previous history of smoking (HR 2.1, $p < 0.001$), multiple tumors (HR 1.75, $p < 0.001$), and not performing BCG therapy (HR 1.81, $p < 0.001$).

Tumor progression developed in 38 patients (6.28 %), consisting of 26 patients with pre-NLR ≥ 2.2 and 12 with pre-NLR < 2.2. A Kaplan–Meier curve revealed that the rate of stage progression was significantly lower for patients with pre-NLR < 2.2 than for their counterparts ($p = 0.016$; Fig. 1b). The 5- and 10-year PFS rates were 96.4 and 91.4 % for patients with pre-NLR < 2.2 and 91.8 and 90.0 % for patients with pre-NLR ≥ 2.2, respectively. Table 2 shows the results of uni- and multivariate analysis for stage progression in overall NMIBC patients. The multivariate analysis identified T1 tumors (HR 2.1, $p = 0.035$), multiple tumors (HR 2.75, $p = 0.011$), and pre-NLR ≥ 2.2 (HR 2.37, $p = 0.016$) as independent risk factors for stage progression. Similar results were also observed using a cutoff value of 2.43, which is the mean value of NLR, and that of 2.16, which is the median value of NLR in the overall population, and furthermore that of 2.38, which is the ideal cutoff value for stage progression, and that of 2.5, which is frequently used in previous studies.[15,16]

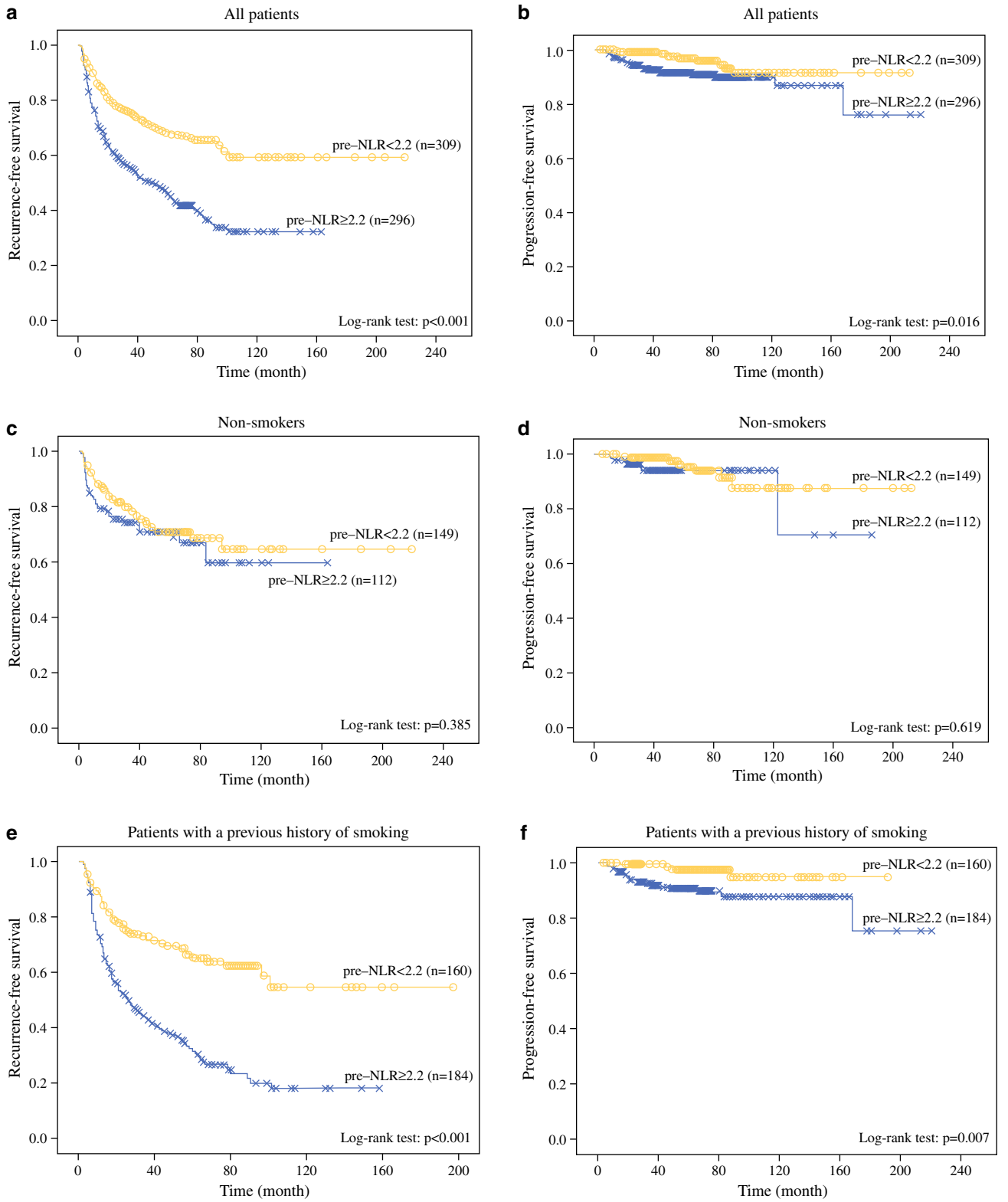

FIG. 1 Kaplan–Meier curve of recurrence-free survival in **a** the overall population, **c** nonsmokers, and **e** patients with a previous history of smoking and progression-free survival in **b** the overall population, **d** nonsmokers, and **f** patients with a previous history of smoking, as stratified by the preoperative NLR level

TABLE 2 Uni- and multivariate analysis for tumor recurrence and progression in 605 overall NMIBC patients

	No. recurrence	Tumor recurrence			No. progression	Stage progression		
		Univariate	Multivariate			Univariate	Multivariate	
		p value	HR (95 % CI)	*p* value		*p* value	HR (95 % CI)	*p* value
Sex		0.408				0.438		
Male	212				29			
Female	43				9			
Age at diagnosis (years)		0.595				0.246		
<70	129				21			
≥70	126				17			
Smoking history		<0.001		<0.001		0.776		
Yes	179		2.1 (1.58–2.77)		23			
No	76		1		15			
Tumor grade		0.914				0.002		0.056
Low	157				15		1	
High	98				23		2.08 (0.98–4.41)	
Tumor stage		0.089				<0.001		0.035
Ta	168				17		1	
T1	87				21		2.1 (1.05–4.18)	
Tumor multiplicity		0.007		<0.001		0.001		0.011
Solitary	109		1		9		1	
Multiple	146		1.75 (1.34–2.28)		29		2.75 (1.27–5.99)	
Tumor size (cm)		0.066				0.798		
<3	123				15			
≥3	27				3			
Unknown	105				20			
Concomitant CIS		0.593				0.463		
Yes	24				5			
No	231				33			
BCG therapy		0.009		<0.001		0.104		
Performed	106		1		23			
Not performed	149		1.81 (1.35–2.44)		15			
Pre-NLR		<0.001		<0.001		0.016		0.016
<2.2	95		1		12		1	
≥2.2	160		2.08 (1.6–2.7)		26		2.37 (1.17–4.78)	

NMIBC nonmuscle invasive bladder cancer, *HR* hazard ratio, *CI* confidence interval, *CIS* carcinoma in situ, *BCG* bacillus Calmette–Guérin, *NLR* neutrophil-to-lymphocyte ratio

Relationship of Pre-NLR with Tumor Recurrence and Stage Progression in Nonsmokers

In the nonsmoker population ($N = 261$), 112 patients (42.9 %) had pre-NLR ≥ 2.2 and 149 (57.1 %) had pre-NLR < 2.2. A Kaplan–Meier curve revealed that the rate of tumor recurrence as well as stage progression was not significantly different between patients with pre-NLR < 2.2 and pre-NLR ≥ 2.2 ($p = 0.385$, Fig. 1c and $p = 0.619$, Fig. 1d, respectively). Furthermore, univariate and multivariate Cox regression analyses showed that pre-NLR was not associated with tumor recurrence or stage progression (data not shown). Similar results were also observed using a cutoff value of 2.26, which was the mean value of NLR, and that of 2.06, which was the median value of NLR in the nonsmokers, and furthermore that of 2.38, which is the ideal cutoff value for tumor progression, and that of 2.5, which is frequently used in previous studies.[15,16]

Prognostic Significance of Pre-NLR on Tumor Recurrence and Stage Progression in Patients with a Previous History of Smoking

The relationships between pre-NLR and clinicopathological characteristics in patients with a previous history of smoking ($N = 344$) are shown in Table 3. In patients with a

previous history of smoking, tumor recurrence developed in 179 patients (52.0 %), consisting of 125 patients with pre-NLR $\geq$ 2.2 and 54 patients with pre-NLR $<$ 2.2. A Kaplan–Meier curve revealed that the rate of tumor recurrence was significantly lower for patients with pre-NLR $<$ 2.2 than for their counterparts ($p < 0.001$, Fig. 1e). The 5- and 10-year RFS rates were 66.3 and 54.8 % for patients with pre-NLR $<$ 2.2 and 31.7 and 18.2 % for patients with pre-NLR $\geq$ 2.2, respectively. Table 4 shows the results of uni- and multivariate analysis for tumor recurrence in patients with positive smoking history. The multivariate analysis identified multiple tumors (HR 1.69, $p = 0.001$) and pre-NLR $\geq$ 2.2 (HR 2.58, $p < 0.001$) as independent risk factors for tumor recurrence in NMIBC patients with a previous history of smoking. In a subgroup of patients who were current smokers ($N = 175$), a multivariate analysis revealed that pre-NLR $\geq$ 2.2 (HR 2.48, $p < 0.001$) was the only independent predictor for tumor recurrence. Furthermore, in a subgroup of former smokers ($N = 169$), a multivariate analysis demonstrated that pre-NLR $\geq$ 2.2 (HR 2.86, $p < 0.001$) was also an independent predictor for tumor recurrence in addition to a smoking cessation period of less than 15 years (HR 2.08, $p = 0.004$).

Among patients with a previous history of smoking, stage progression developed in 23 patients (6.7 %), consisting of 19 with pre-NLR $\geq$ 2.2 and 4 with pre-NLR $<$ 2.2. A Kaplan–Meier curve revealed that the rate of stage progression was significantly lower for patients with pre-NLR $<$ 2.2 than for their counterparts ($p = 0.007$, Fig. 1f). The 5- and 10-year PFS rates were 97.5 and 94.5 % for patients with pre-NLR $<$ 2.2 and 90.4 and 87.9 % for patients with pre-NLR $\geq$ 2.2, respectively. Table 4 shows the results of uni- and multivariate analysis for stage progression in patients with positive smoking

TABLE 3 Association between pre-NLR and clinicopathological features in patients with previous smoking history

	Pre-NLR $\geq$ 2.2 ($n = 184$)	Pre-NLR $<$ 2.2 ($n = 160$)	p value
Sex			0.074
Male	174 (94.6 %)	142 (88.8 %)	
Female	10 (5.4 %)	18 (11.2 %)	
Age at diagnosis (years)			0.21
Mean ± SD (range)	68 ± 12 (29–94)	66 ± 12 (25–89)	
Smoking intensity (No. of CPD)			0.336
Mean ± SD (range)	22.1 ± 12.0 (5–80)	20.8 ± 12.2 (3–80)	
Smoking duration (years)			0.909
Mean ± SD (range)	34.4 ± 14.4 (5–70)	34.6 ± 14.9 (2–66)	
Tumor grade			0.18
Low	122 (66.3 %)	94 (58.8 %)	
High	62 (33.7 %)	66 (41.2 %)	
Tumor stage			0.103
Ta	119 (64.7 %)	117 (73.1 %)	
T1	65 (35.3 %)	43 (26.9 %)	
Tumor multiplicity			0.589
Solitary	95 (51.6 %)	77 (48.1 %)	
Multiple	89 (48.4 %)	83 (51.9 %)	
Tumor size (cm)			0.531
<3	95 (89.6 %)	93 (86.1 %)	
≥3	11 (10.4 %)	15 (13.9 %)	
Unknown	78	52	
Concomitant CIS			0.993
Yes	15 (8.2 %)	13 (8.1 %)	
No	169 (91.8 %)	147 (91.9 %)	
BCG therapy			0.278
Performed	78 (42.4 %)	78 (48.7 %)	
Not performed	106 (57.6 %)	82 (51.3 %)	

NLR neutrophil-to-lymphocyte ratio, *CPD* cigarettes per day, *SD* standard deviation, *CIS* carcinoma in situ, *BCG* bacillus Calmette–Guérin

TABLE 4 Uni- and multivariate analysis for tumor recurrence and progression in 344 patients with positive smoking history

	No. recurrence	Tumor recurrence			No. progression	Stage progression		
		Univariate	Multivariate			Univariate	Multivariate	
		p value	HR (95 % CI)	*p* value		*p* value	HR (95 % CI)	*p* value
Sex		0.194				0.899		
Male	167				21			
Female	12				2			
Age at diagnosis (years)		0.535				0.027		0.158
<70	94				8		1	
≥70	85				15		1.93 (0.77–4.83)	
Smoking intensity		0.145				0.545		
<1 pack/day	50				6			
≥1 pack/day	129				17			
Smoking duration		0.815				0.766		
<30 years	59				7			
≥30 years	120				16			
Tumor grade		0.315				0.018		0.246
Low	118				10		1	
High	61				13		1.85 (0.66–5.18)	
Tumor stage		0.102				0.005		0.197
Ta	120				10		1	
T1	59				13		1.83 (0.73–4.63)	
Tumor multiplicity		0.024		0.001		0.001		0.011
Solitary	81		1		4		1	
Multiple	98		1.69 (1.23–2.34)		19		4.31 (1.4–13.3)	
Tumor size		0.487				0.679		
<3 cm	90				8			
≥3 cm	15				2			
Unknown	74				13			
Concomitant CIS		0.895				0.174		
Yes	13				3			
No	166				20			
BCG therapy		0.071				0.141		
Performed	74				21			
Not performed	105				2			
Pre-NLR		<0.001		<0.001		0.007		0.016
<2.2	54		1		8		1	
≥2.2	125		2.58 (1.86–3.58)		15		3.86 (1.28–11.6)	

NMIBC non-muscle invasive bladder cancer, *HR* hazard ratio, *CI* confidence interval, *CIS* carcinoma in situ, *BCG* bacillus Calmette–Guérin, *NLR* neutrophil-to-lymphocyte ratio

history. The multivariate analysis identified multiple tumors (HR 4.31, $p = 0.011$) and pre-NLR ≥ 2.2 (HR 3.86, $p = 0.016$) as independent risk factors for stage progression in patients with a previous history of smoking. Similar results were also observed using a cutoff value of 2.56, which was the mean value of NLR, and that of 2.25, which was the median value of NLR in patients with a previous history of smoking, and furthermore that of 2.38, which is the ideal cutoff value for stage progression, and that of 2.5, which is frequently used in previous studies.[15,16]

DISCUSSION

We retrospectively analyzed the records of patients treated for NMIBC with TUR-BT at our 3 institutions and investigated the relationship between tumor recurrence and progression in NMIBC and pre-NLR levels. Our results

revealed that in the overall population, pre-NLR $\geq$ 2.2, a previous history of smoking, multiple tumors, and not performing BCG therapy were independent risk factors for tumor recurrence, while pre-NLR $\geq$ 2.2, T1 tumors, and multiple tumors were independent risk factors for stage progression in NMIBC. In a subgroup of nonsmoker patients, pre-NLR $\geq$ 2.2 was not an independent predictor, whereas in patients with a previous history of smoking, pre-NLR $\geq$ 2.2 was an independent predictor for tumor recurrence and stage progression.

The relationship between inflammatory markers including pre-NLR and tumor prognosis has recently been investigated in various types of cancers. A high pre-NLR reflects a heightened neutrophil-dependent inflammatory reaction and decreased lymphocyte-mediated antitumor immune response.[17] Circulating neutrophils have been shown to produce cytokines, such as interleukin (IL)-1 and IL-6, and secrete pro-angiogenic vascular endothelial growth factor. These factors may contribute to an aggressive tumor biology and poor prognosis.[8,18]

Several investigators reported that cigarette smoking may affect systemic immune and inflammation marker levels. Shiels et al. investigated the level of systemic soluble immune/inflammatory markers in 1819 patients in a screening population for prostate, lung, colorectal, and ovarian cancers and found that smoking was associated with a broad range of alterations in systemic immune and inflammation marker levels, particularly in long-term smokers.[14] Arnson et al. reported that the systemic inflammatory response triggered by exposure to smoking is characterized by the stimulation of the hematopoietic system, specifically bone marrow, which results in the release of leukocytes and platelets into the circulation, ascribed to the relative increase in polymorphonuclear neutrophil counts in the circulation of smokers, and smoking also modulates the proliferation and death pathways of lymphocytes.[19] Furthermore, Takahashi et al. reported that lung adenocarcinoma patients with a smoking history $\geq$10 pack-years had a significantly higher level of NLR than their counterparts.[11]

A correlation has been reported between elevated pre-NLR and the poor prognosis of bladder cancer.[15,16,20–27] Most of these studies were conducted on patients with muscle-invasive bladder cancer (MIBC) undergoing radical cystectomy, or included a mixed study of MIBC as well as NMIBC. Mano et al. showed that the pre-NLR level was an independent factor for predicting tumor recurrence as well as disease progression in 107 patients with NMIBC.[7] In contrast, Ozyalvacli et al. showed that pre-NLR > 2.43 was an independent factor for predicting tumor recurrence, but not disease progression in 166 patients with pT1 high grade NMIBC.[9] Our results showed a clear relationship between NLR levels and a worse prognosis in NMIBC patients not only in the overall population, but also in a subgroup with a positive smoking history. This is the first study to show the independence of a high pre-NLR in tumor recurrence and stage progression in NMIBC patients and NMIBC patients with a previous history of smoking. What we wanted to determine was who has aggressive properties and what is a useful biomarker for identifying a higher risk population, especially in NMIBC patients with a previous history of smoking. We found that pre-NLR is one of the useful markers for identifying a higher risk of tumor recurrence and/or stage progression. Therefore, the pre-NLR level could assist with therapeutic decision-making and identify appropriate candidates for more aggressive therapy, such as BCG maintenance therapy for intermediate-risk NMIBC (multiple and/or recurrence low grade Ta) and immediate radical cystectomy for high-risk NMIBC (T1 and/or high grade and/or carcinoma in situ).

There were several limitations to the present study. It was performed in a retrospective manner and, thus, unknown sources of bias may exist in the results obtained. We focused on the status of the smoking history, which strongly affects bladder tumor initiation as well as its promotion in the present study; however, other environmental factors, such as drinking, family history, and previous medical history, also may affect the clinical outcomes of NMIBC patients or pre-NLR levels. Smoking statuses were self-reported and collected retrospectively from our three institutions, in which somewhat different question patterns were provided. Furthermore, smoking statuses were only measured by two interviewers in the initial consultation and in surgery for TUR-BT, respectively. This may have produced an intrinsic selection bias. Due to the long accrual period in the present study, current standard management for NMIBC, such as immediate postoperative single instillation of chemotherapy, maintenance BCG therapy, and second TUR-BT was not provided consistently for our study population. Furthermore, tumor grade and stage, which are thought to be strong indicators for predicting a poor outcome in NMIBC patients, were not selected in our multivariate analyses. We do not know the exact reason; however, we can speculate that pre-NLR level might be strongly associated with tumor recurrence and stage progression compared with such standard prognostic indicators in our study. Therefore, a larger study would be warranted to clarify the prognostic significance of pre-NLR level for predicting a poor outcome in NMIBC patients, especially those with a previous smoking history.

CONCLUSIONS

A high pre-NLR level was a significant predictor for worse clinical outcomes in patients with NMIBC.

Furthermore, pre-NLR levels may be a useful marker for identifying an inferior clinical outcome in NMIBC patients with a previous history of smoking.

DISCLOSURE All authors certify that this study has no financial or other relationships that 3 institutions might lead to a conflict of interest.

REFERENCES

1. Babjuk M, Burger M, Zigeuner R, Shariat SF, Van Rhijn BW, Comperat E, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol.* 2013;64(4):639–53.
2. van Rhijn BW, Burger M, Lotan Y, Solsona E, Stief CG, Sylvester RJ, et al. Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. *Eur Urol.* 2009;56(3):430–42.
3. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol.* 2013;63(2):234–41.
4. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. *JAMA.* 2011;306(7):737–45.
5. Ogihara K, Kikuchi E, Yuge K, Ito Y, Tanaka N, Matsumoto K, et al. Refraining from smoking for 15 years or more reduced the risk of tumor recurrence in non-muscle invasive bladder cancer patients. *Ann Surg Oncol.* 2016;23(5):1752–9.
6. Hong C, Wei Y, Jiang J, Zhao C, Liang G, Wang G, et al. Associations between lifestyles and neutrophil-lymphocyte and platelet-lymphocyte ratios in colorectal cancer. *Asian Pac J Clin Oncol.* 2014;10(2):168–74.
7. Mano R, Baniel J, Shoshany O, Margel D, Bar-On T, Nativ O, et al. Neutrophil-to-lymphocyte ratio predicts progression and recurrence of nonmuscle-invasive bladder cancer. *Urol Oncol.* 2015;33(2):61–7.
8. Ohno Y, Nakashima J, Ohori M, Hatano T, Tachibana M. Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. *J Urol.* 2010;184(3):873–8.
9. Ozyalvacli ME, Ozyalvacli G, Kocaaslan R, Cecen K, Uyeturk U, Kemahli E, et al. Neutrophil-lymphocyte ratio as a predictor of recurrence and progression in patients with high-grade pT1 bladder cancer. *Can Urol Assoc J.* 2015;9(3–4):126–31.
10. Sun XD, Shi XJ, Chen YG, Wang CL, Ma Q, Lv GY. (2015) Elevated preoperative neutrophil-lymphocyte ratio is associated with poor prognosis in hepatocellular carcinoma patients treated with liver transplantation: a meta-analysis. *Gastroenterol Res Pract.* doi:10.1155/2016/4743808.
11. Takahashi Y, Kawamura M, Hato T, Harada M, Matsutani N, Horio H. Neutrophil-lymphocyte ratio as a prognostic marker for lung adenocarcinoma after complete resection. *World J Surg.* 2016;40(2):365–72.
12. Tanaka N, Kikuchi E, Kanao K, Matsumoto K, Shirotake S, Miyazaki Y, et al. A multi-institutional validation of the prognostic value of the neutrophil-to-lymphocyte ratio for upper tract urothelial carcinoma treated with radical nephroureterectomy. *Ann Surg Oncol.* 2014;21(12):4041–8.
13. Wong BY, Stafford ND, Green VL, Greenman J. Prognostic value of the neutrophil-to-lymphocyte ratio in patients with laryngeal squamous cell carcinoma. *Head Neck.* 2016;38(1):1903–8.
14. Shiels MS, Katki HA, Freedman ND, Purdue MP, Wentzensen N, Trabert B, et al. Cigarette smoking and variations in systemic immune and inflammation markers. *J Natl Cancer Inst.* 2014. doi:10.1093/jnci/dju294.
15. Demirtas A, Sabur V, Akinsal EC, Demirci D, Ekmekcioglu O, Gulmez I, et al. Can neutrophil-lymphocyte ratio and lymph node density be used as prognostic factors in patients undergoing radical cystectomy? *Sci World J.* 2013. doi:10.1155/2013/703579.
16. Gondo T, Nakashima J, Ohno Y, Choichiro O, Horiguchi Y, Namiki K, et al. Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. *Urology.* 2012;79(5):1085–91.
17. Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, et al. Pretreatment neutrophil-to-lymphocyte ratio is associated with advanced pathologic tumor stage and increased cancer-specific mortality among patients with urothelial carcinoma of the bladder undergoing radical cystectomy. *Eur Urol.* 2014;66(6):1157–64.
18. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients with colorectal cancer. *Br J Cancer.* 2013;109(2):401–7.
19. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun.* 2010;34(3):258–65.
20. Can C, Baseskioglu B, Yilmaz M, Colak E, Ozen A, Yenilmez A. Pretreatment parameters obtained from peripheral blood sample predicts invasiveness of bladder carcinoma. *Urol Int.* 2012;89(4):468–72.
21. Ceylan C, Doluoglu OG, Keles I, Gazel E, Temuçin T, Odabaş Ö, et al. Importance of the neutrophil-to-lymphocyte ratio in muscle-invasive and non-muscle invasive bladder tumors. *Urologia.* 2014;81(2):120–4.
22. Hermanns T, Bhindi B, Wei Y, Yu J, Noon AP, Richard PO, et al. Pre-treatment neutrophil-to-lymphocyte ratio as predictor of adverse outcomes in patients undergoing radical cystectomy for urothelial carcinoma of the bladder. *Br J Cancer.* 2014;111(3):444–51.
23. Kang M, Jeong CW, Kwak C, Kim HH, Ku JH. The prognostic significance of the early postoperative neutrophil-to-lymphocyte ratio in patients with urothelial carcinoma of the bladder undergoing radical cystectomy. *Ann Surg Oncol.* 2016;23(1):335–42.
24. Potretzke A, Hillman L, Wong K, Shi F, Brower R, Mai S, et al. NLR is predictive of upstaging at the time of radical cystectomy for patients with urothelial carcinoma of the bladder. *Urol Oncol.* 2014;32(5):631–6.
25. Seah JA, Leibowitz-Amit R, Atenafu EG, Alimohamed N, Knox JJ, Joshua AM, et al. Neutrophil-lymphocyte ratio and pathological response to neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer. *Clin Genitourin Cancer.* 2015;13(4):229–33.
26. Kawahara T, Furuya K, Nakamura M, Sakamaki K, Osaka K, Ito H, et al. Neutrophil-to-lymphocyte ratio is a prognostic marker in bladder cancer patients after radical cystectomy. *BMC Cancer.* 2016;16:185.
27. Morizawa Y, Miyake M, Shimada K, Hori S, Tatsumi Y, Nakai Y, et al. Neutrophil-to-lymphocyte ratio as a detection marker of tumor recurrence in patients with muscle-invasive bladder cancer after radical cystectomy. *Urol Oncol.* 2016;34(6):257.e11–7.