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Original Article

Prognostic value of preoperative systemic inflammatory responses in patients with non-muscle invasive bladder cancer undergoing transurethral resection of bladder tumor

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Abstract: Several systemic inflammatory response biomarkers are associated with oncological outcomes. We aimed to evaluate the clinical significance of preoperative C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) for prediction of tumor recurrence and progression in patients with non-muscle invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor (TURBT). A total of 207 patients with NMIBC, who underwent TURBT, were enrolled in this single-center study. Receiver operating characteristic curve (ROC) was performed to assess the optimal cut-off values for four biomarkers. The endpoints were recurrence-free survival (RFS) and progression-free survival (PFS). The Kaplan-Meier method and the log-rank test were used for RFS and PFS estimation. To identify an optimal prognostic model for survival, Cox proportional hazards regression method was used with forward stepwise selection. The median follow-up after TURBT was 21 months. Univariate analysis revealed elevated preoperative CRP, NLR, PLR, and low LMR was significantly associated with worse RFS and PFS. On multivariable analyses, elevated PLR was an independent predictor of RFS and PFS after adjusting for potential confounding variables (Hazard ratio [HR]: 2.736; 95% Confidence interval [CI]: 1.455-5.144; *P*=0.002; HR: 4.089; 95% CI: 1.516-11.027, *P*=0.005; respectively). CRP was also independently predictive of PFS (HR: 5.222; 95% CI: 1.687-16.160, *P*=0.004), but not RFS. Elevated preoperative PLR was significantly associated with a higher risk of disease progression and recurrence in patients with NMIBC who underwent TURBT. Preoperative PLR may be an independent predictor of oncological outcomes in patients with NMIBC.

Keywords: Preoperative platelet-lymphocyte ratio, biomarker, non-muscle invasive bladder cancer, recurrence, progression

Introduction

Urinary bladder cancer (BC) is the ninth most common cancer in the world, with >380,000 new cases and >150,000 deaths estimated to occur every year [1]. At any point in time, 2.7 million people in the world have a history of BC [2], and nearly 75% of newly diagnosed patients present with non-muscle invasive bladder cancer (NMIBC) [3]. The standard treatment for NMIBC is transurethral resection of bladder tumor (TURBT) with intravesical chemotherapy or intravesical Bacillus Calmette-Guérin (BCG) immunotherapy. However, the recurrence and progression rates of NMIBC for 5 years range from 31% to 78% and from 1% to 45%, respectively [4].

The European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancer Group has developed a scoring system as well as risk-tables to stratify patients into low-, intermediate-, and high-risk groups [4]. Based on the EORTC criteria, early radical cystectomy for patients with high-risk NMIBC is strongly recommended to improve oncological outcomes [5]. Despite this aggressive therapy, long-term clinical outcomes following radical cystectomy (RC) are not satisfactory, and the 5-year overall survival (OS) is only about

50% [6]. More aggressive approach increases the risk of overtreatment and surgical complications [7]. Thus, identification of reliable markers that allow for risk-stratification of patients and guide the treatment approach is a key imperative.

Inflammation is considered to be an important hallmark of cancer [8]. Systemic inflammation and inflammatory microenvironment play a critical role in carcinogenesis [9] and complete blood count (CBC)-based biomarkers reflect the role of immunity and inflammation in cancer development and progression [10]. High C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and low lymphocyte-monocyte ratio (LMR) have been shown to be associated with adverse outcomes in a variety of malignancies [11-17]. In MIBC [18-23], emerging evidence indicates that CRP, NLR, PLR and LMR are independent prognostic factors for oncological outcomes. Recently, studies also show CRP and NLR may potentially serve as prognostic markers for prediction of disease recurrence and progression of NMIBC [24, 25]. Additionally, several other blood biomarkers have also been investigated for BC, including absolute platelet count [23, 26-28] and absolute lymphocyte count [23, 29]. Taken together, systemic inflammatory response could be useful biomarkers for improving the risk stratification of BC, thereby potentially facilitating therapeutic strategy.

However, evidence of prognostic value for preoperative systemic inflammatory responses in NMIBC is relatively scarce. Specially, studies of prognostic value of PLR and LMR in NMIBC have not been reported. Therefore, we sought to evaluate the prognostic significance of blood inflammatory biomarkers for tumor recurrence and progression in patients with NMIBC treated with TURBT.

Materials and methods

Patients and treatment

Approval was obtained from the ethics committee of Shanghai Tenth People's Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of Shanghai Tenth People's Hospital (SHSY-IEC-pap-17-1) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all of the patients, prior to treatment. A total of 207 patients with Ta-T1 stage urothelial carcinoma, who underwent TURBT between January 2010 and December 2012 at the Shanghai Tenth People's Hospital, were included in the study. The exclusion criteria were: incomplete clinical data, lost to follow-up, preoperative adjuvant treatment, and had history of recurrent or persistent inflammatory diseases. Clinical and pathological data were collected from medical records. Patient characteristics included age and sex, history of hypertension and diabetes, history of postoperative bladder instillation, TNM staging, differential grading, number of tumors, size of the largest tumor, and the presence of coexisting carcinoma in situ (CIS).

Staging was defined according to the TNM classification by Union for International Cancer Control; tumor grade was assessed according to the World health Organization criteria. Preoperative blood counts were obtained within a week prior to surgery. Candidate parameters considered in this study included CRP, individual cell counts (absolute neutrophil, platelet counts lymphocyte, and monocyte), and the cell count ratios NLR, PLR, and LMR. The last follow-up date was December 30, 2013.

A second TURBT was routinely performed in patients who had a T1 or high-grade tumor, or coexisting CIS on initial TURBT. Postoperative bladder instillation was based on tumor characteristics and on the discretion of the treating urologist. The treatment strategy included single immediate instillation of chemotherapy alone, or further instillations of chemotherapy or BCG immunotherapy.

Follow-up and evaluation

Patients were followed up after TURBT every 3 months for 2 years, and every 6 months for another 3 years, followed by annual follow-ups. Postoperative investigations primarily included cystoscopy and urinary cytology; imaging was performed only if clinically indicated. Missing survival data were obtained by telephonic contact. Recurrence-free survival (RFS) was defined as the time from the initial TURBT to the date of first recurrence in the bladder, regardless of the tumor stage. Progression-free survival (PFS) was defined as the time from initial TURBT to the date of first increase in T category from CIS or Ta to T1, development of T2 or high-

Table 1. Baseline Characteristics

Variables	Total n=207
Age (years), median (IQR)	66 (59-80)
Sex (Male), n (%)	169 (82%)
Hypertension, n (%)	93 (45%)
Diabetes, n (%)	26 (13%)
Tumor category, n (%)	
Ta	170 (82%)
T1	37 (18%)
Tumor grade, n (%)	
G1+G2	130 (63%)
G3	77 (37%)
Tumor size, n (%)	
<3 cm	157 (76%)
≥3 cm	50 (24%)
Number of tumors, n (%)	
Single	129 (62%)
Multiple	78 (38%)
Coexisting CIS, n (%)	
No	205 (99%)
Yes	2 (1%)
Postoperative bladder instillation, n (%)	
No	66 (32%)
Yes	141 (68%)
CRP	3.3 (3.2-3.4)
Neutrophils (10^9/l), median (IQR)	3.7 (2.8-4.7)
Lymphocytes (10^9/l), median (IQR)	1.8 (1.4-2.3)
Platelets (10^9/l), median (IQR)	200 (164-229)
Monocytes (10^9/l), median (IQR)	0.4 (0.3-0.5)
NLR, median (IQR)	2.0 (1.5-3.0)
LMR, median (IQR)	4.6 (3.2-6.2)
PLR, median (IQR)	108 (81-146)

IQR interquartile range, *CIS* carcinoma in situ, *CRP* C-reactive protein, *NLR* neutrophil-lymphocyte ratio, *LMR* lymphocyte-monocyte ratio, *PLR* platelet- lymphocyte ratio.

er, or lymph node (N+) disease or distant metastasis (M1), or an increase in grade, based on criteria for progression in NMIBC recommended by the International Bladder Cancer Group [30].

Statistical analysis

The endpoints of this study were RFS and PFS. Data pertaining to patients who showed no evidence of disease recurrence or progression was censored at the time of death or at the date of most recent follow-up. The ideal cut-off value for blood biomarkers was determined on receiver operating characteristics (ROC) curve analysis. To avoid issues with multicollinearity in multivariate analyses, similar predictors were compared and only those with superior areas under the ROC curves were included for further evaluation.

Between-group differences with respect to disease-specific categorical variables were assessed using Chi-squared test or Fisher's exact test; those for continuous variables were assessed using Mann-Whitney *U*. Kaplan-Meier method were performed to calculate the survival curves and between-group differences compared by the log-rank test. Univariate and multivariate analyses were performed using backward stepwise Cox proportional hazards model to determine associations of RFS and PFS with age, sex, T-stage, tumor grade, hypertension and diabetes, postoperative bladder instillation, the number of tumors, size of the largest tumor, and the presence of coexisting CIS and preoperative blood biomarkers.

All continuous variables are expressed as median and interquartile ranges (IQRs). All statistical analyses were performed using the SPSS Statistics version 19.0 (SPSS, Chicago, IL, USA). All *P* values were two-sided; *P* value <0.05 was considered as statistically significant.

Results

The study cohort comprised of 169 men and 38 women; median age was 66 years (IQR: 59-80). Most patients (68%) underwent bladder instillation during follow-up; 134 patients (65%) received intravesical chemotherapy; and 7 patients (3%) received intravesical BCG immunotherapy. Clinical and pathological characteristics are further summarized in **Table 1**.

The area under the curves (AUCs) of the ROC curve analyses for RFS was used to identify the best predictors among those that are similar to each other. The AUCs for LMR were superior to those for absolute lymphocyte count and absolute monocyte count (0.655 vs. 0.616 and 0.546). Thus, in subsequent analyses, only CRP, NLR, PLR, and LMR were included, whereas those similar and inferior predictors were excluded in order to avoid collinearity. The opti-

Table 2. Clinicopathological characteristics of the study cohort stratified by CRP, NLR, PLR, and LMR

Variables	CRP<3.4	CRP≥3.4	*p*	NLR<2.0	NLR≥2.0	*p*	PLR<123	PLR≥123	*p*	LMR<4.3	LMR≥4.3	*p*
	n (%)	n (%)	*value*	n (%)	n (%)	*value*	n (%)	n (%)	*value*	n (%)	n (%)	*value*
Age (years)			<0.001			0.007			0.005			0.004
<66	65 (64.4)	38 (35.8)		59 (59.6)	44 (40.7)		74 (57.4)	29 (37.2)		32 (37.6)	71 (58.2)	
≥66	36 (35.6)	68 (64.2)		40 (40.4)	64 (59.3)		55 (42.6)	49 (62.8)		53 (62.4)	51 (41.8)	
Sex			0.214			0.036			0.801			0.006
Female	22 (21.8)	16 (15.1)		24 (24.2)	14 (13.0)		23 (17.8)	15 (19.2)		8 (9.4)	30 (24.6)	
Male	79 (78.2)	90 (84.9)		75 (75.8)	94 (87.0)		106 (82.2)	63 (80.8)		77 (90.6)	92 (75.4)	
Hypertension			0.345			<0.001			0.045			0.172
No	59 (58.4)	55 (51.9)		71 (71.7)	43 (39.8)		78 (60.5)	36 (46.2)		42 (49.4)	72 (59.0)	
Yes	42 (41.6)	79 (48.1)		28 (28.3)	65 (60.2)		51 (39.5)	42 (53.8)		43 (50.6)	50 (41.0)	
Diabetes			0.773			0.063			0.340			0.773
No	89 (88.1)	92 (86.8)		91 (91.9)	90 (83.3)		115 (89.1)	66 (84.6)		75 (88.2)	106 (86.9)	
Yes	12 (11.9)	14 (13.2)		8 (8.1)	18 (16.7)		14 (10.9)	12 (15.4)		10 (11.8)	16 (13.1)	
Pathologic stage			0.141			0.015			0.467			0.160
Ta	87 (86.1)	83 (78.3)		88 (88.9)	82 (75.9)		104 (80.6)	66 (84.6)		66 (77.6)	104 (85.2)	
T1	14 (13.9)	23 (21.7)		11 (11.1)	26 (24.1)		25 (19.4)	12 (15.4)		19 (22.4)	18 (14.8)	
Tumor grade			0.014			0.599			0.007			0.323
G1+G2	72 (71.3)	58 (54.7)		64 (64.6)	66 (61.1)		72 (55.8)	58 (74.4)		50 (58.8)	80 (65.6)	
G3	29 (28.7)	48(45.3)		35 (35.4)	42 (38.9)		57 (44.2)	20 (25.6)		35 (41.2)	42 (34.4)	
Tumor size			0.016			0.004			0.290			0.252
<3 cm	84 (83.2)	73 (68.9)		84 (84.8)	73 (67.6)		101 (78.3)	56 (71.8)		61 (71.8)	96 (78.7)	
≥3 cm	17 (16.8)	33 (31.1)		15 (15.2)	35 (32.4)		28 (21.7)	22 (28.2)		24 (28.2)	26 (21.3)	
Number of tumors			0.002			0.930			0.857			0.001
Single	74 (73.3)	55 (51.9)		62 (62.6)	67 (62.0)		81 (62.8)	48 (61.5)		42 (49.4)	87 (71.3)	
Multiple	27 (26.7)	51 (48.1)		37 (37.4)	41 (38.0)		48 (37.2)	30 (38.5)		43 (50.6)	35 (28.7)	
Coexisting CIS			0.614			0.607			0.292			1.000
No	99 (98.0)	105 (99.1)		97 (98.0)	107 (99.1)		126 (21.8)	78 (21.8)		84 (98.8)	120 (98.4)	
Yes	2 (2.0)	1 (0.9)		2 (2.0)	1 (0.9)		3 (78.2)	0 (0)		1 (1.2)	2 (1.6)	
Postoperative bladder instillation			0.952			0.185			0.565			0.524
No	32 (31.7)	34 (32.1)		36 (36.4)	30 (27.8)		43 (33.3)	23 (29.5)		25 (29.4)	41 (33.6)	
Yes	69 (68.3)	72 (67.9)		63 (63.6)	78 (72.2)		86 (66.7)	55 (70.5)		60 (70.6)	81 (66.4)	

CIS carcinoma in situ, *CRP* C-reactive protein, *NLR* neutrophil- lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *LMR* lymphocyte-monocyte ratio.

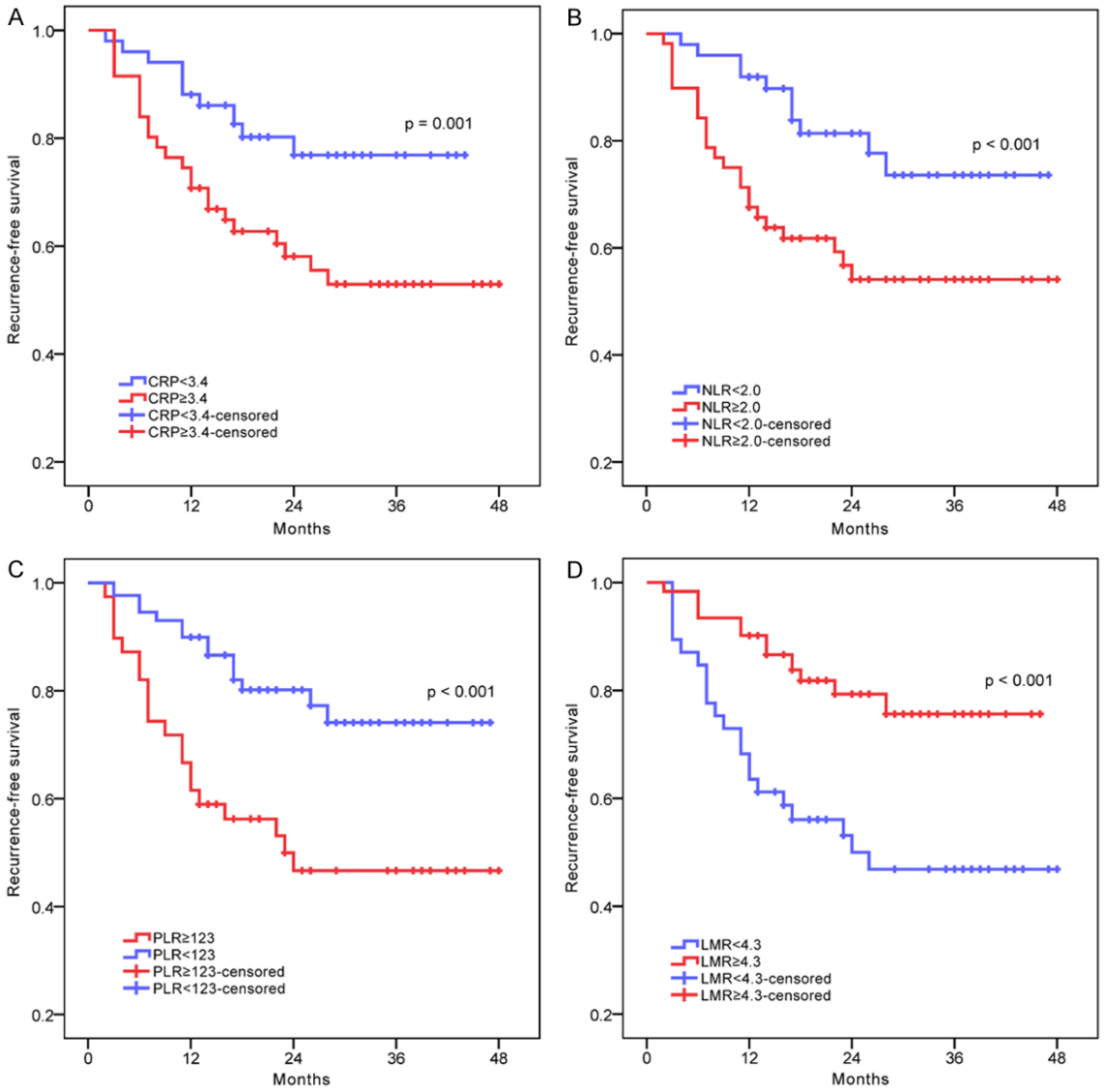

Figure 1. Kaplan-Meier curves for recurrence-free survival following transurethral resection of bladder tumor for non-muscle invasive bladder cancer, stratified by C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR).

mal cutoff levels of CRP, NLR, PLR, and LMR were 3.4, 2.0, 123, and 4.3 by ROC curves analysis. Patients were stratified according to these cutoff values (**Table 2**). High CRP was significantly associated with age (P<0.001), tumor grade (P=0.014), tumor size (P=0.016), and number of tumors (P=0.002). High NLR was associated with age (P=0.007), sex (P=0.036), hypertension (P<0.001), tumor stage (P=0.015), and tumor size (P=0.004). High PLR was associated with age (P=0.005), hypertension (P=0.045), and tumor stage (P=0.007). High LMR was associated with age (P=0.004), sex (P=0.006), and number of tumors (P=0.001).

The median duration of follow-up was 21 months (IQR: 13-33). During the follow-up period, 68 patients (33%) experienced recurrence at a median time of 11 months (IQR: 6-16); 35 patients (17%) experienced progression at a median time of 8 months (IQR: 6-14). Kaplan-Meier analyses showed that higher CRP, NLR and PLR, and lower LMR increased the risk of disease recurrence (**Figure 1**) and progression (**Figure 2**) in patients with NMIBC. The estimated 2-year recurrence-free survival rate in the low and high CRP groups was 76.9% and 58.1%, respectively (P=0.001). The estimated 2-year recurrence-free survival rate in the low and high NLR groups was 81.4% and 54.1%, respec-

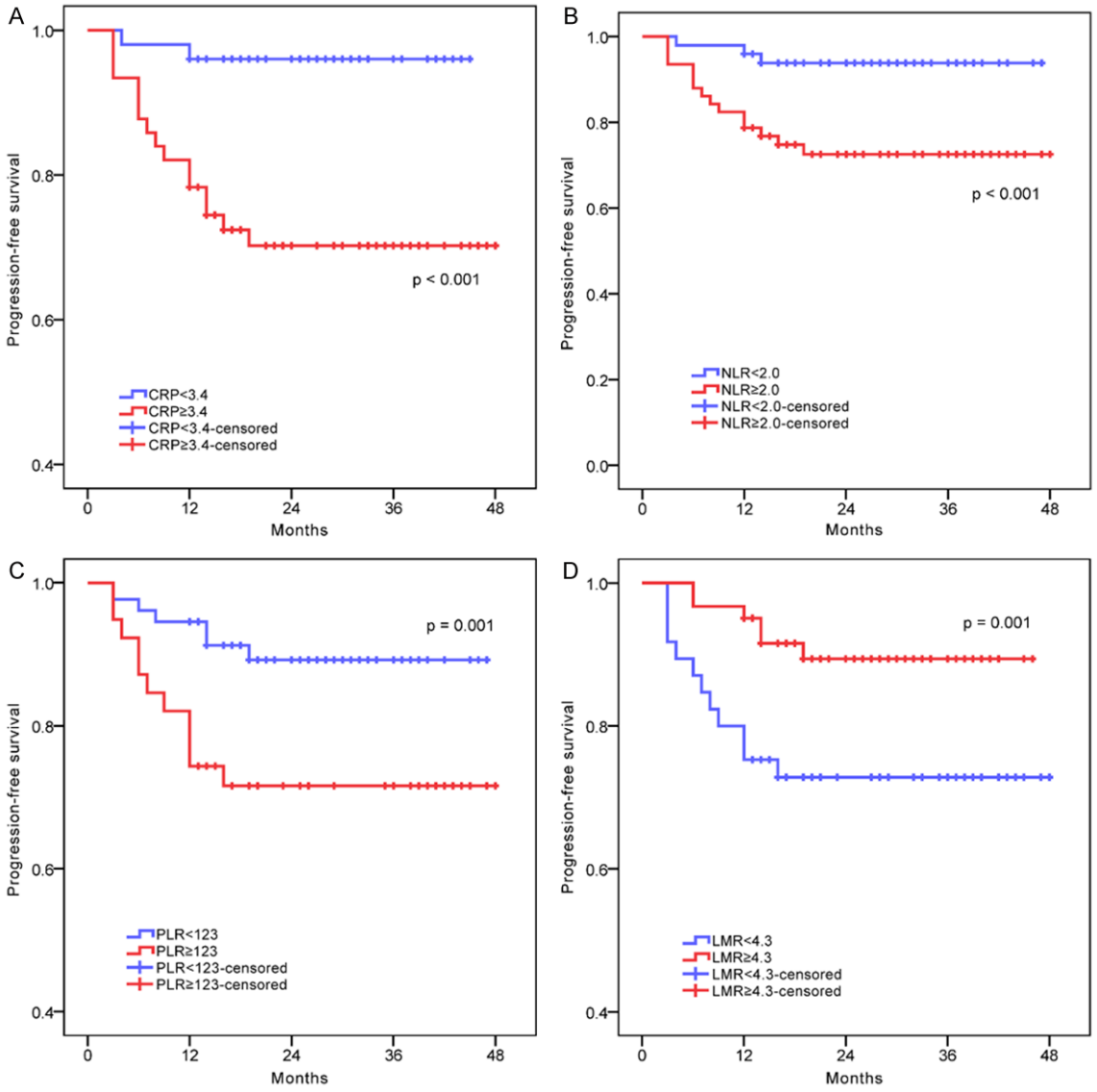

Figure 2. Kaplan-Meier curves for progression-free survival following transurethral resection of the bladder tumor for non-muscle invasive bladder cancer, stratified by C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR).

tively (*P*<0.001). The estimated 2-year recurrence-free survival rate in the low and high PLR groups was 80.2% and 46.7%, respectively (*P*<0.001). The estimated 2-year recurrence-free survival rate in the low and high LMR groups was 50.0% and 79.3%, respectively (*P*<0.001). Progression-free survival rate at 2 years in the low and high CRP groups was 96.0% and 70.2%, respectively (*P*<0.001). Progression-free survival rate at 2 years in the low and high NLR groups was 93.8% and 72.6%, respectively (*P*<0.001). Progression-free survival rate at 2 years in the low and high PLR groups was 89.2% and 71.6%, respectively (*P*=0.001). Progression-free survival rate at 2 years in the low and high LMR groups was 72.8% and 89.4%, respectively (*P*=0.001).

The results of the univariate Cox-regression analyses are indicated in **Tables 3** and **4**. In addition, while these blood biomarkers were evaluated as continuous variables, the results revealed that CRP was associated with worse RFS (HR: 1.048; 95% CI: 1.010-1.087, *P*=0.013) and PFS (HR: 1.080; 95% CI: 1.041-1.122, *P*< 0.001), whereas NLR was not significantly associated with RFS (HR: 1.111; 95% CI: 0.995-1.240, *P*=0.060) and PFS (HR: 1.143; 95% CI:

Table 3. Univariate and multivariate Cox proportional hazard regression analyses of recurrence-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p value*	HR (95% CI)	*p value*
Age (years)				
<66	(ref)		(ref)	
≥66	1.994 (1.218-3.266)	0.006	1.447 (0.824-2.542)	0.198
Sex				
Female	(ref)			
Male	2.147 (0.982-4.695)	0.056	-	
Hypertension				
No	(ref)			
Yes	1.227 (0.763-1.975)	0.399	-	
Diabetes				
No	(ref)			
Yes	0.877 (0.419-1.834)	0.727	-	
Pathologic stage				
Ta	(ref)		(ref)	
T1	2.190 (1.288-3.723)	0.004	1.339 (0.722-2.483)	0.354
Tumor grade				
G1+G2	(ref)		(ref)	
G3	2.593 (1.604-4.191)	<0.001	2.645 (1.503-4.657)	0.001
Tumor size				
<3 cm	(ref)			
≥3 cm	1.365 (0.810-2.300)	0.243	-	
Number of tumors				
Single	(ref)		(ref)	
Multiple	2.012 (1.250-3.240)	0.004	1.578 (0.929-2.681)	0.091
Coexisting CIS				
No	(ref)			
Yes	1.078 (0.150-7.764)	0.941	-	
Postoperative bladder instillation				
No	(ref)		(ref)	
Yes	0.599 (0.370-0.972)	0.038	0.520 (0.312-0.869)	0.012
CRP				
CRP<3.4	(ref)		(ref)	
CRP≥3.4	2.343 (1.399-3.922)	0.001	1.292 (0.703-2.373)	0.409
NLR				
NLR<2.0	(ref)		(ref)	
NLR≥2.0	2.468 (1.474-4.130)	0.001	1.369 (0.714-2.622)	0.344
PLR				
PLR<123	(ref)		(ref)	
PLR≥123	2.889 (1.781-4.686)	<0.001	2.736 (1.455-5.144)	0.002
LMR				
<4.3	(ref)		(ref)	
≥4.3	0.340 (0.207-0.557)	<0.001	0.813 (0.422-1.565)	0.535

HR hazards ratio, *CI* confidence interval, *CIS* carcinoma in situ, *CRP* C-reactive protein, *NLR* neutrophil-lymphocyte ratio, *PLR* platelet lymphocyte ratio, *LMR* lymphocyte-monocyte ratio, *ref* reference.

0.984-1.329, *P*=0.080). PLR was associated with worse RFS (HR: 1.009; 95% CI: 1.004-1.013, *P*<0.001) and PFS (HR: 1.012; 95% CI: 1.006-1.018, *P*<0.001). LMR was associated with improved RFS (HR: 0.853; 95% CI: 0.750-0.969, *P*=0.015) and PFS (HR: 0.746; 95% CI: 0.616-0.903, *P*=0.003).

On multivariate analysis, our results revealed PLR was an independent prognostic factor for RFS (HR: 2.736; 95% CI: 1.455-5.144; *P*= 0.002), along with age, pathologic stage, tumor grade, number of tumors, postoperative bladder instillation (**Table 3**). In addition, CRP (HR: 5.222; 95% CI: 1.687-16.160; *P*=0.004) and PLR (HR: 4.089; 95% CI: 1.516-11.027; *P*= 0.005) remained independent predictors of PFS after adjusting for age, pathologic stage, tumor grade, tumor size, and multiple tumors (**Table 4**).

Discussion

Inflammation may be frequently associated with different stages of tumor development, including tumorigenesis and progression, invasion, and metastasis [9]. Bioactive molecules secreted by inflammatory cells, as a result of cancer cell and immune cell interaction, regulate the growth, progression, and differentiation of all cell types in the tumor microenvironment, including cancer cells, fibroblasts, endothelial cells, immune inflammatory cells, and pericytes [8]. Several markers of systemic inflammation responses, including CRP, NLR, PLR, and LMR, have been demonstrated as a valid prognostic factor in a variety of cancers. Until recently, however, these biomarkers for NMIBC had not been evaluated together in independent data. Therefore, we sought to evaluate the clinical significance of these biomarkers for prediction of tumor recurrence and progression together in patients with NMIBC treated with TURBT.

In our study, PLR was the sole blood biomarker to be independently predictive of recurrence and progression together in patients with NMIBC. Elevated pretreatment PLR was associated with poor prognosis in breast cancer [31], esophageal squamous cell carcinoma [32], gastric cancer, colorectal cancer, hepatocellular carcinoma, ovarian cancer, and non-small cell lung cancer, but not pancreatic cancer [23]. The prognostic value of pretreatment PLR in BC patients has, until now, been rarely reported. Kaynar et al. investigated the relationship between preoperative PLR and pathological features of BC but found no significant association with pathological stage [33]. Recently, studies reported the potential ability of PLR as a prognostic indicator for MIBC, but preoperative PLR was not an independent predictor of prognosis once adjusting for other variables [10, 18]. Ku et al. reported that PLR remained independently associated with poorer disease-specific survival and OS in 419 patients undergoing radical cystectomy for BC while controlling for clinicopathological variables [23]. In this study, we conform that elevated preoperative PLR was associated with advanced pathological grade at the time of TURBT, along with a significantly increased risk of disease recurrence and progression for NMIBC. The association was statistically significant after adjusting for clinicopathological features, which suggested an independent association of elevated preoperative PLR with worse oncologic outcomes in patients with NMIBC treated with TURBT.

The association between increased preoperative PLR with tumor recurrence and progression is yet to be completely elucidated. PLR represents the combination of platelet and lymphocyte count. Reactive thrombocytosis is commonly caused by acute infection, tissue damage, chronic inflammatory disorders, and malignancy [34]. Thrombocytosis is a frequent finding in cancer patients (10-57%). Thrombocytosis can be induced by growth factors and cytokines secreted by tumor cells. Platelets promote tumor development and metastasis formation via inducing new blood vessel formation [35]. Meanwhile, many studies reported a better outcome of the presence of tumor-infiltrating lymphocytes in several types of malignancies including BC [9, 22]. Tumor infiltration by CD3+ and CD8+ lymphocytes was associated with superior outcomes in MIBC, after adjustment for tumor stage and other prognostic factors for MIBC [36, 37]. Moreover, studies have shown that circulating lymphocytes in the peripheral blood can contribute to prolonged survival [38]. Thus, lymphocytopenia may reflect a weak, insufficient immunological reaction to a tumor, leading to poor outcomes. Both of these factors may contribute to aggressive tumor biology, cancer progression, and poor prognosis. Platelet count was found to be the predictors of invasiveness of urothelial carcinoma [26]. Platelet count was independently associ-

Table 4. Univariate and multivariate Cox proportional hazard regression analyses of progression-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p value*	HR (95% CI)	*p value*
Age (years)				
<66	(ref)		(ref)	
≥66	2.690 (1.292-5.601)	0.008	1.231 (0.540-2.804)	0.621
Sex				
Female	(ref)			
Male	1.819 (0.642-5.152)	0.260	-	
Hypertension				
No	(ref)			
Yes	1.524 (0.784-2.965)	0.214	-	
Diabetes				
No	(ref)			
Yes	1.421 (0.590-3.422)	0.434	-	
Pathologic stage				
Ta	(ref)		(ref)	
T1	3.275 (1.648-6.509)	0.001	1.190 (0.540-2.619)	0.667
Tumor grade				
G1+G2	(ref)		(ref)	
G3	6.762 (3.069-14.897)	<0.001	8.543 (3.237-22.545)	<0.001
Tumor size				
<3 cm	(ref)		(ref)	
≥3 cm	2.982 (1.532-5.803)	0.001	0.957 (0.415-2.208)	0.919
Number of tumors				
Single	(ref)		(ref)	
Multiple	2.140 (1.100-4.162)	0.025	1.103 (0.465-2.614)	0.824
Coexisting CIS				
No	(ref)			
Yes	2.224 (0.304-16.260)	0.431	-	
Postoperative bladder instillation				
No	(ref)			
Yes	0.584 (0.299-1.140)	0.115	-	
CRP				
CRP<3.4	(ref)		(ref)	
CRP≥3.4	8.198 (2.893-23.231)	<0.001	5.222 (1.687-16.160)	0.004
NLR				
NLR<2.0	(ref)		(ref)	
NLR≥2.0	4.910 (2.038-11.829)	<0.001	2.134 (0.757-6.017)	0.152
PLR				
PLR<123	(ref)		(ref)	
PLR≥123	3.071 (1.547-6.099)	0.001	4.089 (1.516-11.027)	0.005
LMR				
<4.3	(ref)		(ref)	
≥4.3	0.325 (0.162-0.653)	0.002	1.195 (0.464-3.074)	0.712

HR hazards ratio, *CI* confidence interval, *CIS* carcinoma in situ, *CRP* C-reactive protein, *NLR* neutrophil-lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *LMR* lymphocyte-monocyte ratio, *ref* reference.

ated with poorer OS [27] and worse CSS [28] after RC for bladder cancer. Recently, platelet count and lymphocyte count were shown as independent prognostic predictors of DSS and OS in patients undergoing RC for BC [23]. A recent study demonstrated lymphocytopaenia was is an independent adverse prognostic factor in both muscle-invasive and advanced bladder cancer [29]. Conceptually, PLR represents the ratio of platelet count and lymphocyte count. Our study demonstrates that an elevated PLR is a negative predictor for RFS and PFS for patients with NMIBC who underwent TURBT.

CRP is recognized to be an activator of innate immunity and a modulator of adaptive immunity [10] CRP was the most widely studied blood inflammatory marker. Studies published consistently provide evidence that patients with a high CRP level have a poorer prognosis in MIBC, independently of standard clinical or pathologic factors [22]. In addition, a recent study has confirmed the prognostic significance of CRP in patients with NMIBC [25]. In the present study, we found high CRP was associated with worse RFS and PRS. However, we further conformed CRP was independently predictive of PFS in NMIBC, but not RFS. This finding is consistent with those of Mbeutcha et al. [25].

Neutrophils can release reactive oxygen species that are capable of inducing cell DNA damage and genetic instability and secrete various cytokines to control and shape tumor growth. NLR reflects the balance between neutrophil-dependent, tumor promoting inflammation and lymphocyte-mediated, antitumor immune response [9]. Recently, studies have separately reported the prognostic value of NLR in MIBC [10, 20, 23] and NMIBC [24, 25]. Several studies have shown that elevated NLR was associated with worse cancer-specific survival and OS in a group of patients with MIBC. Specifically, NLR has been shown as an independent predictor of disease progression and recurrence in NMIBC. The Kaplan-Meier analyses in our study are consistent with those findings. However, after adjusting for confounding variables, we found that preoperative NLR was not an independent predictor of oncologic outcomes in NMIBC.

Lymphocytes may aid in an anti-tumor response, and the density of tumor-associated macrophages in many cancers correlates with increased angiogenesis, tumor invasion, and poor prognosis [9]. Recent studies also suggest LMR to be a comparable to NLR in terms of its ability to predict clinical outcome of BC treated with RC [18]. Lower lymphocyte-monocyte ratio (LMR) was demonstrated to be associated with reduced disease-free survival and OS [19, 39]. The Kaplan-Meier analyses in our study, similar to those findings, revealed low preoperative LMR was significantly associated with worse RFS and PFS in NMIBC. However, after controlling for clinicopathological features, LMR was not remained as an independent predictor of oncologic outcomes.

The study limitations include its retrospective and non-randomized design, which may have introduced a recall bias. In addition, this is a single-institution study and, as such, it requires external validation. Furthermore, despite the use of standard treatment protocols, information regarding the drugs used for intravesical instillations is lacking. Finally, our cohort excluded patients who had received neo-adjuvant chemotherapy, and therefore further studies are needed to evaluate whether blood biomarkers can predict response to neo-adjuvant chemotherapy. However, to our knowledge, this is the first study to assess the prognostic relevance of PLR and LMR in patients with NMIBC undergoing TURBT. We confirm that PLR is a potential prognostic marker for prediction of disease progression and recurrence in patients after TURBT. This parameter warrants further validation as a potential selection criterion for risk factor-stratified patient management in NMIBC.

In conclusion, preoperative PLR seems to be an independent predictor of disease progression and recurrence in NMIBC patients undergoing TURBT. Large-scale prospective and multiple-institution studies are warranted to validate our findings.

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Disclosure of conflict of interest

None.

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