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Predictive value of pretreatment inflammation-based prognostic scores (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio) for invasive bladder carcinoma

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Purpose: Inflammation-based prognostic scores including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are associated with oncologic outcomes in diverse malignancies. We evaluated the predictive value of pretreatment prognostic scores in differentiating nonmuscle invasive (NMIBC) and muscle invasive bladder cancer (MIBC).

Materials and Methods: Consecutive transurethral resection of bladder tumour (TURBT) cases from January 2011 to December 2013 were analysed retrospectively. Patient demographics, tumour characteristics and prognostic scores results were recorded. Receiver operating characteristics curves were used to determine prognostic score cutoffs. Univariate and multivariate binomial logistic regression analysis was performed to evaluate the association between variables and MIBC.

Results: A total of 226 patients were included, with 175 and 51 having NMIBC (stages Ta and T1) and MIBC (stage T2+) groups, respectively. Median age was 75 years and 174 patients were male. The NLR cutoff was 3.89 and had the greatest area under the curve (AUC) of 0.710, followed by LMR (cutoff<1.7; AUC, 0.650) and PLR (cutoff>218; AUC, 0.642). Full blood count samples were taken a median of 12 days prior to TURBT surgery. Multivariate logistic regression analysis identified tumour grade G3 (odds ration [OR], 32.848; 95% confidence interval [CI], 9.818–109.902; p=0.000), tumour size≥3 cm (OR, 3.353; 95% CI, 1.347–8.345; p=0.009) and NLR≥3.89 (OR, 8.244; 95% CI, 2.488–27.316; p=0.001) as independent predictors of MIBC.

Conclusions: NLR may provide a simple, cost-effective and easily measured marker for MIBC. It can be performed at the time of diagnostic flexible cystoscopy, thereby assisting in the planning of further treatment.

Keywords: Blood platelets; Lymphocytes; Neutrophils; Urinary bladder neoplasms

INTRODUCTION

Bladder cancer represents the ninth most common cancer worldwide and the most common malignancy of the urinary tract [1]. Approximately 75%–85% of patients present with nonmuscle invasive bladder cancer (NMIBC), for which transurethral resection of bladder tumour (TURBT) remains the standard first-line treatment [2]. Management drastically changes in muscle-invasive bladder cancer (MIBC) and may include radical cystectomy, radiotherapy and chemotherapy. At present, bladder cancer staging is most accurately performed with TURBT pathology specimens; however, errors in the staging process are common, with many patients upstaged at time of radical cystectomy [3].

Current theories suggest that cancer triggers a systemic inflammatory response, leading to changes in circulating inflammatory cells. The main changes include a neutrophilia with relative lymphocytopenia or thrombocytosis. These cells, along with the cytokines and chemokines they produce, play a role in the growth, maturation and differentiation of cells within the tumour microenvironment [4]. A number of inflammation-based prognostic scores that measure these changes, including preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have been found to be associated with the oncologic outcomes in a range of diverse malignancies, including, but not limited to renal, colorectal, hepatic, breast and lung [5-8].

While previous studies establishing a relationship between elevated NLR and invasive bladder cancer have been published [9-11], these have neglected other, alternate inflammation-based scores including PLR and LMR. The aim of the current study was to evaluate the predictive value of pretreatment inflammation-based prognostic scores for differentiating muscle-invasive and non–muscle-invasive disease in patients undergoing TURBT surgery for primary bladder cancer.

MATERIALS AND METHODS

1. Patients

Consecutive patients with primary transitional cell bladder cancer who underwent TURBT between January 2011 and December 2013 at a large district general hospital were retrospectively reviewed. Patients with recurrent bladder tumours, nontransitional cell bladder carcinoma, metastatic disease, alternative cancer/haematological disorder diagnosis, evidence of active infection (including urinary tract infection) or lacking preoperative blood

tests were excluded from the study. At time of surgery, all patients had undergone flexible cystoscopic evaluation and had negative urinalyses. Diagnosis of bladder cancer was confirmed by histology, and samples were categorised as NMIBC (stage pTa or T1) or MIBC (stage T2+). All specimens were confirmed to contain detrusor muscle for quality assurance; patients with specimens lacking detrusor muscle had a repeat TURBT at 6 weeks. Clinicopathologic variables recorded included age, sex, preoperative full blood count, tumour size, tumour grade, and multiplicity.

2. Blood analysis

Routine full blood counts were routinely collected as part of a preoperative protocol. Samples were collected in ethylenediaminetetraacetic acid anticoagulated tubes and analysed using Sysmex XE-2100 and XE-5000 Haematology Analysers (Sysmex UK, Milton Keynes, UK). Patients attending preoperative assessment clinic had concurrent urine dipstick and blood tests. Positive urine dipstick tests were sent for midstream urine microbiology and culture and antibiotics were prescribed. In these patients, repeat urine dipstick and blood tests were performed prior to the operation. Preoperative full blood counts within 60 days of TURBT were used for analysis. When multiple values existed for a patient, the sample values closest to the date or resection were analysed.

3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. LMR was defined as the absolute lymphocyte count divided by the absolute monocyte count. Receiver operating characteristics (ROC) curves were generated to determine cutoff points for each prognostic score. Patients were stratified into groups based upon the cutoff/threshold points, and characteristics compared using a chi-square test. Multivariate analysis was performed for the variables identified as statistically significant in univariate analysis, using logistic regression.

RESULTS

A total of 226 patients were included in the study, 175 and 51 with NMIBC and MIBC, respectively. The majority of the patients were male (174 of 226, 77.0%), with a median age of 75 years (interquartile range [IQR], 65–81 years). Of
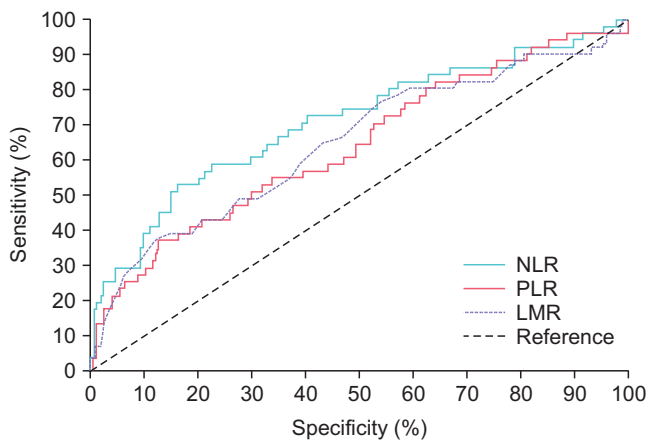
the NMIBC patients, 129 had Ta disease and 46 had T1 disease. Grade G1 of G2 disease was found in 128 of 175 (73.1%) NMIBC patients and 2 of 51 (3.9%) MIBC patients. Full blood count samples were taken a median of 12 days (IQR, 6–21 days) prior to TURBT surgery.

Using MIBC (stage T2 or greater disease) as a classification variable, ROC curves for the four inflammation-based prognostic scores, NLR, PLR, and LMR, are displayed in Fig. 1. Of the prognostic scores, NLR (threshold, >3.89) had the greatest area under the ROC curve (AUC) of 0.710 (sensitivity, 52.9%; specificity, 84.0%; p<0.0001), followed by

Fig. 1. Receiver operating characteristics curves for inflammation-based prognostic scores. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

LMR (threshold, <1.8; AUC, 0.650; sensitivity, 37.3%; specificity, 88.0%; p=0.0015). The threshold value for PLR was >218 with AUC of 0.642 (sensitivity. 37.3%; specificity. 87.4%; p=0.0022).

Patients were stratified into groups based upon the ROC threshold values. The patients' baseline characteristics and comparisons of the patients' clinicopathological characteristics stratified by NLR, PLR, and LMR are described in Table 1. Groups were compared using chi-square analysis, with p-values <0.05 considered significant.

To identify factors associated with MIBC, binomial logistic regression analysis was performed, including prognostic scores, patient characteristics and tumour characteristics (Table 2). Univariate analysis identified age, tumour grade, tumour size, NLR, PLR, and LMR as significant predictors of muscle-invasive disease. The multivariate logistic regression model identified tumour grade (OR, 32.848; 95% CI, 9.818–109.902; p=0.000), tumour size (OR, 3.353; 95% CI, 1.347–8.345; p=0.009) and NLR (OR, 8.244; 95% CI, 2.488–27.316; p=0.001) as independent predictors of MIBC.

DISCUSSION

Bladder cancer is a heterogeneous disease and optimum management of bladder cancer is guided by accurate staging, for which pathological analysis is the gold standard. Staging error is extremely common, with reports demon-

Table 1. Baseline characteristics of patients, stratified by NLR, PLR, and LMR

Characteristic	Total	NLR			PLR			LMR		
		<3.89	≥3.89	p-value	<218	≥218	p-value	>1.8	≤1.8	p-value
Age (y)				0.019*			0.164			0.008*
<70	82 (36.3)	69 (40.6)	13 (23.2)		71 (38.4)	11 (26.8)		76 (40.0)	6 (16.7)	
≥70	144 (63.7)	101 (59.4)	43 (76.8)		114 (61.6)	30 (73.2)		114 (60.0)	30 (83.3)	
Sex				0.490			0.521			0.903
Male	174 (77.0)	129 (75.9)	45 (80.4)		144 (77.8)	30 (73.2)		146 (76.8)	28 (77.8)	
Female	52 (23.0)	41 (24.1)	11 (19.6)		41 (22.2)	11 (26.8)		44 (23.2)	8 (22.2)	
Tumour grade				0.036*			0.015*			0.003*
G1/G2	132 (58.4)	106 (62.4)	26 (46.4)		115 (62.2)	17 (41.5)		119 (62.6)	13 (36.1)	
G3	94 (41.6)	64 (37.6)	30 (53.6)		70 (37.8)	24 (58.5)		71 (37.4)	23 (63.9)	
Tumour stage				0.000*			0.000*			0.000*
Ta/T1	175 (77.4)	146 (85.9)	29 (51.8)		153 (82.7)	22 (53.7)		156 (82.1)	19 (52.8)	
T2+	51 (22.6)	24 (14.1)	27 (48.8)		32 (17.3)	19 (46.3)		34 (17.9)	17 (47.2)	
Tumour size (cm)				0.029*			0.000*			0.002*
<3 (small)	133 (58.8)	107 (62.9)	26 (46.4)		119 (64.3)	14 (34.1)		120 (63.2)	13 (36.1)	
≥3 (large)	93 (41.9)	63 (37.1)	30 (53.6)		66 (35.7)	27 (65.9)		70 (36.8)	23 (63.9)	
Multiplicity				0.048*			0.011*			0.627
Solitary	149 (65.9)	106 (62.4)	43 (76.8)		115 (62.2)	34 (82.9)		124 (65.3)	25 (69.4)	
Multiple	77 (34.1)	64 (37.6)	13 (23.2)		70 (37.8)	7 (17.1)		66 (34.7)	11 (30.6)	

Values are presented as number (%).
NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.
*p<0.05, statistically significant difference.

Table 3. Previous studies comparing NLR and bladder cancer staging

Source	Patient	NLR	Analysis
Can et al. (2012) [9]	182 Patients: NMIBC (n=80), MIBC (n=102)	ROC cutoff: 2.57	NLR>2.57 was independent predictor of MIBC (OR, 2.78; 95% CI, 1.383–5.588; p=0.004*)
Ceylan et al. (2014) [10]	198 Patients: NMIBC (n=162), MIBC (n=36)	Mean NLR: MIBC, 4.14±2.76; NMIBC, 3.36±2.88 ROC cutoff: 3.96	Mean NLR differed significantly between MIBC and NMIBC on Mann-Whitney U test (p=0.03*)
Kaynar et al. (2014) [11]	291 Patients: NMIBC (n=192), MIBC (n=99)	Mean NLR: MIBC, 2.9±0.2; NMIBC, 2.4±0.1	Mean NLR differed significantly between MIBC and NMIBC on Mann-Whitney U test (p=0.028*) Significant correlation between NLR and MIBC on univariate analysis (r=0.138, p=0.031*)
Krane et al. (2013) [21]	68 Patients with recurrent T1 disease or MIBC undergoing radical cystectomy	Mean NLR: 4.0±2.8 (overall) Cutoff: 2.5 (as per previous publications)	NLR>2.5 was independent predictor of extravesical disease (RR, 3.18; 95% CI, 1.09–9.79; no p-value given)
Potretzke et al. (2014) [22]	102 Patients undergoing radical cystectomy: NMIBC (n=25), MIBC (n=77)	Mean NLR: 4.33±0.87 (upstaged to ≥pT3) and 2.66±0.29 (≤pT2)	NLR (continuous variable) was independent predictor of upstaging (OR, 1.36; 95% CI, 1.01–1.84; p=0.04*) and extravesical disease (OR, 1.5; 95% CI, 1.07–2.1; p=0.02*) at radical cystectomy
Viers et al. (2014) [23]	899 Patients undergoing radical cystectomy: NMIBC (n=363), MIBC (n=524)	Cutoff: 2.7 (obtained visually)	NLR (continuous variable) was independent predictor of extravesical disease (OR, 1.07; 95% CI, 1.01–1.15; p=0.03*) and lymph node involvement (OR, 1.09; 95% CI, 1.02–1.16; p=0.02*)

NLR, neutrophil-to-lymphocyte ratio; NMIBC, nonmuscle invasive bladder cancer; MIBC, muscle invasive bladder cancer; ROC, receiver operating characteristics; OR, odds ratio; CI, confidence interval; RR, relative risk.

cystectomy, elevated NLR was associated with upstaging or extra-vesical disease [21-23]. It is important to note the wide range of ROC curve cutoff values for NLR in these publications. This variation may be explained by the nature of NLR as a nonspecific marker that may rise secondary to a number of insults, such as infection. A consensus NLR cutoff value remains to be determined.

NLR has been shown to be inversely associated with disease recurrence and progression in bladder cancer, first in a mixed cohort of patients undergoing radical cystectomy for MIBC and recurrent NMIBC. A number of authors have found patients with elevated NLR to an independent predictor recurrence-free, disease-specific and overall survival [21,23]. More recently, Mano et al. [24] examined a group of NMIBC patients and found an elevated NLR to be significantly associated with disease recurrence and progression. Ozyalvacli et al. [25] further limited their patient cohort to those with stage pT1 bladder tumours, and confirmed the association of NLR with disease recurrence and progression. This association of elevated NLR with invasive disease, disease recurrence and survival could signify a marker for a subset of patients with high risk, aggressive tumour biology.

We recognise the limitations in the retrospective nature

of our study. While patients with concurrent inflammatory conditions (e.g., infection, haematological disorder) were omitted, the confounding effect of these cannot be completely excluded. In addition, preoperative blood tests were taken a median of 12 days prior to the TURBT surgery. While we excluded patients with blood tests more than 60 days before the date of surgery, it is possible that the full blood count changed during this time. However, the NLR study in patients undergoing radical cystectomy by Viers et al. [23] determined that NLR remains stable over a period as long as 90 days.

Furthermore, the main aim of our study was to differentiate muscle-invasive from superficial disease, as an aid to clinicians. The groups were separated into NMIBC (Ta/T1) and MIBC (T2+) as these differentiated patients who would be appropriately managed with TURBT as compared to radical surgery, radiotherapy or chemotherapy, as per current European Association of Urology guidelines [26]. It is noted that muscle-invasive, or T2+ disease does include a wide range of disease. This can include cancer that has invaded the muscularis propria (T2), up to adjacent structures (T4), such as the prostate, vagina or pelvic wall, and it is likely that the systemic inflammatory response increases with tumour stage. While the use of inflammation-

based prognostic scoring to differentiate each stage of MIBC was beyond the scope of our study, it merits further study to identify patients most appropriate for radical surgery.

Despite these limitations, NLR appears to be a promising marker for invasive bladder cancer and may be a useful variable in future predictive nomograms. Larger, prospective studies are required to fully define the utility of NLR within a clinical setting.

CONCLUSIONS

Accurate pathological staging in bladder cancer is vital as it guides early management. Our comparison of pretreatment inflammation-based prognostic scores indicates that NLR is an independent predictor of muscle-invasive disease and may provide a simple, cost-effective and easily measured marker for MIBC. It can be performed at the time of diagnostic flexible cystoscopy, thereby assisting in the planning of further treatment and follow-up, including tumour resection and provision of intravesical therapy.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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