

## Neutrophil-to-lymphocyte ratio is elevated in recurring nonmuscle invasive bladder cancer

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**Background/aim:** Although it has been shown that the neutrophil-to-lymphocyte ratio (NLR) may predict the progression of nonmuscle invasive bladder cancer (NMIBC), its association with the recurrence of NMIBC has been poorly studied. The aim of this study is to evaluate the association between NLR and disease recurrence in patients with NMIBC.

**Materials and methods:** The medical records of 428 consecutive initially diagnosed NMIBC patients who underwent transurethral resection between January 2010 and July 2014 were retrospectively reviewed. Patients without a preoperative NLR (n = 6), without a minimum of 6 months of follow-up (n = 56), who were lost to follow-up (n = 38), or who had progressive disease during follow-up (n = 42) were excluded. The demographics, tumor characteristics, and NLRs of patients with and without tumor recurrence were compared.

**Results:** Of 286 patients who met the inclusion criteria, 68 (17.43%) had recurrent disease. Tumor size (P = 0.198), tumor type (P = 0.929), and the presence of carcinoma in situ (P = 0.373) were also similar between groups. Patients with recurrent disease had a higher mean NLR (2.62 ± 0.99 vs. 2.2 ± 0.96, P = 0.002).

**Conclusion:** Our results show that NLR may be used as a predictor of recurrence in patients with NMIBC; however, prospective studies are required to validate these findings.

**Key words:** Bladder cancer, lymphocyte, neutrophil, nonmuscle invasive, recurrence

### 1. Introduction

Urologists are faced with several specific challenges in managing patients diagnosed with nonmuscle invasive bladder cancer (NMIBC), a neoplasm that is characterized by tumors that frequently recur and often progress to potentially lethal muscle-invasive disease. Early diagnosis and life-long surveillance are required to provide patients with a reduced risk of tumor recurrence, as well as potentially prevent disease progression. In spite of the well-designed follow-up programs recommended by current guidelines (1,2), recurrence is still seen in nearly three-fourths of patients, and disease progression is seen in a significant number (3). Even with a well-trained eye the conventional follow-up of in-office cystoscopy and urine cytology may still miss tumor recurrence in a significant number of cases (4-7). Current advances in molecular biomarkers that could potentially work synergistically with conventional surveillance to improve overall sensitivity are hopeful; however, their use is still not widely accepted due to several limitations (8).

There is increasing evidence that supports the involvement of systematic inflammation in cancer development and progression (9). The neutrophil-to-lymphocyte ratio (NLR) can be used as a marker of this systematic inflammatory response (10). Poor outcomes have been associated with an increased pretreatment NLR in some cancers (11-14). Most recently evidence has emerged supporting that the NLR can be correlated with outcomes in bladder cancer managed with radical cystectomy (15), as well as determining tumor invasiveness (16). NLR may have a potential use for predicting outcomes in bladder cancer patients; however, to our knowledge, no study has investigated the prognostic significance of NLR in the recurrence of NMIBC patients to date. Thus, we evaluated the significance of NLR with regards to recurrence of NMIBC.

### 2. Materials and methods

#### 2.1. Study design

After approval by our institutional review board, the medical records of 428 consecutive initially diagnosed

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NMIBC patients who underwent transurethral resection (TURBT) between January 2010 and July 2014 were retrospectively reviewed. Only the patients with primary bladder tumors were included. Patients without a preoperative NLR ( $n = 6$ ), who did not have a minimum of 6 months of follow-up ( $n = 56$ ), who were lost to follow-up ( $n = 38$ ), or who were referred for cystectomy or radiotherapy because of disease progression during the follow-up ( $n = 42$ ) were excluded. Of the patients with progression to pT2 disease, 18 (42.9%) were diagnosed as having a muscle-invasive disease in the second TURBT and 24 (57.1%) during the follow-up period.

The NLR was calculated by using the neutrophil and lymphocyte numbers measured in a pretreatment complete blood count (CBC), a week before the operation. If the patient required blood transfusion during the preoperative period, NLR was calculated using the initial CBC. The demographics, tumor characteristics, and NLRs of patients with and without tumor recurrence were compared.

## 2.2. TURBT procedure

After verification of a bladder tumor either by ultrasonography or office cystoscopy, all patients were initially treated with TURBT. The procedures were performed under general anesthesia unless contraindicated by anesthesiology. Before the operation, urine cultures of all patients were checked and they were treated accordingly in order to prevent septic complications. Resections were performed using a Gyrus PlasmaKinetic Generator and a 27-F resectoscope (Gyrus ACMI, Southborough, MA, USA). After systematic cystoscopy, tumors up to 1 cm in diameter were resected en bloc while larger tumors were resected and referred to the pathologist separately in fractions including the exophytic portion, underlying bladder wall, and edges of the tumor. The pathological specimens were evaluated by a single genitourinary pathologist. Tumors were graded according to both WHO 1973 and 2004 grading systems (17,18) and staged to the 2009 TNM classification of urinary bladder cancer (19). A single, immediate, postoperative intravesical instillation of epirubicin was administered to all patients except for those with overt/suspected bladder perforation or bleeding that required bladder irrigation. A second TURBT was performed after incomplete or insufficient initial TURBT and in patients with T1 or grade 3 tumors.

## 2.3. Follow-up scheme

Risk scores for recurrence and progression of the disease were calculated using EORTC risk tables and patients were referred to intravesical chemotherapy or immunotherapy whenever indicated (20). Patients were followed with regular cystoscopy and urinary cytology at intervals decided according to the risk scores of the individual patients. Annual upper tract imaging using computerized

tomography-urography was performed in high-risk patients. The first pathologically confirmed tumor relapse in the bladder regardless of the tumor stage was accepted as tumor recurrence.

## 2.4. Statistical analysis

Statistical analyses were performed using the Number Cruncher Statistical System 2007 statistical software package program (NCSS, LLC, Kaysville, UT, USA). In addition to descriptive statistics (mean, standard deviation, median, interquartile range), data were evaluated by independent t-test for variables with normal distribution, or by Fisher exact test and chi-square test for comparison of qualitative data. To define the factors predictive of recurrence, logistic regression analysis was performed. Statistical significance was set at  $P < 0.05$ .

## 3. Results

Overall 286 patients with a mean age of  $65.65 \pm 11.4$  years (range: 18–95) and a mean follow-up period of  $19.84 \pm 17.66$  months (range: 6–108) were included. The follow-up durations of patients with and without recurrence were  $32.3 \pm 25.7$  and  $16.6 \pm 12.2$  months, respectively ( $P < 0.001$ ). Recurrence was seen in 68 (17.43%) patients. Characteristics of the patients with and without tumor recurrence are summarized in the Table.

The mean age, sex distribution, history of diabetes, and rates of hypertension, coronary artery disease, and hyperlipidemia were similar in patients with and without recurrence (Table). Ta disease was reported in 77 (26.9%), T1 disease in 201 (70.3%), and carcinoma in situ (CIS) in 8 (2.8%) patients. Of the entire cohort, 174 patients (60.8%) had low-grade and 112 (39.2%) patients had high-grade disease. Neither T stage ( $P = 0.121$ ) nor grade ( $P = 0.205$ ) was associated with recurrence during the follow-up period. Overall 99 (34.6%) patients did not receive postoperative immediate instillation due to overt perforation (11 patients), suspected perforation (74 patients), or bleeding necessitating continued irrigation (14 patients). Tumor size ( $P = 0.198$ ), tumor appearance ( $P = 0.929$ ), and presence of CIS ( $P = 0.373$ ) were also similar between groups. A second TURBT was performed in 217 (75.9%) patients. Having a second TURBT was not associated with recurrence ( $P = 0.386$ ). Recurrence rates were similar among patients with (148 [51.7%] patients) and without (138 [48.3%] patients) intravesical induction and maintenance treatments ( $P = 0.620$ ). However, single tumors ( $P < 0.001$ ) and postoperative epirubicin installation ( $P < 0.001$ ) were associated with reduced risk of recurrence. Moreover, the mean NLR of patients with recurrent disease ( $2.62 \pm 0.99$ ) was significantly higher than that of nonrecurrent patients ( $2.2 \pm 0.96$ ) ( $P = 0.002$ , odds ratio = 1.69, 95% confidence interval: 1.03–2.79).

**Table.** Comparison of patient demographics, accompanying comorbidities, and tumor characteristics in patients with and without recurrence (CIS: carcinoma in situ).

| Characteristics                      | Recurrence<br>n = 68 | No recurrence<br>n = 218 | P*     |
|--------------------------------------|----------------------|--------------------------|--------|
| Age                                  | 65.87 ± 10.94        | 62.22 ± 11.89            | 0.690  |
| Sex                                  |                      |                          |        |
| Male                                 | 59 (86.76%)          | 194 (88.99%)             | 0.616  |
| Female                               | 9 (13.24%)           | 24 (11.01%)              |        |
| Diabetes mellitus                    | 16 (23.53%)          | 38 (17.43%)              | 0.262  |
| Coronary artery disease              | 13 (19.12%)          | 42 (19.27%)              | 0.978  |
| Hypertension                         | 32 (47.06%)          | 78 (35.78%)              | 0.095  |
| Hyperlipidemia                       | 2 (2.94%)            | 4 (1.83%)                | 0.578  |
| Preoperative blood transfusion       | 1 (1.47%)            | 7 (3.21%)                | 0.447  |
| Postoperative blood transfusion      | 2 (4.17%)            | 4 (2.30%)                | 0.480  |
| Size                                 |                      |                          |        |
| <3 cm                                | 9 (13.24%)           | 44 (20.18%)              | 0.198  |
| ≥3 cm                                | 59 (86.76%)          | 174 (79.82%)             |        |
| Number                               |                      |                          |        |
| Single                               | 32 (47.06%)          | 155 (71.10%)             | 0.0001 |
| Multiple                             | 36 (52.94%)          | 63 (29.90%)              |        |
| Appearance                           |                      |                          |        |
| Papillary                            | 60 (88.24%)          | 192 (88.89%)             | 0.929  |
| Solid/flat                           | 8 (11.76%)           | 24 (11.11%)              |        |
| Presence of CIS                      | 3 (4.41%)            | 5 (2.23%)                | 0.373  |
| Postoperative immediate instillation |                      |                          |        |
| Epirubicin                           | 39 (57.35%)          | 146 (67.0%)              | 0.001  |
| None                                 | 29 (42.65%)          | 70 (32.0%)               |        |

\*Fischer exact test and chi-square test.

Of note, blood transfusion was needed in 8 (2.79%) patients in order to increase hemoglobin levels during the preoperative period, whereas 6 (2.09%) patients required transfusion during the postoperative period.

#### 4. Discussion

An ideal biomarker to be used for monitoring recurrence of NMIBC would be noninvasive, easily applicable, and affordable, with both high sensitivity and specificity (21). In theory this could potentially decrease the morbidity associated with frequent cystoscopy, improve the patient's quality of life, and decrease costs by substituting a less expensive noninvasive test for the more expensive

endoscopic procedure (22). For example, a highly specific noninvasive adjunct to cystoscopy already used today is voided urine cytology. This biomarker has good sensitivity for detecting high-grade urothelial cancer; however, sensitivity for the detection of low-grade tumors ranges from only 4% to 31% (23). Cytology is also highly user-dependent and dependent on the quality of the specimen (24). A significant number of laboratory and clinical investigations have developed numerous new urine markers for the detection and diagnosis of bladder cancer in an attempt to improve upon the shortcomings of urine cytology. Indicators such as microsatellite polymorphism analysis (25), ImmunoCyt (Diagnocure Inc, Quebec

City, Canada) (26,27), the nuclear matrix protein-22 (Matritech, Newton, MA, USA) (28), fluorescence in situ hybridization (FISH) analysis (Urovysion Systems Vysis, Abbott Laboratories, Abbott Park IL, USA) (29), urinary epidermal growth factor receptor, and epithelial cell adhesion molecules have been studied (30). However, as the sensitivity and specificity of these are low, they have not become standard procedures for patients' diagnosis and follow-up surveillance (8,31). Thus, there is currently no noninvasive standard method for screening for NMIBC surveillance other than standard cystoscopy with urine cytology. Other predictive factors of tumor recurrence such as tumor number, diameter, prior recurrences, presence of T1 disease, presence of CIS, and grade of the tumor have been well established (32), and we hypothesized that NLR could be used adjunctively as a prognostic biomarker to predict the likelihood of recurrence of NMIBC.

The NLR is a nonspecific marker of systemic inflammation that can easily be calculated by the ratio of neutrophils to lymphocytes in a patient's peripheral blood sample. Obvious advantages of the NLR include low cost, ease of application, and broad availability. This biomarker could be useful in determining initial prognosis when determining how often to screen patients. We demonstrated that in a group of 286 patients with NMIBC, patients with recurrent disease had a higher mean NLR. The NLR has already been associated with different types of cancer, as increased pretreatment NLR is associated with poor prognosis in colorectal, gastric, renal cell, and ovarian cancer (11–14), as well as malignant mesothelioma and upper tract urothelial carcinoma (33,34). Gondo et al. also recently demonstrated that a NLR threshold value of  $<2.5$  and  $\geq 2.5$  is an independent prognostic factor for disease-specific survival risk in bladder cancer patients treated with radical cystectomy (15). Another study by Mano et al., which included 107 patients with NMIBC, calculated that a NLR of  $>2.41$  was associated with disease progression and  $>2.43$  was associated with disease recurrence based on multivariate analysis (35). Similarly, our study of a larger cohort found that not only could the NLR have prognostic indications, but it could also possibly be applied as an adjuvant tool to risk stratification of patients on surveillance for NMIBC.

Although previous reports demonstrated the association between tumor stage and grade (32), we could not find such an association. This may be partly attributed to the high second TURBT rates reported in the current series. In a study by Sfakianos et al., it was reported that a single TURBT was the only predictor of recurrence at 5 years (36).

The idea behind this is that inflammation may be associated with different stages of tumor development including initiation, promotion, malignant conversion, invasion, and metastasis (37). Tachibana et al. previously showed that bladder cancer cells produce granulocyte-colony stimulating factor (G-CSF) and express G-CSF receptors; thus, G-CSF production by bladder cancer cells augments autocrine growth. This suggests that the inflammatory response may play a crucial role in malignant progression of bladder tumors (38). Neutrophils in particular may also play a direct role in tumor development as they are known to contain and secrete vascular endothelial growth factor, a proangiogenic factor (39). Cho et al. reported that patients with elevated NLR exhibit relative lymphocytopenia and, as a result, may mount a poor lymphocyte-mediated immune response to malignancy, allowing for potential tumor progression and in turn worsening their prognosis (13). In multivariate analysis, pretreatment NLR is an independent prognostic factor among these inflammatory parameters (15). It would be reasonable to expect the NLR to correlate with any amount of tumor recurrence, whether or not muscle invasion is present, as the proposed inflammatory response of neoplasia should be present.

This study has several limitations. It was performed in a retrospective manner with a limited number of patients, and our follow-up period was relatively short. In addition, as only univariate analysis was performed, confounding variables that were not accounted for could have skewed our results. Both of these limitations may be responsible for not demonstrating a statistically significant difference in tumor size ( $P = 0.198$ ), tumor appearance ( $P = 0.929$ ), and presence of CIS ( $P = 0.373$ ) between patients with and without recurrence. It is possible that patients with CIS had a higher rate of disease progression and were thus not included in the recurrence group. We also did not collect data regarding corticosteroid use, immunosuppression, other ongoing malignancies, or antibiotic therapies that could affect a patient's NLR. Although further study with a larger sample size is necessary to validate the significance of NLR in recurrence of NMIBC, we think that our results represent a cost-effective adjuvant to current standards in patients undergoing surveillance for recurrent NMIBC.

NLR may be used as a predictor of recurrence patients with NMIBC; however, prospective studies are required to validate these findings. Further research with regards to both serum and urine biomarkers should have a goal of being easily applied and cost-effective with both high sensitivity and specificity.

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