Validation of Neutrophil-to-lymphocyte Ratio in a Multi-institutional Cohort of Patients With T1G3 Non–muscle-invasive Bladder Cancer

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Abstract

Neutrophil-to-lymphocyte ratio was found associated with worse disease recurrence and progression in patients with T1 non–muscle-invasive bladder cancer in some single-center studies. We validated high pretreatment neutrophil-to-lymphocyte ratio (cutoff, 3) as an independent predictor of disease recurrence, progression, and cancer-specific survival in patients with primary T1 HG/G3 non–muscle-invasive bladder cancer treated with intravesical bacillus Calmette-Guérin therapy.

Introduction: The aim of this multicenter study was to investigate the prognostic role of neutrophil-to-lymphocyte ratio (NLR) and to validate the NLR cutoff of 3 in a large multi-institutional cohort of patients with primary T1 HG/G3 non–muscle-invasive bladder cancer (NMIBC). **Patients and Methods:** The study period was from January 2002 through December 2012. A total of 1046 patients with primary T1 HG/G3 who had NMIBC on re-transurethral bladder resection (TURB) who received adjuvant intravesical bacillus Calmette-Guérin therapy with maintenance from 13 academic institutions were included. Endpoints were time to disease, and recurrence-free (RFS), progression-free

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Submitted: Mar 9, 2018; Revised: Jun 15, 2018; Accepted: Jul 3, 2018; Epub: Jul 6, 2018

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1558-7673/$ - see frontmatter
https://doi.org/10.1016/j.clgc.2018.07.003

(PFS), overall (OS), and cancer-specific survival (CSS). **Results:** A total of 512 (48.9%) of patients had NLR $\geq$ 3 prior to TURB. High pretreatment NLR was associated with female gender and residual T1HG/G3 on re-TURB. The 5-year RFS estimates were 9.4% (95% confidence interval [CI], 6.8%-12.4%) in patients with NLR $\geq$ 3 compared with 58.8% (95% CI, 54%-63.2%) in patients with NLR $<$ 3; the 5-year PFS estimates were 57.1% (95% CI, 51.5%-62.2%) versus 79.2% (95% CI, 74.7%-83%; $P < .0001$); the 10-year OS estimates were 63.6% (95% CI, 55%-71%) versus 66.5% (95% CI, 56.8%-74.5%; $P = .03$); the 10-year CSS estimates were 77.4% (95% CI, 68.4%-84.2%) versus 84.3% (95% CI, 76.6%-89.7%; $P = .004$). NLR was independently associated with disease recurrence (hazard ratio [HR], 3.34; 95% CI, 2.82-3.95; $P < .001$), progression (HR, 2.18; 95% CI, 1.71-2.78; $P < .001$) and CSS (HR, 1.65; 95% CI, 1.02-2.66; $P = .03$). The addition of NLR to a multivariable model that included established features increased its discrimination for predicting of RFS (+6.9%), PFS (+1.8%), and CSS (+1.7%). **Conclusions:** Pretreatment NLR $\geq$ 3 was a strong predictor for RFS, PFS, and CSS in patients with primary T1 HG/G3 NMIBC. It could help in the decision-making regarding intensity of therapy and follow-up.

Clinical Genitourinary Cancer, Vol. 16, No. 6, 445-52
Keywords: High-grade, High risk, NLR, Progression, Recurrence

Introduction

Bladder cancer (BC) is the seventh most common cancer in men and the seventeenth most common cancer in women worldwide; it is estimated that more than 80,000 new cases will be diagnosed in the United States alone in 2018.[1] In western countries, approximately three-quarters of patients with newly diagnosed BC present with non−muscle-invasive (NMIBC) disease.[2,3] Standard treatment for NMIBC is trans-urethral resection of the bladder (TURB) followed by adjuvant intravesical instillation therapy, based on the patient's risk stratification.[4,5] Despite risk-based therapy, recurrence rates are as high as 70% and progression rate as high as 30%, depending on the case-mix of patients.[6]

The current prognostic model for NMIBC, which relies on standard clinicopathologic features such as T stage, grade, multifocality, tumor diameter, recurrence rate, and concomitant carcinoma in situ (CIS), does not provide sufficient accuracy to discern those patients most likely to benefit from early radical cystectomy (RC) from those who should receive intravesical therapy.[7] This is especially true for patients with T1 HG/G3 BC, as these tumors harbor a highly variable behavior with a high mortality.[8(p1)]

Better tools for prediction of disease recurrence and progression, especially in T1 HG/G3 NMIBC, are necessary to improve the management by helping clinicians to accurately stratify patients for individualized follow-up, early RC, or inclusion in clinical trials of novel therapies such as immune checkpoint inhibitors or device-assisted intravesical chemotherapy.[9,10]

There is growing evidence that inflammation plays a key role in various malignancies such as urothelial cancer.[11,12] One of the most studied inflammation markers is the neutrophil-to-lymphocyte ratio (NLR).[13] Recently, a meta-analysis showed that NLR impacts outcomes in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy.[14] In BC, NLR was a predictor of overall survival (OS) (hazard ratio [HR], 1.19), cancer-specific survival (CSS) (HR, 1.40), recurrence-free survival (RFS) (HR, 1.58), and progression-free survival (PFS) (HR, 1.33) in the most recent meta-analysis, which included 17 studies (only 4 of these studies included patients with NMIBC).[15] Although evidence is mounting, only small single-center studies investigated the prognostic role of NLR in the focus group of patients with T1 HG/G3 NMIBC for prediction of disease recurrence and progression.[16,17]

The aim of this multicenter study was to investigate the prognostic role of NLR in a large multi-institutional cohort of patients with primary T1 HG/G3 NMIBC.

Material and Methods

Patient Selection and Data Collection

Institutional review board approval at each institution was obtained, with all participating sites providing institutional data-sharing agreements prior to the initiation of the study. Inclusion criteria were: (1) pathologic T1 HG/G3 confirmed after first TURB; (2) a repeat TURB performed within 4 to 6 weeks after a complete first TURB; (3) pretreatment NLR available prior to TURB; and (4) intravesical BCG treatment with maintenance. Patients with evidence of acute and chronic prostatitis or cystitis, urinary tract infection, yeast infections, endometriosis, systemic inflammatory disease, or incomplete data were excluded.[18] A total of 1046 of 1155 patients with primary T1 HG/G3 treated between January 1, 2002 and December 31, 2012 at 13 academic institutions met the inclusion criteria. The maintenance schedule was generally according to the European Association of Urology guidelines at the time.[19] Demographic, clinical, pathologic, and outcomes data were collected and entered in a computerized database. Data integrity, completeness, and quality were ensured through internal and external revisions.

Management and Follow-up

All patients had a standard TURB with curative intent followed by a re-TURB at 4 to 6 weeks.[4] Informed consent was obtained from each patient. Complete resection of all papillary tumors was a condition for BCG therapy in concordance with the European Association of Urology guidelines. Pathologic evaluation was carried out according to the TNM system of the Union for International Cancer Control and to the 1973 World Health Organization grading classification. Patients with NMIBC on re-TURB and those with no residual tumor received a 6-week course of intravesical

BCG induction followed by a standard maintenance scheme, which consisted of intravesical BCG every week for 3 weeks given at 3, 6, 12, 18, 24, 30, and 36 months from initiation of therapy. A total of 303 (29%) patients completed the treatment protocol as planned.[20] All patients were generally followed with cystoscopy and voiding urine cytology every 3 to 4 months for the first 2 years, every 6 months for the third and fourth year, and annually thereafter. Diagnostic imaging of the upper tract was generally performed at least annually or when clinically indicated. Recurrence was defined as any tumor on follow-up and progression as muscle-invasive BC (MIBC) on follow-up. Endpoints were time to RFS, PFS, OS, and CSS. Cause of death was determined by the treating physician, based on chart review and corroborated by death certificates when possible.[21]

Statistical Analysis

We divided patients into 2 groups according to an NLR cutoff of 3, which was chosen according to previous studies.[16,22,23] The association of NLR with categorical variables was assessed using χ^2 tests; differences in continuous variables were analyzed using the Mann-Whitney *U* test. The Kaplan-Meier method was used to estimate RFS, PFS, OS, and CSS; log-rank tests were applied for pair-wise comparison of survival. Univariable and multivariable Cox regression models addressed associations with RFS, PFS, OS, and CSS, adjusting for the effects of standard clinicopathologic features. All *P* values were 2-sided, and statistical significance was defined as $P < .05$. Statistical analyses were performed using Stata 11.0 statistical software (Stata Corp, College Station, TX).

Results

Baseline Clinicopathologic Features

A total of 512 (48.9%) patients had NLR ≥ 3 prior to TURB. There was no difference between these patients and those with NLR < 3 in terms of age, smoking status, tumor size, multifocality, and concomitant CIS. However, there were more female patients ($P = .006$) and a higher rate of residual T1 HG/G3 on re-TURB ($P = .001$) (Table 1).

Association of Preoperative NLR With Disease Recurrence

Within a median follow-up of 26 months (interquartile range [IQR], 10-47 months), 466 (91%) of the 512 patients with high pretreatment NLR experienced disease recurrence compared with 212 (39.7%) patients with NLR < 3 ($P < .001$). The 5-year RFS was 9.4% (95% confidence interval [CI], 6.8%-12.4%) in patients with NLR ≥ 3, compared with 58.8% (95% CI, 54%-63.2%) in patients with NLR < 3 ($P < .001$) (Figure 1A). Univariable Cox regression analyses revealed that high pretreatment NLR was associated with worse RFS using either the cutoff of 3 (HR, 3.48; 95% CI, 2.95-4.1; $P < .001$) or as a continuous variable (HR, 1.16; 95% CI, 1.13-1.18; $P < .001$). When adjusted for the effects of standard clinical and pathologic features from the initial and re-TURB, NLR retained its association both as a cutoff (HR, 3.34; 95% CI, 2.82-3.95; $P < .001$) or as a continuous variable (HR, 1.15; 95% CI, 1.13-1.18; $P < .001$). Other independent predictors of disease recurrence were tumor size (HR, 1.24; 95% CI, 1.05-1.46; $P = .008$) and residual T1 HG/G3 on re-TURB (HR, 1.46; 95% CI, 1.23-1.73; $P < .001$). The addition of NLR to a model that

Table 1 Association of Clinic and Pathologic Features With NLR in 1046 Patients Treated With Maintenance BCG After Primary T1G3

	Total Cohort, N (%)	NLR < 3, N (%)	NLR ≥ 3, N (%)	*P* Value
Total	1046	534 (51.1)	512 (48.9)	
Mean age, y (range)	70 (29-91)	70.1 (42-91)	69.7 (29-90)	.6
Gender				
Male	864 (82.6)	458 (85.8)	406 (79.3)	.006
Female	182 (17.4)	76 (14.2)	106 (20.7)	
Smoker				
No	297 (28.4)	147 (29.3)	150 (27.5)	.52
Yes[a]	749 (71.6)	387 (70.7)	362 (72.5)	
Multifocality				
Single	585 (55.9)	314 (58.8)	271 (52.9)	.056
Multiple	461 (44.1)	220 (41.2)	241 (47.1)	
Size, cm				
< 3	371 (35.5)	190 (35.6)	181 (35.4)	.93
≥ 3	675 (64.5)	344 (64.4)	331 (64.6)	
Concomitant CIS				
No	896 (85.7)	468 (87.6)	428 (83.6)	.06
Yes	150 (14.3)	66 (12.4)	84 (16.4)	
T1 G3 on re-TURB				
No	789 (75.4)	425 (79.6)	364 (71.1)	.001
Yes	257 (24.6)	109 (20.4)	148 (28.9)	

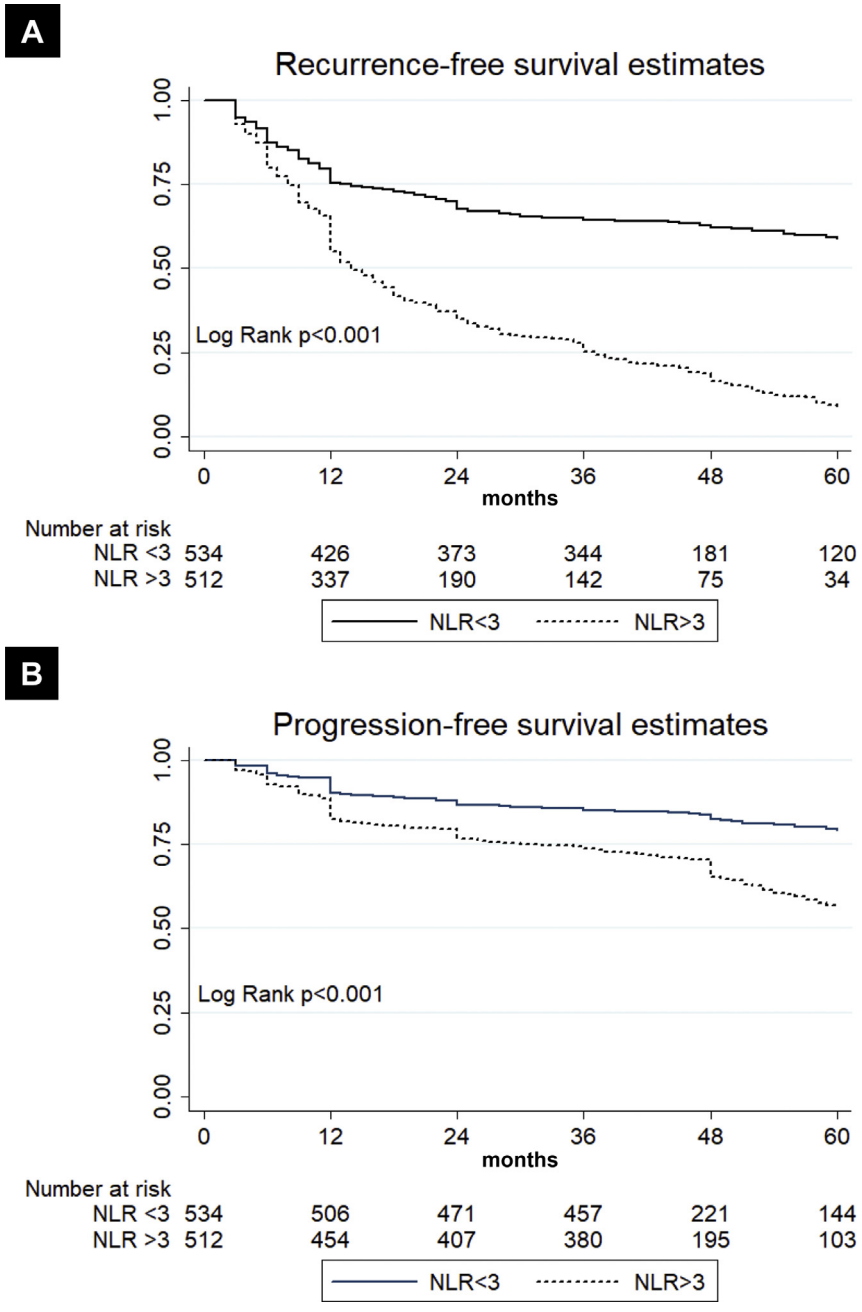
Abbreviations: BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; NLR = neutrophil-to-lymphocyte ratio; NMIBC = non–muscle-invasive bladder cancer; TURB = transurethral resection of bladder tumor.
[a]Includes former and current smokers.

included the features of the initial and re-TURB significantly improved the C-index by 6.9% for prediction of disease recurrence (Table 2).

Association of Preoperative NLR With Disease Progression

Within a median follow-up of 43 months (IQR, 36-58 months), 203 (39.7%) of the 512 patients with high pretreatment NLR experienced disease progression compared with 100 (18.7%) patients with NLR < 3 ($P < .001$). The 5-year PFS was 57.1% (95% CI, 51.5%-62.2%) in patients with NLR ≥ 3, compared with 79.2% (95% CI, 74.7%-83%) in patients with NLR < 3 ($P < .0001$) (Figure 1B). Univariable Cox regression analyses revealed that high pretreatment NLR was associated with worse PFS using either a cutoff of 3 (HR, 2.41; 95% CI, 1.9-3.07; $P < .001$)

Figure 1 Comparison of Recurrence-Free Survival (A) and Progression-Free Survival (B) According to NLR in 1046 Patients With Primary T1 HG/G3 Non-Muscle Invasive Bladder Cancer



Abbreviation: NLR = neutrophil-to-lymphocyte ratio.

Table 2 Multivariable Cox Regression Analyses Predicting Disease Recurrence and Progression of 1046 Patients Treated With BCG After Primary T1 HG/G3 NMIBC

Variables	Recurrence			Progression		
	HR	95% CI	*P*	HR	95% CI	*P*
Age cont.	0.99	0.98-1	.11	0.99	0.98-1	.24
Gender (male vs. female)	1	0.83-1.21	.95	1.18	0.89-1.56	.23
Smoking (no vs. yes)	0.84	0.71-1	.052	1.37	1.02-1.83	.03
Size (<3 vs. ≥ 3) cm	1.24	1.05-1.46	.008	1.59	1.23-2.06	< .001
Multifocality (single vs. multiple)	1.16	0.99-1.35	.053	1.28	1.02-1.61	.03
Concomitant CIS (no vs. yes)	1	0.81-1.23	.99	1.8	1.38-2.36	< .001
T1 HG/G3 on re-TURB	1.46	1.23-1.73	< .001	1.38	1.08-1.77	.009
Harrell C-index	59.3			65.6		
NLR (<3 vs. ≥ 3)	3.34	2.82-3.95	< .001	2.18	1.71-2.78	< .001
Harrell C-index	66.2			67.4		

Abbreviations: BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HG = high grade; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; NMIBC = non–muscle-invasive bladder cancer; TURB = transurethral resection of bladder tumor.

or as a continuous variable (HR, 1.1; 95% CI, 1.07-1.14; $P < .001$). When adjusted for the effects of standard clinical and pathologic features from the initial and re-TURB, NLR retained its association both as a cutoff (HR, 2.18; 95% CI, 1.71-2.78; $P < .001$) or as a continuous variable (HR, 1.09; 95% CI, 1.05-1.13; $P < .001$). Other independent predictors of disease progression were smoking (HR, 1.37; 95% CI, 1.02-1.83; $P = .03$), tumor size (HR, 1.59; 95% CI, 1.23-2.06; $P < .001$), multifocality (HR, 1.28; 95% CI, 1.02-1.61; $P = .03$), concomitant CIS (HR, 1.8; 95% CI, 1.38-2.36; $P < .001$), and residual T1 HG/G3 on re-TURB (HR, 1.38; 95% CI, 1.08-1.77; $P = .009$). The addition of NLR to a model that included the features of the initial and re-TURB improved its C-index by 1.8% for prediction of disease progression (Table 2).

Association of NLR With OS and CSS

Within a median follow-up of 48 months (IQR, 40-68 months), 84 (16.4%) of the 512 patients with high pretreatment NLR were dead compared with 66 (12.4%) patients with NLR < 3 ($P = .06$). A total of 49 (9.6%) of the 512 patients with high pretreatment NLR died owing to BC compared with 28 (5.2%) with NLR < 3 ($P = .007$). The 10-year OS estimate was 63.6% (95%CI, 55%-71%) in patients with NLR ≥ 3 compared with 66.5% (95% CI, 56.8%-74.5%) in patients with NLR < 3 ($P = .03$) (Figure 2A). High pretreatment NLR was associated with worse OS using only the cutoff value (HR, 1.4; 95% CI, 1.01-1.93; $P = .04$) on univariable Cox regression analyses. When adjusted for the effects of standard clinical and pathologic features from the initial and re-TURB, NLR ≥ 3 was no longer associated with OS. Independent predictors of OS were patient age (HR, 1.05; 95% CI, 1.02-1.07; $P < .001$), concomitant CIS (HR, 2.03; 95% CI, 0.81-1.23; $P < .001$), and residual T1 HG/G3 on re-TURB (HR, 1.74; 95% CI, 1.23-2.47; $P = .002$). The addition of NLR to a model that included the features of the initial and second TURB did not improve its discrimination (Table 3).

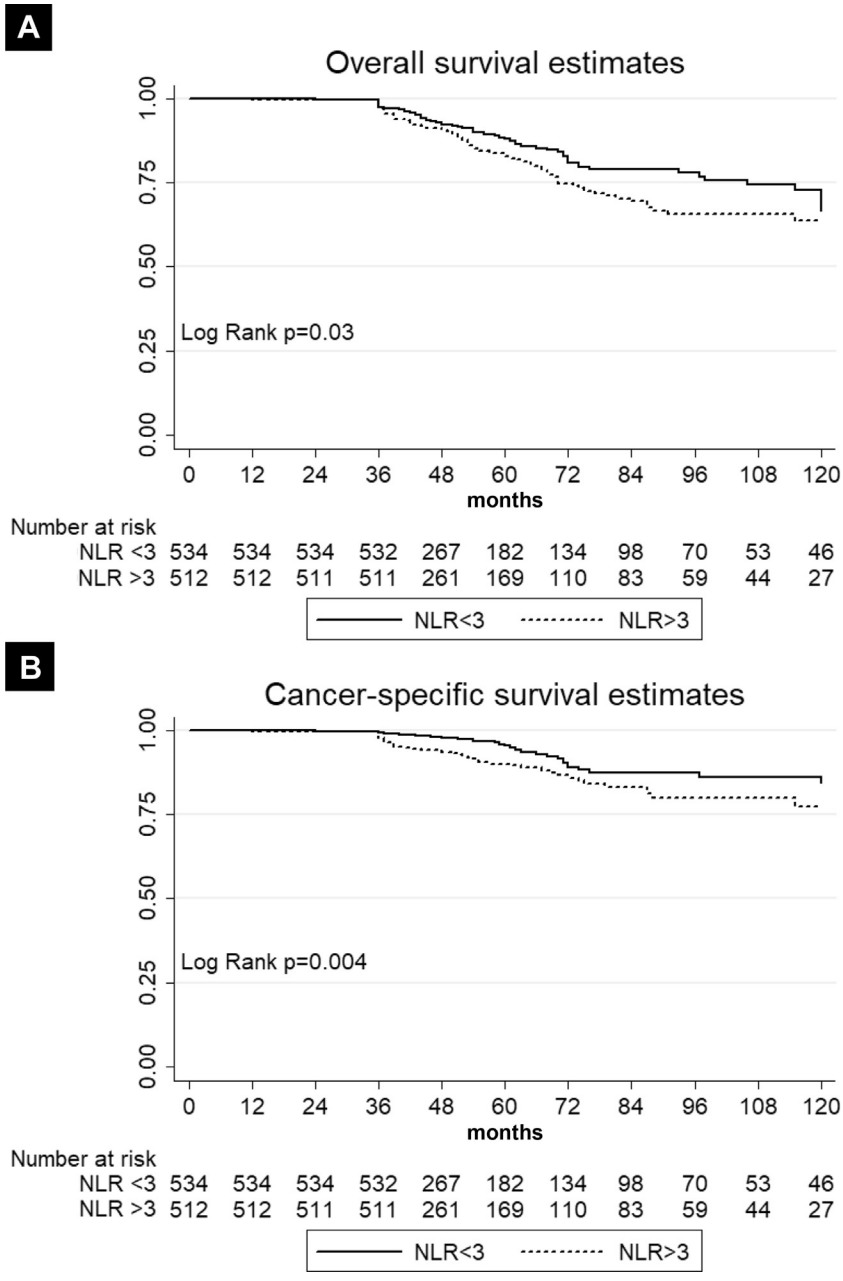
The 10-year CSS estimates was 77.4% (95% CI, 68.4%-84.2%) in patients with NLR ≥ 3 compared with 84.3% (95% CI, 76.6%-89.7%) in patients with NLR < 3 ($P = .004$) (Figure 2B). High pretreatment NLR was associated with worse CSS using only the cutoff value (HR, 1.92; 95% CI, 1.2-3.06; $P = .006$) on univariable Cox regression analyses. When adjusted for the effects of standard clinic and pathologic features from the initial and re-TURB, NLR retained its association only as a cutoff value (HR, 1.65; 95% CI, 1.02-2.66; $P = .03$). Other independent predictors of CSS were patient age (HR, 1.04; 95% CI, 1.01-1.06; $P = .003$), concomitant CIS (HR, 2.66; 95% CI, 1.62-4.35; $P < .001$), and residual T1 HG/G3 on re-TURB (HR, 1.63; 95% CI, 1-2.65; $P = .04$). The addition of NLR to a model that included the features of the initial and re-TURB improved its C-index by 1.7% for CSS (Table 3).

Discussion

Overall, our findings confirm that elevated preoperative NLR is associated with poor prognosis in patients with T1 HG/G3 BC treated with intravesical BCG. We found that NLR ≥ 3 was significantly associated with an increased risk of disease recurrence. Similar results were reported by Ozyalvacli et al[17] using a 2.43 NLR cutoff. The investigators found a strong association of NLR (HR, 3.81) with RFS in a cohort of 166 patients with T1 HG NMIBC. On the other hand, other studies failed to demonstrate an association between NLR and recurrence in high-risk NMIBC. D'Andrea et al[23] reported that in a subpopulation of 110 patients with high-risk NMIBC, NLR ≥ 3 was not associated with RFS (HR, 1.6; $P = .4$). Similar results were reported by Martha et al[16] in a single-center study that included 44 patients with T1 NMIBC (HR, 1.67; $P = .27$). However, they also included patients with low-grade disease, and the median follow-up was only 18 months. We found that the addition of NLR significantly increased the accuracy of a model that included age, gender, smoking status, tumor size and multifocality, concomitant CIS, and stage on re-TURB by 6.9% for prediction of disease recurrence.

Although prediction of disease recurrence is important to identify patients who are at risk for additional treatment, prediction of disease progression is more important, as patients who experience disease progression to MIBC seem to have worse outcomes than those with de novo MIBC.[24] Moreover, in the present study, high

Figure 2 Comparison of Overall Survival (A) and Cancer-Specific Survival (B) According to NLR in 1046 Patients With Primary T1 HG/G3 Non-Muscle Invasive Bladder Cancer



Abbreviation: NLR = neutrophil-to-lymphocyte ratio.

pretreatment NLR was associated with worse PFS using both cutoff value (HR, 2.18; $P < .001$) and the continuous variable (HR, 1.09; $P < .001$). This is in agreement with the study from Martha et al[16] (HR, 4.57; NLR cutoff, 3) and Mbeutcha et al[25] (HR, 1.76; NLR cutoff, 2.5). Two smaller studies failed to found an association of NLR with disease progression in high-risk NMIBC.[17,23] However, in other cohorts that included patients with all stages of NMIBC, NLR was found to be associated with disease recurrence[22,26,27] and progression.[26,27]

We also found that NLR is an independent predictor of cancer-specific mortality, but not for OS. To our knowledge, none of the previous studies investigated NLR as a predictive biomarker for survival in high-risk NMIBC. A prospective study with a median follow-up of 18.6 years showed that NLR was not prognostic for OS in MIBC (HR, 1.04).[28] On the other hand, elevated NLR (cutoff, 2) was identified as an independent predictor of OS (HR, 1.52) and for CSS (HR, 1.12) after a median follow-up of 52 months in a study that included 1551 patients, from which

Table 3 Multivariable Cox Regression Analyses Predicting Overall and Cancer-specific Mortality of 1046 Patients Treated With BCG After Primary T1 HG/G3 NMIBC

Variables	Overall Survival			Cancer-Specific Survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Age cont.	1.05	1.02-1.07	< .001	1.04	1.01-1.06	.003
Gender (male vs. female)	1.02	0.68-1.55	.98	0.82	0.44-1.5	.52
Smoking (no vs. yes)	1.02	0.67-1.56	.9	1.09	0.59-2.01	.77
Size (<3 vs. ≥ 3) cm	1.09	0.77-1.54	.61	1.32	0.8-2.19	.26
Multifocality (single vs. multiple)	1.11	0.8-1.54	.52	1.12	0.71-1.77	.6
Concomitant CIS (no vs. yes)	2.03	0.81-1.23	< .001	2.66	1.62-4.35	< .001
T1 HG/G3 on re-TURB	1.74	1.23-2.47	.002	1.63	1-2.65	.04
Harrell C-index	64.3			67.9		
NLR (<3 vs. ≥ 3)	1.2	0.86-1.67	.27	1.65	1.02-2.66	.03
Harrell C-index	64.6			69.6		

Abbreviations: BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HG = high grade; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; NMIBC = non–muscle-invasive bladder cancer; TURB = transurethral resection of bladder tumor.

597 (38.5%) were T1 and 755 (48.9%) had high-grade NMIBC.[29]

Recent meta-analyses that analyzed the impact of high pretreatment NLR on oncologic outcomes of patients with urothelial carcinomas showed that an ideal cutoff has not yet been established. The cutoff varied between 2 and 3.43 in studies that included patients with NMIBC and from 2.43 to 3 in BCG-treated patients.[30] Similar cutoffs were used in studies that investigated the role of pretreatment NLR in patients with MIBC (from 2 to 3)[15] or with upper tract urothelial carcinoma (from 2.2 to 3).[14] Indeed, there is important to validate a specific cutoff as it is easier to stratify patients; further, we showed that NLR as a continuous variable was independently associated with an increased risk of disease recurrence and progression.

Nowadays, there is an increasingly growing evidence about a possible role of NLR as a marker of treatment response to immune checkpoint inhibitors (ICIs).[31,32] In genitourinary cancers, recent studies reported that a decline of NLR after treatment with programmed cell death protein 1/programmed death-ligand 1 for metastatic renal cell carcinoma was a predictor of improved outcomes.[33,34] Similar results were reported in studies that included patients with non–small-cell lung cancer[35] or melanoma.[36] In BCG nonresponders, the role of ICIs is largely theoretical with limited supportive data, but several ongoing trials might provide new information regarding a possible role of ICIs in BC treatment.[37,38]

Limitations of our study should be acknowledged. The retrospective study design can lead to selection and attrition bias. Second, histology specimens were not reviewed by a central pathology, and relevant prognostic factors like lymphovascular invasion[39,40] and variant histology[41,42] were not assessed. Patients' comorbidities may have influenced the decision-making regarding further surgery or instillation therapy, leading to an exclusion bias. However, because patients underwent RC only for progression to MIBC, there is no spectrum or observer bias as often seen in other studies secondary to early RC indications. Last, we acknowledge that we did not search for the optimal NLR cutoff as our intent was to validate the cutoff of 3 already investigated in previous studies.

Conclusion

Using a cutoff of 3, NLR seems to be a strong predictor of disease recurrence, progression, and CSS in patients with primary T1 HG/G3 NMIBC treated with intravesical BCG therapy. NLR significantly increases the accuracy of established clinicopathologic features for prediction of disease recurrence. Taken together, these findings support the prognostic role of inflammation in NMIBC and its therapeutic implications.

Clinical Practice Points

- Multiple retrospective studies have been performed to identify NLR as a prognostic factor in NMIBC; however, this is the first multi-institutional study to include patients with T1 HG/G3 disease.
- Our findings confirm that elevated preoperative NLR is associated with poor prognosis in patients with T1 HG/G3 NMIBC treated with intravesical BCG.
- The addition of NLR significantly increased the accuracy of a model that included age, gender, smoking status, tumor size and multifocality, concomitant CIS, and stage on re-TURB by 6.9% for prediction of disease recurrence.
- In patients with T1 HG/G3 NMIBC, NLR could help in the decision-making regarding intensity of therapy and follow-up.

Acknowledgments

M.D.V. is supported by the Scholarship Foundation of the Republic of Austria - OeAD and by the EUSP Scholarship - European Association of Urology.

Disclosure

The authors have stated that they have no conflicts of interest.

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