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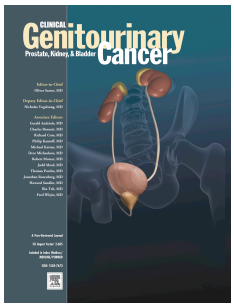

Validation of neutrophil-to-lymphocyte ratio in a multi-institutional cohort of patients with T1G3 non-muscle invasive bladder cancer

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Validation of neutrophil-to-lymphocyte ratio in a multi-institutional cohort of patients with T1G3 non-muscle invasive bladder cancer

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MICRO ABSTRACT

Neutrophil-to-lymphocyte ratio (NLR) was found associated with worse disease recurrence and progression in patients with T1 non-muscle invasive bladder cancer (NMIBC) in some mono-center studies. We validated high pretreatment NLR (cut-off 3) as an independent predictor of disease recurrence, progression and cancer-specific survival in patients with primary T1 HG/G3 NMIBC treated with intravesical Bacillus Calmete Guerin (BCG) therapy.

ABSTRACT

OBJECTIVE: The aim of this multicenter study was to investigate the prognostic role of NLR and to validate the NLR cut-off of 3 in a large multi-institutional cohort of patients with primary T1 HG/G3 NMIBC. **PATIENTS AND METHODS:** Study period was from 1/2002 and 12/2012. A total of 1046 patients with primary T1 HG/G3 who had non-muscle invasive bladder cancer (NMIBC) on re-TURB who received adjuvant intravesical Bacillus Calmette Guerin (BCG) therapy with maintenance from 13 academic institutions were included. **Endpoints were time to disease recurrence-free, progression-free, overall and cancer-specific survival. RESULTS:** A total of 512 (48.9%) of patients had NLR ≥3 prior to TURB. High pretreatment NLR was associated with female gender and residual T1HG/G3 on re-TURB. Five-year RFS estimates were 9.4% (CI:6.8-12.4) in patients with NLR≥3 compared to 58.8% (CI:54-63.2) in patients with NLR<3; five-year PFS estimates were 57.1% (CI:51.5-62.2) vs. 79.2% (CI:74.7-83), p<0001; ten-year OS estimates were 63.6% (CI:55-71) vs. 66.5% (CI: 56.8-74.5), p=0.03; ten-year CSS estimates were 77.4% (CI:68.4-84.2) vs. 84.3% (CI:76.6-89.7), p=0.004. NLR was independently associated with disease recurrence (HR 3.34, CI:2.82-3.95, p<0.001), progression (HR 2.18, CI:1.71-2.78, p<0.001) and CSS (HR 1.65, CI:1.02-2.66, p=0.03). 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≥3 was a strong predictor for recurrence, progression and cancer-specific mortality in patients with primary T1 HG/G3 NMIBC. It could help in the decision-making regarding intensity of therapy and follow-up.

INTRODUCTION

Bladder cancer (BC) is the 7th most common cancer in men and the 17th most common cancer in women worldwide; it is estimated that more than 80000 newly cases will be diagnosed in the US only in 2018[1]. In western countries, aproximative ¾ of patients with newly diagnosed with 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 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].

Current prognostic model for NMIBC relying on standard clinico-pathological features such as T stage, grade, multifocality, tumor diameter, recurrence rate and concomitant carcinoma in situ (CIS) do not provide sufficient accuracy to discern 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 radical cystectomy (RC), or inclusion in clinical trials of novel therapies such as immune check-point 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 bladder cancer, 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 studies with NMIBC patients)[15]. While evidence is mounting, only small mono-center studies

investigated the prognostic role of NLR in the focus group of T1 HG/G3 NMIBC patients 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) pathological T1 HG/G3 confirmed after first TURB; (2) a repeat TURB performed within 4 to 6 weeks after a complete first TURB; (3) pretreatment neutrophil-to-lymphocytes ratio (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 (UTI), yeast infections, endometriosis, systemic inflammatory disease or incomplete data were excluded [18]. A total of 1046 out of 1155 patients with primary T1 HG/G3 treated between 1stJanuary 2002 and 31st December 2012 at 13 academic institutions met the inclusion criteria. The maintenance schedule was generally according to the EAU guidelines at the time [19]. Demographical, clinical, pathological, 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 4-6 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 EAU guidelines. Pathological evaluation was carried out according to the TNM system of the Union for International Cancer Control (UICC) and to the 1973 World Health Organization (WHO) grading classification. Patients with NMIBC on re-TURB and those with no residual tumor received an 6 weeks course of intravesical BCG induction followed by 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%) of patients completed the treatment protocol as planned [20]. All patients were generally followed with cystoscopy and voiding urine cytology every 3-4 months for the first two 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 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 corroborated by death certificates when possible [21].

Statistical analysis

We divided patients in two groups according to NLR cut-off of 3, which was chosen according to previous studies [16,22,23]. Association of NLR with categorical variables was assessed using $\chi 2$ tests; differences in continuous variables were analyzed using Mann-Whitney U test. 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 clinico-pathologic features. All p values were two-sided, and statistical significance was defined as a $p < 0.05$. Statistical analyses were performed using Stata 11.0 statistical software (Stata Corp., College Station, TX, USA).

RESULTS

Baseline clinico-pathologic 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=0.006) and a higher rate of residual T1 HG/G3 on re-TURB (p=0.001).

Association of preoperative NLR with disease recurrence

Within a median follow-up of 26 months (IQR 10-47), 466 (91%) of the 512 patients with high pretreatment NLR experienced disease recurrence compared to 212 (39.7%) patients with NLR<3(p<0.001). Five-year RFS was 9.4% (95%CI: 6.8-12.4) in patients with NLR≥3, compared to 58.8% (95%CI: 54-63.2) in patients with NLR<3, p<0.001 (Fig. 1a). Univariable Cox regression analyses revealed that high pretreatment NLR was associated with worse RFS using either the cut-off of 3 (HR 3.48; 95%CI: 2.95-4.1, p<0.001) or as a continuous variable (HR 1.16; 95%CI: 1.13-1.18, p<0.001). When adjusted for the effects of standard clinical and pathologic features from the initial and re-TURB, NLR retained its association both as a cut-off (HR 3.34; 95%CI: 2.82-3.95, p<0.001) or as a continuous variable (HR 1.15; 95%CI: 1.13-1.18, p<0.001). Other independent predictors of disease recurrence were tumor size (HR 1.24; 95%CI: 1.05-1.46, p=0.008) and residual T1 HG/G3 on re-TURB (HR 1.46; 95%CI: 1.23-1.73, p<0.001). Addition of NLR to a model, that included the features of the initial and re-TURB, significantly improved 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), 203(39.7%) of the 512 patients with high pretreatment NLR experienced disease progression compared to 100 (18.7%) in patients with NLR<3 (p<0.001). Five-year PFS was 57.1% (95%CI: 51.5-62.2) in patients with NLR≥3, compared to 79.2% (95%CI: 74.7-83) in patients with NLR<3, p<0001(Fig. 1b). Univariable Cox regression analyses revealed that high pretreatment NLR was associated with worse PFS using either a cut-off of 3(HR 2.41; 95%CI: 1.9-3.07, p<0.001) or as a continuous variable (HR 1.1; 95%CI: 1.07-1.14, p<0.001). When adjusted for the effects of standard clinical and pathologic features from the initial and re-TURB, NLR retained its association both as a cut-off (HR 2.18; 95%CI: 1.71-2.78, p<0.001) or as a continuous variable (HR 1.09; 95%CI: 1.05-1.13, p<0.001). Other independent predictors of disease progression were smoking (HR 1.37; 95%CI: 1.02-1.83, p=0.03), tumor size (HR 1.59; 95%CI: 1.23-2.06, p<0.001), multifocality (HR 1.28; 95%CI: 1.02-

1.61, p=0.03), concomitant CIS (HR 1.8; 95%CI: 1.38-2.36, p<0.001) and residual T1 HG/G3 on re-TURB (HR 1.38; 95%CI: 1.08-1.77, p=0.009). 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 overall and cancer-specific survival

Within a median follow-up of 48 months (IQR 40-68), 84(16.4%) of the 512 patients with high pretreatment NLR were dead compared to 66 (12.4%) patients with NLR<3 (p=0.06). A total of 49 (9.6%) of the 512 patients with high pretreatment NLR died due to BC compared to 28 (5.2%) with NLR<3 (p=0.007). Ten-year OS estimates was 63.6% (95%CI: 55-71) in patients with NLR≥3 compared to 66.5% (95%CI: 56.8-74.5) in patients with NLR<3, p=0.03(Fig. 2a). High pretreatment NLR was associated with worse OS using only the cut-off value (HR 1.4; 95%CI: 1.01-1.93, p=0.04) 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 not anymore associated with OS. Independent predictors of OS were patient age (HR 1.05; 95%CI: 1.02-1.07, p<0.001), concomitant CIS (HR 2.03; 95%CI: 0.81-1.23, p<0.001) and residual T1 HG/G3 on re-TURB (HR 1.74; 95%CI: 1.23-2.47, p=0.002). Addition of NLR to a model that included the features of the initial and second TURB did not improve its discrimination (Table 3).

Ten-year CSS estimates was 77.4% (95%CI: 68.4-84.2) in patients with NLR≥3 compared to 84.3% (95%CI: 76.6-89.7) in patients with NLR<3, p=0.004(Fig. 2b). High pretreatment NLR was associated with worse CSS using only the cut-off value (HR 1.92; 95%CI: 1.2-3.06, p=0.006) 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 cut-off value (HR 1.65; 95%CI: 1.02-2.66, p=0.03). Other independent predictors of CSS were patient age (HR 1.04; 95%CI: 1.01-1.06, p=0.003), concomitant CIS (HR 2.66; 95%CI: 1.62-4.35, p<0.001) and residual T1 HG/G3 on re-TURB (HR 1.63; 95%CI: 1-2.65, p=0.04). 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 cut-off. 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 and 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=0.4). Similar results were reported by Martha et al. [16] in a mono-center study that included 44 patients with T1 NMIBC (HR 1.67, p= 0.27). However, they also included patients with low grade disease and median follow-up was only 18 months. We found that, 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.

While, prediction of disease recurrence is important to identify patients who are at risk to 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 pretreatment NLR was associated with worse PFS using both cut-off value (HR 2.18, p<0.001) and the continuous variable (HR 1.09, p<0.001). This is in agreement with Martha et al study [16] (HR 4.57, NLR cut-off 3) and Mbeutcha et al. [25] (HR 1.76, NLR cut-off 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 (cut-

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

Recent meta-analytic studies that analyzed the impact of high pretreatment NLR on oncologic outcomes of patients with urothelial carcinomas showed that there is not yet established an ideal cut-off. The cut-off varied between 2 to 3.43 in studies that included NMIBC patients and from 2.43 to 3 in BCG treated patients [30]. Similar cut-offs 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 cut-off 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 PD-1/PD-L1 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 non-responders 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 bladder cancer 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. Patient's comorbidities may have influenced the decision-making regarding further surgery or instillation therapy, leading to an exclusion bias. However, since 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 cut-off as our intent was to validate the cut-off of 3 already investigated in previous studies.

CONCLUSION

Using a cut-off of 3, NLR seems to be a strong predictor of disease recurrence, progression and cancer-specific survival in patients with primary T1 HG/G3 NMIBC treated with intravesical BCG therapy. NLR significantly increases the accuracy of established clinico-pathologic 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 neutrophil-to-lymphocytes ratio as a prognostic factor in non-muscle invasive bladder cancer (NMBC); however, this is the first multi-institutional study to include T1 HG/G3 patients.
- Our findings confirm that elevated preoperative NLR is associated with poor prognosis in patients with T1 HG/G3 NMIBC treated with intravesical Bacillus Calmette Guerin (BCG)
- 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.

Ethical standards

This study has been approved by the appropriate ethics committee.

Conflict of interest

The authors declare that they have no conflict of interest.

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Authors' Contribution

Protocol/project development: M. Ferro, M.D. Vartolomei, V. Mirone, S.F. Shariat

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Figures legend

Figure 1 Comparison of recurrence-free survival (a) and progression-free survival (b) according to neutrophil-to-lymphocyte ratio (NLR) in 1046 patients with primary T1 HG/G3 non-muscle invasive bladder cancer

Figure 2 Comparison of overall survival (a) and cancer-specific survival (b) according to neutrophil-to-lymphocyte ratio (NLR) in 1046 patients with primary T1 HG/G3 non-muscle invasive bladder cancer

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Table 1. Association of clinic and pathologic features with neutrophil-to-lymphocyte ratio (NLR) in 1046 patients treated with maintenance BCG after primary T1G3

	All cohort	**NLR<3**	**NLR≥3**	**P value**
Total, n (%)	1046	534 (51.1)	512 (48.9)	
Age mean years (range)	70 (29-91)	70.1 (42-91)	69.7 (29-90)	0.6
Gender, n (%)				
Male	864 (82.6)	458 (85.8)	406 (79.3)	**0.006**
Female	182 (17.4)	76 (14.2)	106 (20.7)	
Smoker, n (%)				
No	297 (28.4)	147 (29.3)	150 (27.5)	0.52
Yes*	749 (71.6)	387 (70.7)	362 (72.5)	
Multifocality, n (%)				
Single	585 (55.9)	314 (58.8)	271 (52.9)	0.056
Multiple	461 (44.1)	220 (41.2)	241 (47.1)	
Size, n (%)				
< 3cm	371 (35.5)	190 (35.6)	181 (35.4)	0.93
≥ 3 cm	675 (64.5)	344 (64.4)	331 (64.6)	
Concomitant CIS, n (%)				
No	896 (85.7)	468 (87.6)	428 (83.6)	0.06
Yes	150 (14.3)	66 (12.4)	84 (16.4)	
T1 G3 on re-TUR, n (%)				
No	789 (75.4)	425 (79.6)	364 (71.1)	**0.001**
Yes	257 (24.6)	109 (20.4)	148 (28.9)	

TUR: transurethral resection of bladder tumor, BCG: Bacillus Calmette-Guérin, NMIBC: non-muscle invasive bladder cancer, CIS: carcinoma in situ, *: includes former and current smokers

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	0.11	0.99	0.98-1	0.24
Gender (male vs. female)	1	0.83-1.21	0.95	1.18	0.89-1.56	0.23
Smoking (no vs. yes)	0.84	0.71-1	0.052	1.37	1.02-1.83	**0.03**
Size (<3 vs. ≥ 3) cm	1.24	1.05-1.46	**0.008**	1.59	1.23-2.06	**<0.001**
Multifocality (single vs. multiple)	1.16	0.99-1.35	0.053	1.28	1.02-1.61	**0.03**
Concomitant CIS (no vs. yes)	1	0.81-1.23	0.99	1.8	1.38-2.36	**<0.001**
T1 HG/G3 on re-TUR	1.46	1.23-1.73	**<0.001**	1.38	1.08-1.77	**0.009**
Harrell's C Index		59.3			65.6	
NLR (<3 vs. ≥ 3)	3.34	2.82-3.95	**<0.001**	2.18	1.71-2.78	**<0.001**
Harrell's C Index		**66.2**			**67.4**	

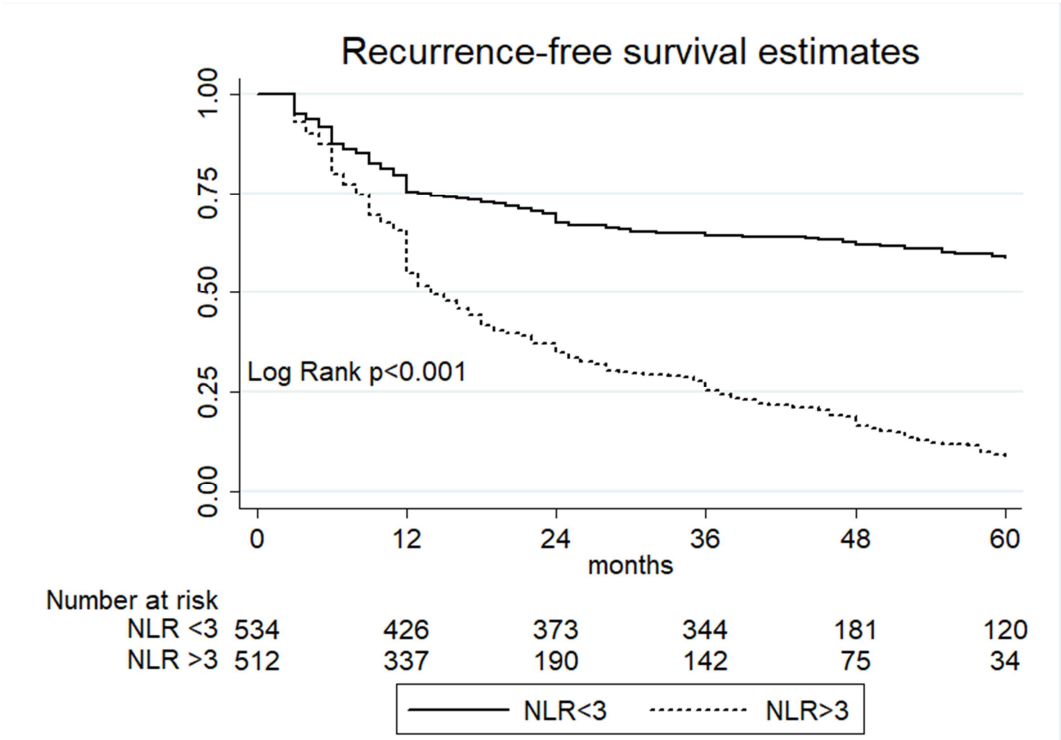
BCG: Bacillus Calmette-Guérin, NMIBC: non-muscle invasive bladder cancer, CI: confidence interval, HR: hazard ratio,P: p value, CIS: carcinoma in situ, HG: high grade, TUR: transurethral resection of bladder tumor, NLR: neutrophil-to-lymphocyte ratio;

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	**<0.001**	1.04	1.01-1.06	**0.003**
Gender (male vs. female)	1.02	0.68-1.55	0.98	0.82	0.44-1.5	0.52
Smoking (no vs. yes)	1.02	0.67-1.56	0.9	1.09	0.59-2.01	0.77
Size (<3 vs. ≥ 3) cm	1.09	0.77-1.54	0.61	1.32	0.8-2.19	0.26
Multifocality (single vs. multiple)	1.11	0.8-1.54	0.52	1.12	0.71-1.77	0.6
Concomitant CIS (no vs. yes)	2.03	0.81-1.23	**<0.001**	2.66	1.62-4.35	**<0.001**
T1 HG/G3 on re-TUR	1.74	1.23-2.47	**0.002**	1.63	1-2.65	**0.04**
Harrell's C Index		64.3			67.9	
NLR (<3 vs. ≥ 3)	1.2	0.86-1.67	0.27	1.65	1.02-2.66	**0.03**
Harrell's C Index		**64.6**			**69.6**	

BCG: Bacillus Calmette-Guérin, NMIBC: non-muscle invasive bladder cancer, CI: confidence interval, HR: hazard ratio, P: p value, CIS: carcinoma in situ, HG: high grade, TUR: transurethral resection of bladder tumor, NLR: neutrophil-to-lymphocyte ratio;

Figure 1. Comparison of recurrence-free survival (a) and progression-free survival (b) according to neutrophil-to-lymphocyte ratio (NLR) in 1046 patients with primary T1 HG/G3 non-muscle invasive bladder cancer



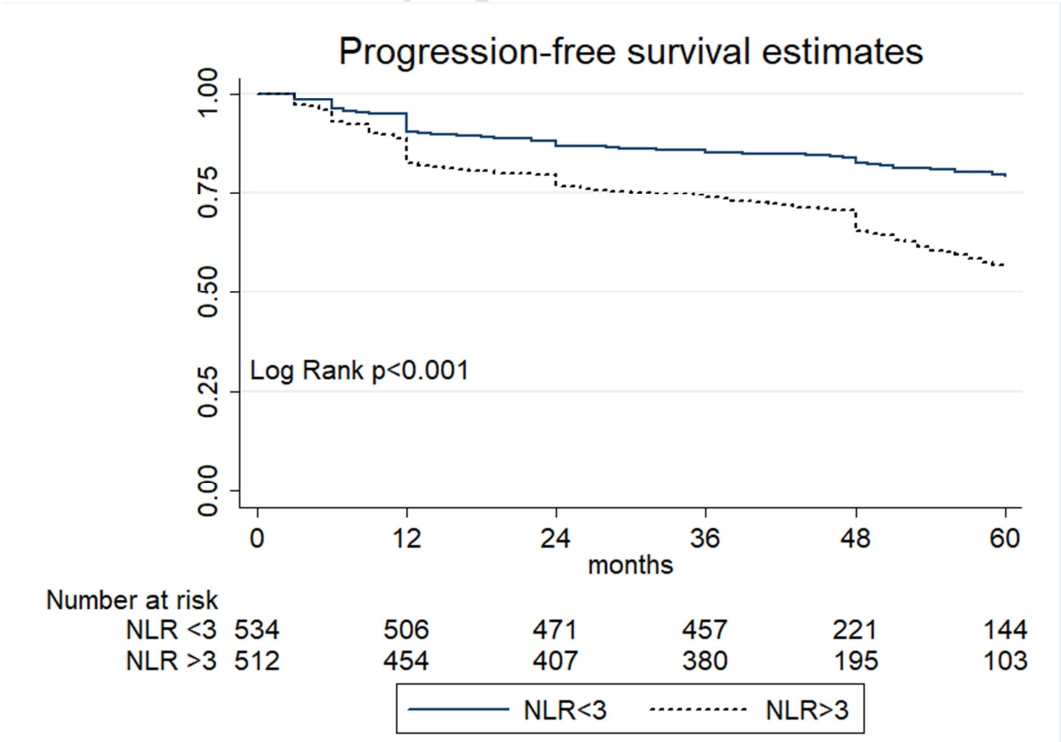


Figure 2. Comparison of overall survival (a) and cancer-specific survival (b) according to neutrophil-to-lymphocyte ratio (NLR) in 1046 patients with primary T1 HG/G3 non-muscle invasive bladder cancer