Running Head: Significance of the NLR with CUETO model-Chung et al.

Prognostic Significance of the Neutrophil-to-Lymphocyte Ratio in Patients with Non-Muscle Invasive Bladder Cancer treated with Intravesical Bacillus Calmette–Guérin and the Relationship with the CUETO Scoring Model

Jae-Wook Chung[1,6†], Jin Woo Kim[1†], Eun Hye Lee[2], So Young Chun[3], Dong Jin Park[4], Kyeong Hyeon Byeon[1], Seock Hwan Choi[5,7], Jun Nyung Lee[1,7], Bum Soo Kim[5,7], Hyun Tae Kim[5,7], Eun Sang Yoo[5,7], Tae Gyun Kwon[1,6,7], Yun-Sok Ha[1,6,7*], Tae-Hwan Kim[1,7*]

1 Department of Urology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea
2 Joint Institute for Regenerative Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea
3 BioMedical Research Institute, Kyungpook National University Hospital, Daegu, Republic of Korea
4 Department of Urology, Dongguk University School of Medicine, Gyeongju, Korea.
5 Department of Urology, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea
6 Joint Institute for Regenerative Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea
7 Department of Urology, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
† These authors contributed equally to this work.

[*]**Correspondence to:** Dr. Yun-Sok Ha, E-mail: yunsokha@gmail.com, Department of Urology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea: Dr. Tae-Hwan Kim, E-mail: doctork@knu.ac.kr, Department of Urology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea

Keywords: Neutrophil-to-lymphocyte ratio; Bacillus Calmette–Guérin; Club Urol*ó*gico Espa*ñ*ol de Tratamiento Oncol*ó*gico risk model; Survival

ABSTRACT

Purpose: In this study, we evaluated the predictability of a modified Club Urológico Español de Tratamiento Oncológico (CUETO) scoring model and preoperative neutrophil-to-lymphocyte ratio (NLR) in patients with non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: From August 2005 to May 2016, a total of 281 patients received intravesical bacillus Calmette–Guérin therapy after transurethral resection of a bladder tumor. The pathologic stage of all patients was Ta or T1. Of 281 patients, 84 (29.9%) experienced recurrence and 14 (5.0%) developed progression. The mean follow-up period was 46 months. The cut-off value for NLRs was 2.29.

Results: One hundred-eight patients (38.4%) displayed a high NLR (> 2.29). In Kaplan–Meier curve analysis, a high NLR was associated with lower recurrence-free survival (RFS) ($P < .001$) and progression-free survival (PFS) ($P = .002$). CUETO scores were associated with RFS ($P < .001$), but not with PFS ($P = .423$). A combination of NLRs and the CUETO risk model correlated with RFS ($P < .001$) and PFS ($P = .002$). In multivariate analysis, female gender, concomitant carcinoma in situ (CIS), tumor number >3, recurrent tumors, and a high NLR were independent factors predicting recurrence (all $P < .05$). Concomitant CIS, recurrent tumors, and a high NLR were independent factors for predicting progression (all $P < .05$).

Conclusion: In patients with NMIBC, an NLR >2.29 was identified as a significant factor for predicting tumor recurrence and progression. Inclusion of preoperative NLR enhanced the accuracy of the CUETO model to predict disease progression.

INTRODUCTION

The most common malignant tumor of the urinary tract is bladder cancer, and the fourth-most common cancer among males in developed countries.[1] Three-quarters of bladder cancer

patients are diagnosed with non-muscle invasive bladder cancer (NMIBC), which includes Tis, Ta and T1 pathologic stages.[2] Transurethral resection of bladder tumor (TUBRT) is a primary surgical treatment used to treat patients with NMIBC.[3] After initial TURBT, immunotherapy with intravesical instillation of bacillus Calmette–Guérin (BCG) is the most effective adjuvant therapy for intermediate- and high-risk NMIBC.[4] Despite the effectiveness and safety of BCG, recurrence rates is 32.6% to 42.1% and progression rates is 9.5% to 13.4%.[5]

The major treatment challenge with NMIBC is preventing progression to muscle invasive bladder cancer (MIBC), which rapidly worsens prognoses.[6] Thus, it is significant to predict risk factors for disease recurrence and progression in NMIBC patients according to individual characteristics, including pathology and choose optimal treatment modalities to enhance oncologic outcomes.

To predict recurrence of NMIBC and progression to MIBC, numerous clinical and pathological factors are commonly used to assign patients to different risk groups. Of these risk models, a scoring model developed by the Club Urológico Español de Tratamiento Oncológico (CUETO, or Spanish Urological Club for Oncological Treatment) is considered the most reliable. The CUETO model was developed as a risk-scoring tool that predicts the probability of disease recurrence and progression in BCG-treated patients at 1, 2, and 5 years.[7] It is now recognized that increased systemic inflammatory responses induced by tumor microenvironments trigger alteration of acute-phase reactive proteins and hematologic parameters.[8] Among these serum markers are neutrophil and lymphocyte counts, which can indicate relative neutrophilia and lymphocytopenia. In various tumor patients, a higher percentage of neutrophils than lymphocyte is associated with reduced cancer-free and overall survival.[9-11]

We evaluated the efficiency of a modified CUETO scoring model combined with preoperative NLRs to predict recurrence and progression of disease in NMIBC patients.

PATIENTS AND METHODS

Ethics statement

This study was approved by the institutional review board of Kyungpook National University, Hospital, Daegu, Republic of Korea (IRB Number KNUH 2020-03-042). The study was carried out in agreement with the applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. The institutional review board of Kyungpook National University Chilgok Hospital waived because of the retrospective nature of the study.

Study design

The study was a single institution, retrospective observational trial. From August 2005 to May 2016, a total of 281 patients who underwent BCG induction therapy after complete TURBT were included in this study. They had not previously received intravesical BCG and showed no side effects of BCG or signs of recurrence during BCG therapy. All patients were diagnosed as histologically Ta or T1. A second TUR was performed 2 to 4 weeks after initial resection if a bladder tumor specimen did not include detrusor muscle or when a high-grade tumor was detected. Patients with only carcinoma in situ (CIS) were excluded, as were those found to have advanced bladder or ureteral tumors or non-urothelial carcinoma at the first TUR. Patients with hematologic malignance and acute or chronic infection were also excluded.

Preoperative NLR was calculated by a complete blood count with differential. Preoperative NLR was measured once at least 2 weeks before surgery. The best cut-off value of NLR was computed to be 2.29 in accordance with the receiver operating characteristic (ROC) curve. And the area under the ROC curve was 0.651 (95% CI 0.578–0.724; $P < .001$) (sensitivity: 59.5%, specificity: 69.5%) (**Figure 1**).

The follow-up period of patients was calculated from the first TURBT to the last cystoscopy examination. We performed urine cytology, cystoscopy, chest X-ray, and abdominopelvic

computed tomography (CT) scans for follow-up study. During the first year after TURBT, follow-up study was conducted at 3, 6, and 12 months. Cystoscopy and urine cytology were performed every 6 months until 2 years after TURBT, and yearly thereafter. Imaging analyses, including chest X-ray and CT scans were examined every 6 months from 1 to 5 years, and annually thereafter.

Recurrence of disease was defined as a newly pathological confirmed bladder cancer regardless of stage after completion of BCG induction therapy. Progression of disease was defined as from Ta or T1 to stage T2 or higher disease (MIBC).

Intravesical bacillus Calmette–Guérin instillation

In all patients, BCG tice strain 12.5 mg (Oncotice) was used. A BCG suspension with 50 mL of 0.9% normal saline was instilled to the bladder via a 10 Fr urethral catheter. Patients were advised not to urination for two hours. Induction BCG therapy was initiated 2 weeks after TUR and repeated once a week for 6 weeks. We did not perform BCG maintenance therapy. There were no patients who received immediate postoperative instillation of chemotherapy.

Club Urol*ó*gico Espa*ñ*ol de Tratamiento Oncol*ó*gico scoring model

Scoring tumor recurrence and progression were calculated according to the CUETO scoring model, which includes age, gender, previous recurrence status, tumor stage (2002 TNM classification) and grade, multiplicity, and concomitant CIS. In accordance with the 2004 World Health Organization (WHO) grading system, we classified tumor grades as low or high.

Statistical analysis

Non-continuous variables of patient characteristics, including gender, T stage, tumor grade, concomitant CIS, size (≦ 3 cm vs > 3 cm), number (≦ 3 vs > 3), recurrence status and CUETO risk model (categorical) were analyzed using the chi-square test. Student's t-test was used to analyze continuous variables such as age, body mass index (BMI), CUETO risk model (non-categorical) and follow up periods. In addition, univariate and multivariate Cox regression

model was used for analysis of tumor recurrence and progression, and Kaplan–Meier curves via a log-rank test were used for analysis of recurrence-free survival (RFS) and progression-free survival (PFS). Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA), and a *P* value < .05 was considered statistically significant.

RESULTS

Table 1 lists the characteristics of patients with NMIBC. A total of 173 patients had an NRL ≤ 2.29 (61.6%) and 108 (38.4%) had an NLR > 2.29. Eighty-four patients (29.9%) experienced recurrence and 14 (5.0%) showed progression after TUR followed by BCG therapy. Female patients accounted for 12.8% (36/281) of the study groups. No significant differences were evident in gender, age, BMI, and follow-up periods between the two NLR groups. There were no significant differences in tumor T stage, grade, concomitant CIS, size, number, and prior recurrence status between the two NLR groups. No significant differences were found in categorical or non-categorical CUETO scores between the two NLR groups. **Table 2** shows subgroup analysis of high risk NMIBC patients (n = 251). High risk group was defined if any high grade tumor or CIS is present.[12] Subgroup analysis of high risk group showed the similar results to the overall group.

Table 3 shows absolute neutrophil, lymphocyte count and NLR according to recurrence and progression. NRL was significantly higher in patients who showed recurrence or progression.

Table 4 shows univariate and multivariate Cox proportional hazards regression model for predicting recurrence. Female gender, concomitant CIS, multiplicity (> 3) and an NLR > 2.29 were independent prognostic factors for tumor recurrence (hazard ratio [HR], 2.103; 95% confidence internal [CI], 1.175–3.450; *P* = .011 / HR, 2.550; 95% CI, 1.362–4.774; *P* = .033 / HR, 2.275; 95% CI, 1.424–3.635; *P* = .009 / HR, 2.514; 95% CI, 1.657–3.483; *P* = .001, respectively).

Table 5 shows univariate and multivariate Cox proportional hazards regression model for predicting progression. Concomitant CIS, prior recurrence status and an NLR >2.29 were independent prognostic factors for progression (HR, 10.254; 95% CI, 2.919–36.018; $P < .001$ / HR, 8.628; 95% CI, 2.446–30.437; $P = .041$ / HR, 6.119; 95% CI, 1.975–21.622; $P = .008$, respectively).

Kaplan–Meier curve analyses with a log-rank test are shown in **Figure 2**, **3**, and **4**. A high NLR (> 2.29) were associated with significantly low RFS and PFS ($P < .001$, $P = .002$) (**Figure 2**). A high CUETO was associated with a significantly low RFS ($P < .001$), but there was no significant association between CUETO scores and PFS ($P = .423$) (**Figure 3**). After combining NLRs (cutoff value = 2.29) and CUETO scoring (cut-off value = 7), the modified risk model showed that high NLR and CUETO scores were significantly associated with low RFS and PFS ($P < .001$, $P = .002$) (**Figure 4**).

DISCUSSION

This study identified NLR as a significant factor for predicting tumor recurrence and progression, and inclusion of preoperative NLR enhanced the accuracy of the CUETO model to predict progression in patients with NMIBC.

In the early stages, NMIBC is not life-threatening, but it will recur in more than half of patients and progress from 10% to 20% to MIBC.[13] Although numerous efforts have been made to predict and prevent tumor recurrence and progression, the exact characteristics of NMIBC are unknown due to its heterogeneity.

The European Organization for Research and Treatment of Cancer (EORTC) has developed a simple scoring system that uses information such as tumor size and number, prior recurrence rate, stage, and concomitant CIS and WHO grade based on data of 2596 patients with NMIBC, to predict the risk of relapse and progression.[14] The CUETO scoring model was created to

compensate for the EORTC with low rates of BCG treatment, using information from 1062 patients who received BCG treatment.[7] Compared to EORTC, where most of the 78% patients received intravesical chemotherapy, all patients in the CUETO study received BCG instillation, and 15% of them received mitomycin C.

Intravesical instillation of BCG is a standard treatment for CIS and an adjuvant option for T1 and higher-grade Ta bladder tumors after TUR.[15] The CUETO model is thought to be more suitable for patients treated with BCG. In this study, as with the CUETO study, we included patients who completed 6 BCG instillations. However, compared with the CUETO scoring model, only female gender, concomitant CIS, multiplicity (> 3), and prior recurrence status were significant factors for predicting tumor recurrence (all $P < .05$). About tumor progression, only concomitant CIS and prior recurrence status were significant factors (all $P < .05$). A Kaplan–Meier curve analysis demonstrated that the CUETO score was associated with RFS ($P < .05$), but not with PFS ($P = .423$). We therefore decided to add the NLR ratio to the CUETO scoring model if inclusion of an NLR would enhance the predictability of CUETO scoring.

Preoperative NLR has proven to be a useful marker and a high NLR has been linked to higher tumor stages and adverse oncologic outcomes in numerous cancers, including not only the gastrointestinal cancer but genitourinary tract cancer, such as urothelial carcinoma of the bladder.[16-19] Although the pathophysiology is not understood clearly, relative neutrophilia may increase inflammatory markers that include proangiogenic factors, growth factors, proteases, and antiapoptotic markers, which facilitate tumor growth and progression.[20] In addition, lymphocytopenia may destroy cell-mediated immune responses and therefore worsen prognoses.[21] In bladder tumors, several previous studies have evaluated the predictive value of NLRs[22]; most focused on MIBC and were conducted mainly on patients who underwent radical cystectomy.[23-26] In 2014, Viers et al. evaluated 899 patients who underwent radical cystectomy without neo-adjuvant chemotherapy and who had a preoperative NLR. An elevated

preoperative NLR (> 2.7) was associated with a significantly higher risk of a locally advanced disease as well as subsequent disease recurrence and cancer-specific and all-cause mortality. In 2012, Can et al. demonstrated that among 80 NMIBC patients and 102 patients with MIBC, an NLR > 2.57 was a predictor of invasive urothelial carcinoma. According to a 2014 study by Potretzke et al., among 102 consecutive patients undergoing radical cystectomy, NLR was significantly related to pathologic tumor staging and to upstaging of non-organ confined disease (≧ pT3). Similarly, Krane et al. reported that, among 68 consecutive cases of radical cystectomy for MIBC, an NLR >2.5 was associated with poor overall and cancer-specific survival, suggesting that such patients may benefit from neo-adjuvant chemotherapy.

When focusing on NMIBC, several trials[8,16,27,28] evaluated the predictive value of the NLR. In 2015, Mano et al. revealed that an NLR > 2.41 was an independent predictor of disease progression and recurrence in 107 patients with NMIBC treated with TUR. According to Favilla et al.'s study in 2016, an NLR ≥ 3 was associated with worse disease recurrence (HR, 2.84; P < .01) in 178 patients with Ta or T1 bladder tumor who underwent TUR. The 5-year RFS was 49% and 62% in patients with an NLR ≥ 3 and < 3 (P < .01). A prospective study of Albayrak et al. in 2016 found that a higher NLR was associated with recurrence and progression of Ta or Ta bladder tumors, although, and in contrast with the finding of previous studies, a significant relationship with NLR was lost after correcting for age. Another prospective trial by Getzler et al. in 2018 demonstrated that an NLR > 2.5 was a significant predictor of disease recurrence and a worse RFS in 113 patients with NMIBC, particularly those treated with BCG. As with the studies described above, we found that an NLR > 2.29 was associated with higher tumor recurrence (HR, 2.451; 95% CI, 1.567–3.834; P < .001) and tumor progression (HR, 5.911; 95% CI, 1.579–22.126; P = .008) according to a multivariate Cox proportional hazards regression model. Kaplan–Meier curve analysis showed that an NLR > 2.29 showed significantly low RFS and PFS (P < .001 and <.002, respectively). However, the four studies mentioned above were

not restricted to patients treated with BCG.

When narrowing the scope of predictive values of NLRs in all BCG treated patients, Racioppi et al. (2019)[29] evaluated whether an NLR ratio can predict the response to BCG in high-risk NMIBC patients. One hundred consecutive patients with newly diagnosed high-risk NMIBC were analyzed retrospectively. All received an induction course of intravesical immunotherapy with BCG followed by a maintenance course for at least a year. Forty-eight patients underwent radical cystectomy for high-grade recurrence or progression to muscle invasive disease (BCG non-responder group). The mean NLR was 2.61 ± 0.77 in the BCG responder group and 3.65 ± 1.16 in the BCG non-responder group ($P = .01$). The NLR was associated with both recurrence ($P = .01$) and progression ($P = .01$). A Kaplan–Meier analysis with a log-rank test showed statistically significant differences between the curves for an NLR < 3 and an NLR ≥ 3 ($P < .05$).

Based on the ability of the NLR to predict tumor recurrence and progression, we added the NLR to the CUETO scoring model. Using the CUETO scoring model alone, a significant association was observed with low RFS ($P < .001$), but not with PFS ($P = .423$) (**Figure 2**). However, after combining the NLR (cut-off value 2.29) and CUETO scoring model (cut-off value 7), the resulting modified risk model showed that a high NLR and high CUETO score were significantly associated with both low RFS and PFS ($P < .001$ and $P = .002$, respectively) (**Figure 3**). Other combined risk models have been shown to enhance the predictability of each risk model.[8,21] Getzler et al. provided statistical evidence that an NLR > 2.5 may improve the predictive power of an EORTC score when the two are calculated together. In 2019, Aydin et al. evaluated the correlation between NLR and EORTC recurrence and progression scores. They reported that as the NLR increased, recurrence ($P < .001$) and progression ($P = .034$) scores increased significantly. Nevertheless, this study is the first to analyze the prognostic significance of the NLR and its synergic relation with the CUETO scoring model in patients with NMIBC after intravesical BCG instillation. Furthermore, interestingly, there were no

differences in the clinical and pathological findings between the two NLR groups. And this highlights that the biological properties of tumor cells may be very different from the pathological and anatomical characteristics of the tumor. As such patients within a specific pathological classification may have differing prognosis due to differing biological properties such as the degree of immune dysfunction.

There were several limitations to be considered in this study. First, it was based on a retrospective analysis of the records of patients treated at a single institution with unavoidable selection biases. Small numbers and heterogeneous patients are also weak points. It should also be noted that in many previous studies, various NLR cut-off values were evaluated and utilized.[30] Each study's results should be interpreted carefully. Because the idealized and generalized NLR have not yet been established, each study selected cut-off values with different sensitivities and specificities. Furthermore, the main limitation concerning NLRs is the volatile counts of neutrophils and lymphocytes. Although we excluded patients with hematologic malignances and acute or chronic infections, it is possible that individual chronic medications, herbs, or antibiotics affected the NLR value. As the NLR is a dynamic parameter (unlike standard pathological parameters), the dynamic changes of NLR after various treatments of bladder cancer may be important in the clinical day-to-day management of patients. Few studies have been reported on the NLR measured after TURBT or BCG instillation, therefore, studies comparing NLR before and after treatment of bladder cancer or optimal timing of NLR determination are also essential, either. A prospective study with a larger cohort is required to solidify the place of NLR in predicting disease recurrence and progression in patients with NMIBC in the future.

CONCLUSIONS

Our study showed that in patients with NMIBC, the NLR was identified as a significant factor for predicting tumor recurrence and progression. Furthermore, inclusion of a preoperative NLR

enhanced the accuracy of the CUETO model to predict disease progression. NLR is promising and inexpensive hematologic biomarker which can be applied to clinical decision making and estimation of oncologic outcomes in the bladder cancer patients. We therefore recommend that patients with a high NLR receive more aggressive management.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), and was funded by the Korean Government (MSIT) (2016R1C1B1011180), (2019R1H1A1079839), (2019R1F1A1044473), (2019R1A2C1004046), (2018R1C1B5040264), (2020R1A2B5B03002344) and (2020R1I1A3071568).

CONFLICT OF INTERESTS

None of the authors has any personal or financial conflict of interest.

Abbreviations

BMI: body mass index

CIS: carcinoma in situ

CT: computed tomography

CUETO: Club Urológico Español de Tratamiento Oncológico

EORTC: European Organization for Research and Treatment of Cancer

MIBC: muscle invasive bladder cancer

NLR: neutrophil-to-lymphocyte ratio

NMIBC: nNon-muscle invasive bladder cancer

PFS: progression-free survival

RFS: recurrence-free survival

WHO: World Health Organization

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-86.
2. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol. 2013;64:639-53.
3. Babjuk M, Bohle A, Burger M, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol. 2017;71:447-61.
4. Malmstrom PU, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol. 2009;56:247-56.
5. Cambier S, Sylvester RJ, Collette L, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. Eur Urol. 2016;69:60-9.
6. Hidas G, Pode D, Shapiro A, et al. The natural history of secondary muscle-invasive bladder cancer. BMC Urol. 2013;13:23.
7. Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol. 2009;182:2195-203.
8. Getzler I, Bahouth Z, Nativ O, Rubinstein J, Halachmi S. Preoperative neutrophil to lymphocyte ratio improves recurrence prediction of non-muscle invasive bladder cancer. BMC Urol. 2018;18:90.
9. Lee BS, Lee SH, Son JH, et al. Neutrophil-lymphocyte ratio predicts survival in patients

with advanced cholangiocarcinoma on chemotherapy. Cancer Immunol Immunother. 2016;65:141-50.

10. Viers BR, Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Tollefson MK. Preoperative neutrophil-lymphocyte ratio predicts death among patients with localized clear cell renal carcinoma undergoing nephrectomy. Urol Oncol. 2014;32:1277-84.
11. Ceylan C, Doluoglu OG, Keles I, et al. Importance of the neutrophil-to-lymphocyte ratio in muscle-invasive and non-muscle invasive bladder tumors. Urologia. 2014;81:120-4.
12. Babjuk M, Burger M, Comperat EM, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. Eur Urol. 2019;76:639-57.
13. Donat SM. Evaluation and follow-up strategies for superficial bladder cancer. Urol Clin North Am. 2003;30:765-76.
14. Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49:466-77.
15. Lamm DL, Blumenstein BA, Crawford ED, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guerin for transitional-cell carcinoma of the bladder. N Engl J Med. 1991;325:1205-9.
16. Mano R, Baniel J, Shoshany O, et al. Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non-muscle-invasive bladder cancer. Urol Oncol. 2015;33.
17. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer. 2011;104:1288-95.

18. Ku JH, Kang M, Kim HS, Jeong CW, Kwak C, Kim HH. The prognostic value of pretreatment of systemic inflammatory responses in patients with urothelial carcinoma undergoing radical cystectomy. Br J Cancer. 2015;112:461-7.

19. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. Surg Oncol. 2014;23:31-9.

20. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436-44.

21. Aydin M, Bitkin A, Kadihasanoglu M, et al. Correlation of neutrophil-lymphocyte ratio and risk scores in non-muscle invasive bladder cancer. Actas Urol Esp. 2019;43:503-8.

22. Zhang LH, Li LQ, Liu JX, et al. Meta-analysis of multiple hematological biomarkers as prognostic predictors of survival in bladder cancer. Medicine. 2020;99.

23. Viers BR, Boorjian SA, Frank I, et al. Pretreatment Neutrophil-to-Lymphocyte Ratio Is Associated with Advanced Pathologic Tumor Stage and Increased Cancer-specific Mortality Among Patients with Urothelial Carcinoma of the Bladder Undergoing Radical Cystectomy. Eur Urol. 2014;66:1157-64.

24. Can C, Baseskioglu B, Yilmaz M, Colak E, Ozen A, Yenilmez A. Pretreatment Parameters Obtained from Peripheral Blood Sample Predicts Invasiveness of Bladder Carcinoma. Urol Int. 2012;89:468-72.

25. Potretzke A, Hillman L, Wong K, et al. NLR is predictive of upstaging at the time of radical cystectomy for patients with urothelial carcinoma of the bladder. Urol Oncol. 2014;32:631-6.

26. Krane LS, Richards KA, Kader AK, Davis R, Balaji KC, Hemal AK. Preoperative Neutrophil/Lymphocyte Ratio Predicts Overall Survival and Extravesical Disease in Patients Undergoing Radical Cystectomy. J Endourol. 2013;27:1046-50.

27. Favilla V, Castelli T, Urzi D, et al. Neutrophil to lymphocyte ratio, a biomarker in non-muscle invasive bladder cancer: a single-institutional longitudinal study. Int Braz J Urol. 2016;42:685-93.

28. Albayrak S, Zengin K, Tanik S, et al. Can the neutrophil-to-lymphocyte ratio be used to predict recurrence and progression of non-muscle-invasive bladder cancer? Kaohsiung J Med Sci. 2016;32:327-33.

29. Racioppi M, Di Gianfrancesco L, Ragonese M, Palermo G, Sacco E, Bassi PF. Can Neutrophil-to-Lymphocyte ratio predict the response to BCG in high-risk non muscle invasive bladder cancer? International Braz J Urol. 2019;45:315-24.

30. Marchioni M, Primiceri G, Ingrosso M, et al. The Clinical Use of the Neutrophil to Lymphocyte Ratio (NLR) in Urothelial Cancer: A Systematic Review. Clin Genitourin Cancer. 2016;14:473-84.

Table 1. Characteristics of patients with NMIBC.

	Total n = 281	NLR ≤ 2.29 n = 173	NLR > 2.29 n = 108	*P*-value
Recurrence	84 (29.9%)	35 (20.2%)	49 (45.4)	< 0.001
Progression	14 (5.0%)	3 (1.7%)	11 (10.2%)	0.002
Gender				0.952
Male	245 (87.2%)	151 (87.3%)	94 (87.0%)	
Female	36 (12.8%)	22 (12.7%)	14 (13.0%)	
Age, years	67.38 ± 10.58	68.00 ± 9.87	66.40 ± 11.60	0.218
Age, categorical				0.340
< 60	63 (22.4%)	34 (19.7%)	29 (26.9%)	
60 ~ 70	98 (34.9%)	64 (37.0%)	34 (31.5%)	
> 70	120 (42.7%)	75 (43.4%)	45 (41.7%)	
Body mass index, kg/m^2	23.88 ± 3.37	23.94 ± 3.07	23.79 ± 3.81	0.727
Follow-up periods, months	46.65 ± 20.80	45.25 ± 19.14	48.89 ± 23.13	0.173
T stage				0.239
Ta	105 (37.4%)	60 (34.7%)	45 (41.7%)	
T1	176 (62.6%)	113 (65.3%)	63 (58.3%)	
Tumor grade				0.327
Low	30 (10.7%)	16 (9.2%)	14 (13.0%)	
High	251 (89.3%)	157 (90.8%)	94 (87.0%)	
Concomitant carcinoma in situ				0.098
No	257 (91.5%)	162 (93.6%)	95 (88.0%)	
Yes	24 (8.5%)	11 (6.4%)	13 (12.0%)	
Tumor size				0.779
≦ 3 cm	195 (69.4%)	119 (68.8%)	76 (70.4%)	
> 3 cm	86 (30.6%)	54 (31.2%)	32 (29.6%)	
Tumor number				0.293
≦ 3	215 (76.5%)	136 (78.6%)	79 (73.1%)	
> 3	66 (23.5%)	37 (21.4%)	29 (26.9%)	
Recurrent tumor				0.792
No	240 (85.4%)	147 (85.0%)	93 (86.1%)	
yes	41 (14.6%)	26 (15.0%)	15 (13.9%)	
CUETO score according to recurrence (non-categorical)	5.58 ± 2.13	5.57 ± 2.08	5.59 ± 2.20	0.938
CUETO score according to recurrence (categorical)				0.826
1~4	92 (32.7%)	55 (31.8%)	37 (34.3%)	
5~6	106 (37.7%)	67 (38.7%)	39 (36.1%)	
7~9	66 (23.5%)	42 (24.3%)	24 (22.2%)	
10~16	17 (6.1%)	9 (5.2%)	8 (7.4%)	
CUETO score according to progression (non-categorical)	8.27 ± 2.26	8.35 ± 2.20	8.15 ± 2.37	0.462
CUETO score according to progression (categorical)				0.453

1~4	22 (7.8%)	12 (6.9%)	10 (9.3%)
5~6	42 (15.0%)	22 (12.7%)	20 (18.5%)
7~9	120 (42.7%)	78 (45.1%)	42 (38.9%)
10~14	97 (34.5%)	61 (35.3%)	36 (33.3%)

Data are presented as mean±SD or number (percent)

Table 2. Characteristics of patients with high risk patients with NMIBC.

	Total n = 251	NRL ≤ 2.29 n = 159	NLR > 2.29 n = 95	*P*-value
Recurrence	78 (30.7%)	34 (21.4%)	44 (46.3%)	<0.001
Progression	14 (5.5%)	3 (1.9%)	11 (11.6%)	0.001
Gender				0.814
Male	223 (87.8%)	139 (87.4%)	84 (88.4%)	
Female	31 (12.2%)	20 (12.6%)	11 (11.6%)	
Age, years	67.59 ± 10.61	68.16 ± 9.96	66.64 ± 11.61	0.270
Body mass index, kg/m^2	23.82 ± 3.44	23.91 ± 3.11	23.68 ± 3.94	0.607

Data are presented as mean±SD or number (percent)

Table 3. Absolute neutrophil, lymphocyte count and NLR according to recurrence and progression.

	No recurrence	Recurrence	*P*-value
Neutrophil count (x10^3)	3.97 ± 1.47	4.50 ± 1.44	0.006
Lymphocyte count (x10^3)	2.03 ± 0.61	1.86 ± 0.69	0.039
NLR	2.11 ± 1.01	2.69 ± 1.17	< 0.001
	No progression	Progression	*P*-value
Neutrophil count (x10^3)	4.11 ± 1.49	4.59 ± 1.14	0.238
Lymphocyte count (x10^3)	1.99 ± 0.64	1.65 ± 0.62	0.054
NLR	2.25 ± 1.09	2.98 ± 0.99	0.013

Data are presented as mean±SD or number (percent)

Table 4. Univariate and multivariate Cox proportional hazards regression model for predicting recurrence.

	P-value		HR (95% CI)
	Univariate	Multivariate	
Age	0.015	0.271	-
Body mass index	0.935	-	-
Gender (male vs. female)	0.005	0.011	2.103 (1.175-3.450)
T stage (Ta vs T1)	0.035	0.236	-
Tumor grade (low vs high)	0.475	-	-
Presence of carcinoma in situ (no vs. yes)	0.024	0.033	2.550 (1.362-4.774)
Multiplicity (≦ 3 vs > 3)	0.004	0.009	2.275 (1.424-3.635)
Tumor size (≦ 3 vs > 3)	0.715	-	-
Prior recurrence status (no vs. yes)	0.080	-	-
NLR (≦ 2.29 vs. > 2.29)	< 0.001	0.001	2.514 (1.657-3.483)

Table 5. Univariate and multivariate Cox proportional hazards regression model for predicting progression.

	P-value		HR (95% CI)
	Univariate	Multivariate	
Age	0.089	-	-
Body mass index	0.722	-	-
Gender (male vs. female)	0.141	-	-
T stage (Ta vs T1)	0.225	-	-
Tumor grade (low vs high)	0.193	-	-
Presence of carcinoma in situ (no vs. yes)	< 0.001	< 0.001	10.254 (2.919-36.018)
Multiplicity (≦ 3 vs > 3)	0.645	-	-
Tumor size (≦ 3 vs > 3)	0.670	-	-
Prior recurrence status (no vs. yes)	0.022	0.041	8.628 (2.446-30.437)
NLR (≦ 2.29 vs. > 2.29)	0.002	0.008	6.119 (1.975-21.622)

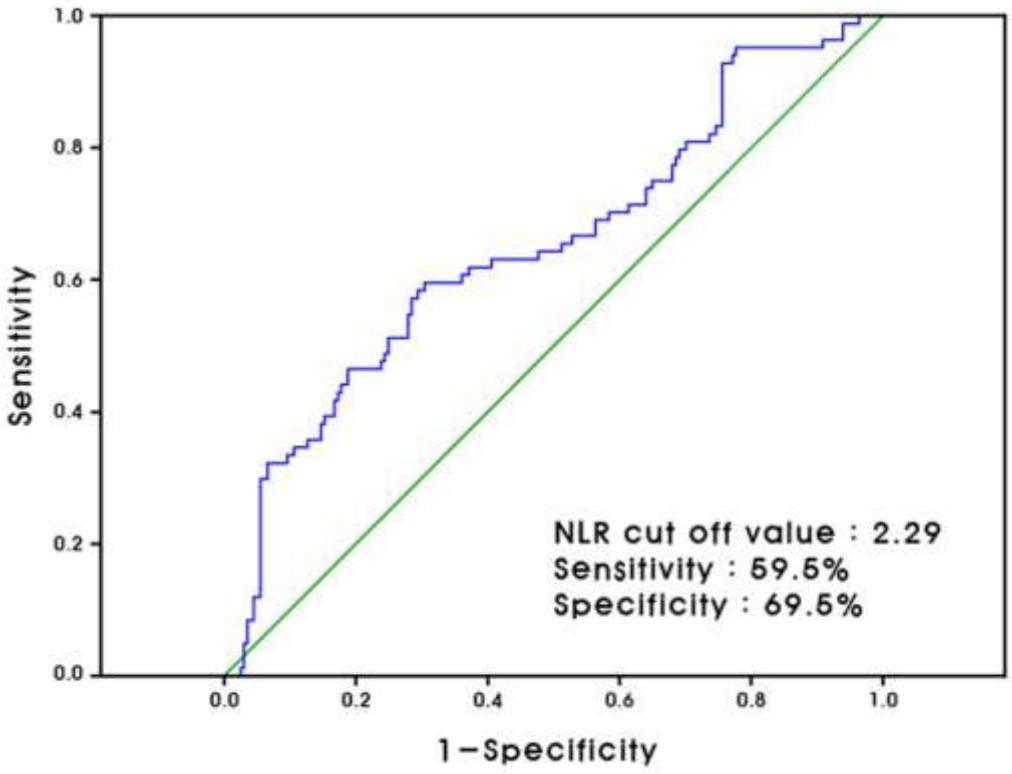

Figure 1. The best cut-off NLR value according to the ROC curve**.**

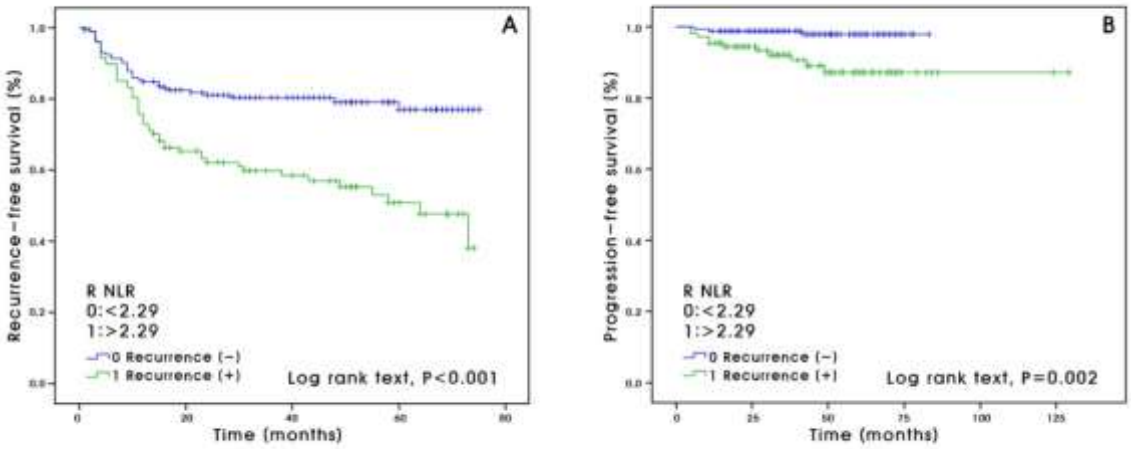

Figure 2. Kaplan–Meier curve analysis for recurrence-free survival (A) and progression-free survival (B), according to NLRs.

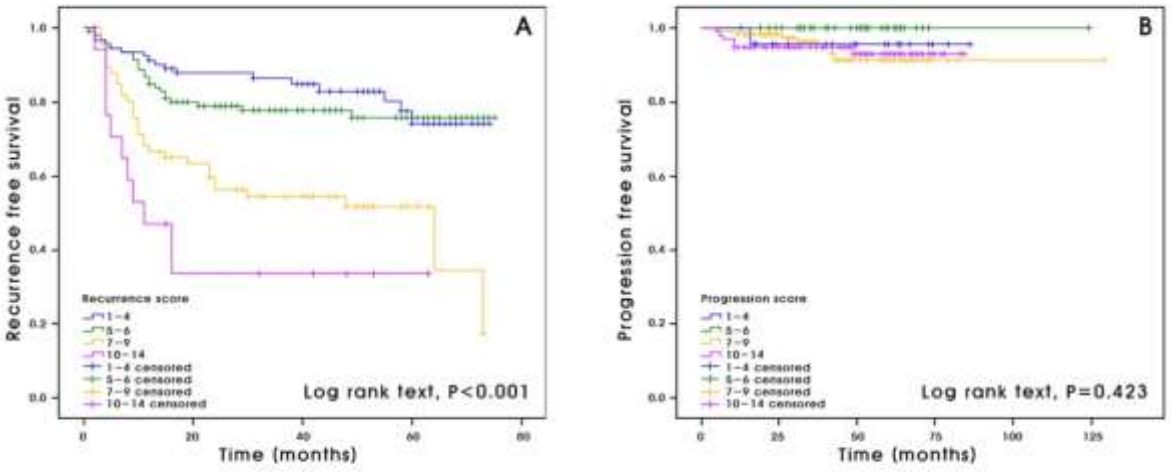

Figure 3. Kaplan–Meier curve analysis for recurrence-free survival (A) and progression-free survival (B), according to CUETO scores.

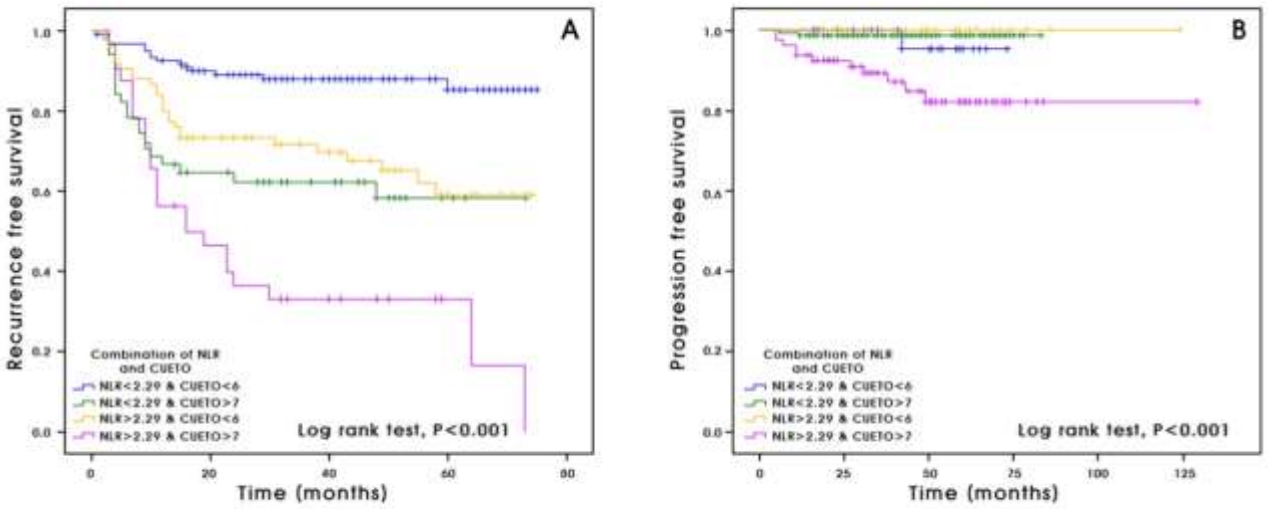

Figure 4. Kaplan–Meier curve analysis for recurrence-free survival (A) and progression-free survival (B), according to a combination of NLRs and CUETO scores.