European Review for Medical and Pharmacological Sciences 2016; 20: 652-656

Preoperative neutrophil-to-lymphocyte ratio (NLR) may be predictive of pathologic stage in patients with bladder cancer larger than 3 cm

O. CELIK[1], M. AKAND[2], M.Z. KESKIN[1], M. YOLDAS[1], Y.O. ILBEY[1]

[1]Department of Urology, Tepecik Education and Research Hospital, Izmir, Turkey
[2]Department of Urology, Selcuk University, School of Medicine, Konya, Turkey

O. Celik and M. Akand should be regarded as co-first Authors

Abstract. – OBJECTIVE: Bladder cancer (BCa) is the most common malignancy of the urinary tract. In this study, we aimed to evaluate the ability of preoperative neutrophil-to-lymphocyte ratio (NLR) to predict pathologic stage of at the time of first transurethral resection of bladder tumor (TUR-BT) in patients with BCa larger than 3 cm.

PATIENTS AND METHODS: Records of consecutive patients undergoing TUR-BT for BCa with a diameter >3 cm were reviewed. A total of 222 patients were eligible for analysis, and were divided into two groups: 162 patients in non-muscle-invasive BCa (NMIBC) group and 60 patients in muscle-invasive BCa (MIBC) group. Differences in preoperative blood parameters and NLR were evaluated between groups with an unequal variance t-test.

RESULTS: In the NMIBC group, 59 patients had low-grade and 103 high-grade papillary urothelial carcinomas. 60 patients had T2 stage carcinoma. The mean age of the patients was 71.8 and 75.7 years, and mean NLR was 3.44 ± 2.03 and 4.6 ± 2.8 in NMIBC and MIBC groups, respectively. In terms of NLR, there was a statistically significant difference between the NMIBC and MIBC groups ($p = 0.005$).

CONCLUSIONS: Our results showed that NLR might act as a significant predictive biomarker on the staging of BCa. Also, NLR could be used as a cost-effective, simple, common usable biomarker in urology clinic practice.

Key Words:
Bladder cancer, Neutrophil, Lymphocyte, Muscle-invasive, Stage.

Abbreviations

BCa = Bladder cancer; CIS = Carcinoma in situ; NMIBC = Non-muscle-invasive bladder cancer; MIBC = Muscle-invasive bladder cancer; NLR = Neutrophil-to-lymphocyte ratio; TUR-BT = Transurethral resection of bladder tumor; Hb = Hemoglobin; Htc = Hematocrit; MPV = Mean platelet volume.

Introduction

Bladder cancer (BCa) is the most common malignancy of the urinary tract and the seventh most common cancer in men and the seventeenth in women[1]. Approximately 74,000 cases of newly diagnosed BCa (at about 56,320 in men and 17,680 in women) and 16,000 deaths from BCa (at about 11,510 in men and 4,490 in women) are estimated for 2015 in the United States by the American Cancer Society[2]. BCa occurs mainly in older people in which nearly 9 of 10 people with BCa are over the age of 55, and the average age at the time of diagnosis is generally between 62 and 73 years[3-6]. At the initial diagnosis, approximately 70% of patients with BCa present with a disease confined to the mucosa (stage Ta or carcinoma *in situ* [CIS]) or submucosa (stage T1), which is called non-muscle-invasive BCa (NMIBC), and 30% of patients with muscle-invasive BCa (MIBC)[7].

General and non-specific immune response may be elicited due to distortion created by the physical effects of the tumor[8]. Most of the recent studies[9-13] showed that neutrophil-to-lymphocyte ratio (NLR) could be used as a useful biomarker of systemic inflammatory response not only in several tumor types but also in other inflammatory conditions and various diseases. A higher NLR in the preoperative evaluation has been reported as a useful predictive marker associated with poor prognosis and pathologic upstaging in some cancers including BCa[14].

In this study, we aimed to evaluate the ability of preoperative NLR to predict pathologic stage of at the time of first transurethral resection of bladder tumor (TUR-BT) in BCa patients.

Corresponding Author: Murat Akand, MD; e-mail: drmuratakand@yahoo.com

Patients and Methods

The data of 222 patients who underwent TUR-BT for BCa with a diameter >3 cm at Tepecik Education and Research Hospital, Department of Urology between March 2009 and September 2014 were analyzed. Patients with an active infection, a history of infection during the last month, any previous transurethral procedure, CIS, < 3 cm diameter, multiple tumors, a second primary cancer, a BCa other than the urothelial cancer subtype, a hematologic disorder with a potential to alter the NLR, and missing data were excluded.

Preoperative hemoglobin (Hb), hematocrit (Htc), neutrophil count, lymphocyte count, platelet count and mean platelet volume (MPV) were evaluated, and NLR was calculated for each patient. After TUR-BT, patients received further treatment according to their initial pathology as stated in European Association of Urology Guidelines (intravesical immunotherapy and/or re-TUR-BT for NMIBC, and radical cystectomy for MIBC)[1,7].

The primary outcome was the difference in pathological stage predicted from preoperative assessment at the time of TUR-BT. A univariate analysis assessed whether NLR, preoperative stage, grade, gender, age were related to pathological staging. Multivariate analyses were performed to evaluate the relationship of NLR to staging and relative organ-confined (≤pT2) disease.

All patients had given written informed consent before the surgery for giving permission for the use of the collected data at any time. Institutional Review Board has approved the study. The principles of the Helsinki Declaration were followed during the study, and the confidentiality of the patients' data was guaranteed.

Statistical Analysis

Numeric values were compared by using Student *t*-test, and chi-square test was used for the comparison of the non-numeric values. A p value <0.05 was considered statistically significant. All statistical analyses were performed with the IBM Statistical Package for Social Sciences (SPSS) Software Version 22 (New York, NY, USA).

Results

Among 222 patients, there were 192 males and 30 females. Of these, 141 male and 21 female patients were in the NMIBC group while 51 male and 9 female patients were in the MIBC group. In the NMIBC group, 59 patients had low-grade and 103 high-grade papillary urothelial carcinomas. The mean age of the patients was 71.8 and 75.7 years in the NMIBC and MIBC group, respectively. The mean NLR was 3.44 ± 2.03 (95% CI: -1.8 – -0.53) and 4.65 ± 2.8 (95% CI: -1.9 – -0.42) in the NMIBC and MIBC group, respectively. In terms of NLR, there was a statistically significant difference between the NMIBC and MIBC groups (p=0.005). The characteristic features of the patients are given in Table I.

Discussion

BCa is the most common malignancy of the urinary tract. Two distinct groups can be identified; namely NMIBC and MIBC[1]. At initial resection, about 70-75% of the patients will be diagnosed with NMIBC. This subgroup has a recurrence rate up to 70-80%, and a subsequent chance of disease progression[1,7]. This means that patients with NMIBC require adequate treatment and thorough follow-up[15,16]. Lack of efficiently prognostic biomarkers is partly responsible for the high mortality rates caused by cancer. Thus, efficiently and reliable biomarkers for providing additional prognostic information are urgently needed[17-20].

BCa is frequently associated with chronic or recurrent inflammation, and a high number of inflammatory cells are found at the tumor site[21]. Suppression of lymphocyte and an enhanced neutrophil response leading to a high NLR might inhibit the anti-tumor immune response and promote carcinogenesis[22,23]. Molecular pathways used by inflammatory mediators could promote angiogenesis and metastasis on cancer cells, thus affecting the tumor response to therapies[24].

Peripheral blood tests before treatment or at the time of diagnosis may reflect inflammatory conditions within the tumor. NLR calculated from a convenient and cheap test could provide appropriate prognostic information for the patients in the treatment of BCa[25]. Mano et al[26] evaluated the medical records of 122 consecutive, newly diagnosed patients with NMIBC treated with TUR-BT between 2003 and 2010. They found an association between an elevated NLR and high tumor grade and T1 stage. It was suggested that NLR was significantly associated with disease progression and recurrence in

Table I. Blood parameters of non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) groups.

	NMIBC (n=162)	MIBC (n=60)	*p*-value
Age (years)	71.8 ± 10.9	75.7 ± 10.2	0.029
Tumor grade			
• Low-grade	59 (36.4%)	2 (3.4%)	
• High-grade	103 (63.6%)	58 (96.6%)	<0.05
WBC	8.8 ± 3.2	9.9 ± 3.4	0.025
Platelet	277.4 ± 88.2	275.3 ± 85.6	0.871
Neutrophil	6.26 ± 3.0	7.23 ± 2.9	0.034
Lymphocyte	2.08 ± 0.7	1.84 ± 0.7	0.042
Monocyte	0.78 ± 0.4	0.72 ± 0.2	0.283
Eosinophil	0.28 ± 0.2	0.26 ± 0.2	0.565
Basophil	0.10 ± 0.2	0.08 ± 0.1	0.411
RBC	4.50 ± 0.6	4.06 ± 0.7	<0.001
Hemoglobin	12.5 ± 2.2	11.1 ± 2.2	<0.001
Hematocrit	38.8 ± 5.1	34.3 ± 6.0	<0.001
MCV	87.5 ± 6.7	84.9 ± 6.9	0.014
MCH	29.3 ± 2.6	28.4 ± 2.7	0.026
MPV	8.76 ± 1.1	8.24 ± 1.0	0.003
NLR	3.44 ± 2.0	4.65 ± 2.8	<0.001

WBC: White blood cell, RBC: Red blood cell, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MPV: Mean platelet volume, NLR: Neutrophil-lymphocyte ratio.
Data are shown as mean ± SD or n (%).

univariate and multivariate analyses adjusted for EORTC risk groups for progression or recurrence and treatment with bladder instillations[26].

Most studies that evaluated the association between NLR and outcome after radical cystectomy reported that elevated NLR was associated with worse recurrence-free, disease-specific, and overall survival[14,27-30]. Contrary to these reports, Demirtas et al[31] did not find a significant association in patients with an NLR>2.5 and overall survival. Wei et al[32] carried out a meta-analysis of 17 published studies including 3159 cases to assess the prognostic value of NLR in patients with urinary cancers. A total of 11 studies explored NLR in the prognosis of renal cell carcinoma and 2 of prostate cancer, 2 of BCa and 2 of urothelial carcinoma, respectively. The cut-off value applied in each study was not consistent ranging from 2 to 5. Subgroup analyses by cancer type showed that high NLR yielded a worse overall survival in renal cell cancer, BCa and urothelial carcinomas. Additionally, this meta-analysis showed that high NLR remained to be a worse prognostic marker regardless of sample size[32].

Our study has certainly some limitations. Firstly, relatively small number of patients was evaluated in each group. Secondly, it is retrospective study instead of a prospective randomized one. Thirdly, there was missing data in the disease-specific and overall survival of all the patients.

Conclusions

We found a statistically significant difference in NLR between NMIBC and MIBC groups which is consistent with the data in the literature. This easy-to-use ratio can be used for the prediction of muscle invasiveness in BCa during the preoperative evaluation of the patients. To better understand the role of NLR in the prognosis of BCa, well-designed, prospective studies with high caseloads are needed.

Acknowledgements

Orcun Celik and Murat Akand contributed equally to this study, and are the first co-authors of the article.
All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Comperat E, Slyvester RJ, Kaasinen E, Böhle A, Palou Redorta J, Roupret M; European Association of Urology. EAU guidelines on non-muscle invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013; 64: 639-653.
2) Martin-Doyle W, Leow JJ, Orsola A, Chang SL, Bellmunt J. Improving selection criteria for early cystectomy in high-grade T1 bladder cancer: a meta-analysis of 15.215 patients. J Clin Oncol 2015; 33: 643-650.
3) Messing EM. Urothelial tumors of the bladder. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 9th ed. Philadelphia: Saunders-Elsevier, 2008; pp. 2407-46.
4) Karbakhsh M, Dabbagh N, Shabani A, Tabibi A, Akhavizadegan H. Age at diagnosis in bladder cancer: does opium addiction play a role? Asian Pac J Cancer Prev 2013; 14: 4723-4725.
5) Kobeissi LH, Yassine IA, Jabbour ME, Moussa MA, Dhaini HR. Urinary bladder cancer risk factors: a Lebanese case-control study. Asian Pac J Cancer Prev 2013; 14: 3205-3211.
6) Nikfarjam Z, Massoudi T, Salehi M, Salehi M, Khoshroo F. Demographic survey of four thousand patients with 10 common cancers in north eastern Iran over the past three decades. Asian Pac J Cancer Prev 2014; 15: 10193-10198.
7) Witjes JA, Comperat E, Cowan NC, de Santis M, Gakis G, Lebret T, Ribal MJ, Van der Heijden AG, Sherif A; European Association of Urology. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol 2014; 65: 778-792.
8) Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860-867.
9) Zahorec R. Ratio of neutrophil to lymphocyte counts – rapid and simple parameter of systemic inflammation and stress in critically ill. Bratislavske Lekarske Listy 2001; 102: 5-14.
10) Emir S, Aydin M, Can G, Bali I, Yildirim O, Oznur M, Yildiz ZD, Sozen S, Gurel A. Comparison of colorectal neoplastic polyps and adenocarcinoma with regard to NLR and PLR. Eur Rev Med Pharmacol Sci 2015; 19: 3613-3618.
11) Yasar Z, Buyuksirin M, Ucsular FD, Kargi A, Erdem F, Talay F, Kurt OK. Is an elevated neutrophil-to-lymphocyte ratio a predictor of metabolic syndrome in patients with chronic obstructive pulmonary disease? Eur Rev Med Pharmacol Sci 2015; 19: 956-962.
12) Okyay K, Yilmaz M, Yildirir A, eroglu S, Sade E, Sahinarslan A, Aydinalp A, Muderrisoglu H. Relationship between neutrophil-to-lymphocyte ratio and impaired myocardial perfusion in cardiac syndrome X. Eur Rev Med Pharmacol Sci 2015; 19: 1881-1887.
13) Balli M, Tasolar H, Cetin M, Tekin K, Cagliyan CE, Turkmen S, Yilmaz M, Elbasan Z, Sahin DY, Cayli M. Use of the neutrophil-to-lymphocyte ratio for prediction of in-stent restenosis in bifurcation lesions. Eur Rev Med Pharmacol Sci 2015; 19: 1866-1873.
14) Gondo T, Nakashima J, Ohno Y, Choichiro O, Horiguchi Y, Namiki K, Yoshioka K, Ohori M, Hatano T, Tachibana M. Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. Urology 2012; 79: 1085-1091.
15) Oude Elferink P, Witjes JA. Blue-light cystoscopy in the evaluation of non-muscle-invasive bladder cancer. Ther Adv Urol 2014; 6: 25-33.
16) Takai T, Inamoto T, Komura K, Yoshikawa Y, Uchimoto T, Saito K, Tanda N, Kouno J, Minami K, Uehara H, Takahara K, Hirano H, Nomi H, Kiyama S, Azuma H. Feasibility of photodynamic diagnosis for challenging TUR-Bt cases including muscle invasive bladder cancer, BCG failure, or 2nd TUR. Asian Pac J Cancer Prev 2015; 16: 2297-2301.
17) Malmström PU. Prognostic markers for urothelial cancer: obstacles and opportunities. Urol Oncol 2012; 30: 516-517.
18) Chen JX, Deng N, Chen X, Chen LW, Qiu SP, Li XF, Li JP. A novel molecular grading model: combination of Ki67 and VEGF in predicting tumor recurrence and progression in non-invasive urothelial bladder cancer. Asian Pac J Cancer Prev 2012; 13: 2229-2234.
19) Wang HF, Wang JS. Research progress in potential urinary markers for the early detection, diagnosis and follow-up of human bladder cancer. Asian Pac J Cancer Prev 2012; 13: 1723-1726.
20) Ghafouri-Fard S, Nekoohesh L, Motevaseli E. Bladder cancer biomarkers: review and update. Asian Pac J Cancer Prev 2014; 15: 2395-2403.
21) Michaud DS. Chronic inflammation and bladder cancer. Urol Oncol 2007; 25: 260-268.
22) Petrie HT, Klassen LW, Kay HD. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous blood granulocytes. J Immunol 1985; 134: 230-234.
23) Schaider H, Oka M, Bogenrieder T, Nesbit M, Satyamoorthy K, Berking C, Matsushima K, Herlyn M. Differential response of primary and metastatic melanomas to neutrophils attracted by IL-8. Int J Cancer 2003; 103: 335-343.
24) Gueron G, De Siervi A, Vazquez E. Advanced prostate cancer: reinforcing the strings between inflammation and the metastatic behavior. Prostate Cancer Prostatic Dis 2012; 15: 213-221.
25) 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: 468-472.

26) Mano R, Baniel J, Shoshany O, Margel D, Bar-On T, Nativ O, Rubinstein J, Halachmi S. Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non-muscle-invasive bladder cancer. Urol Oncol 2015; 33: 67.e1-7.

27) 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: 1046-1050.

28) Potretzke A, Hillman L, Wong K, Shi F, Brower R, Mai S, Cetnar JP, Abel EJ, Downs TM. NLR is predictive of upstaging at the time of radical cystectomy for patients with urothelial carcinoma of the bladder. Urol Oncol 2014; 32: 631-636.

29) Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, Thompson RH, Tollefson MK. 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: 1157-1164.

30) Hermanns T, Bhindi B, Wei Y, Yu J, Noon AP, Richard PO, Bhatt JR, Almatar A, Jewett MA, Fleshner NE, Zlotta AR, Templeton AJ, Kulkarni GS. Pretreatment neutrophil-to-lymphocyte ratio as predictor of adverse outcomes in patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Br J Cancer 2014; 111: 444-451.

31) Demirtas A, Sabur V, Akinsal EC, Demirci D, Ekmekcioglu O, Gulmez I, Tatliesen A. Can neutrophil-lymphocyte ratio and lymph node density be used as prognostic factors in patients undergoing radical cystectomy? ScientificWorldJournal 2013; 2013: 703579.

32) Wei Y, Jiang YZ, Qian WH. Prognostic role of NLR in urinary cancers: a meta-analysis. PloS One 2014; 9: e92079.