J Surg Med. 2019;3(4):324-327.
DOI: 10.28982/josam.557054

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Does neutrophil-lymphocyte ratio show recurrence in patients who underwent curative resection for non-muscle-invasive bladder cancer?

Nötrofil lenfosit oranı, küratif rezeksiyon ile tedavi edilen yüzeyel mesane kanserinde rekürrensi gösterir mi?

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Ethics Committee Approval: Approval for the study was granted by the Committees on Medical Ethics (PAU/Application admission no: 60116787-020/29221).
Etik Kurul Onayı: Çalışma onayı, Tıbbi Etik Kurulları tarafından verildi (PAU / Başvuru kabul no: 60116787-020/29221).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 4/28/2019
Yayın Tarihi: 28.04.2019

Abstract

Aim: The role of inflammation is a critical component of tumor progression and the neutrophil-lymphocyte ratio (NLR) reflects inflammatory status. We aimed to determine the clinical significance of the preoperative NLR in patients with non-muscle-invasive bladder cancer (NMIBC).

Methods: A total of 178 patients, who underwent curative transurethral resection of bladder tumor (TURBT) for NMIBC between 2011 and 2016 in the urology department of Pamukkale University and Uludağ University were included in the study. Data including clinical characteristics, surgery, pathology, and follow-up were obtained from a retrospectively maintained database. Patients were divided into groups according to pre-operative NLR values (h-NLR group: ≥2.5, l-NLR group: NLR <2.5). Their cut-off values were determined through receiver operation characteristics curves analysis. Recurrence rates of the patients were determined in the 1st year follow-up. For further analysis, all of the patients were allocated according to their risk ratio according to European Organization for Research and Treatment of Cancer (EORTC) tables as low, intermediate and high, and all of the groups have been evaluated according to the risk ratio.

Results: NLR patients (55.6% of the cases) were associated with worse risk of bladder cancer recurrence as compared to l-NLR group (P=0.005). Kaplan-Meier plots illustrated that higher pre-operative NLR had decreased disease-free survival (DFS). Low pre-operative PLR and NLR levels correlated with recurrence.

Conclusion: The present research shows that NLR is a prognostic indicator in NMIBC. Calculating NLR value might be useful at predicting recurrence in NMIBC patients.

Keywords: Bladder cancer, Recurrence, Neutrophil-lymphocyte ratio

Öz

Amaç: Enflamasyon, tümörün ilerlemesinin kritik bir bileşenidir ve nötrofil lenfosit oranı (NLR), enflamasyonun bir göstergesidir. Bu araştırmanın amacı; NLR'nin yüzeyel mesane kanserinde (NMIBC) prognostik bir gösterge olup olmadığını göstermekdir.

Yöntemler: Pamukkale ve Uludağ Üniversitesi Üroloji Anabilim Dalları'nda 2011-2016 yılları arasında yüzeyel mesane kanseri nedeni ile, sadece küratif amaçlı transüretral mesane rezeksiyonu uygulanan (TUR-M) toplam 178 hasta çalışmaya dahil edildi. Hastaların klinik ve patolojik verileri retrospektif olarak incelendi. Ameliyat öncesi nötrofil/lenfosit oranına (NLR) göre NLR ≥2.5 (h-NLR) ve <2.5 (l-NLR) olacak şekilde iki gruba ayrıldı. Ayrıca hastalar daha ileri analiz için, Avrupa Üroloji Derneği risk sınıflamasına göre düşük, orta ve yüksek riskli mesane tümörü olarak alt gruplara bölündü ve kendi içinde ayrıca değerlendirildi. 1. Yıl sonunda nüks oranları belirlendi ve rekürrens oranlarına göre istatiksel analiz uygulandı. NLR 2,5 cut-off değerine göre toplam hastalıksız geçen süre Kaplan Meier eğrisi kullanılarak analiz edildi.

Bulgular: Yapılan değerlendirmeler ile h-NLR hastaları (%55,6), l-NLR hastalarına göre istatiksel anlamlı olarak yüksek rekürrens oranlarına sahipti (P=0.005). Kaplan-Meier analizi sonucunda, h-NLR'nin hastalıksız geçen süreyi önemli ölçüde azalttığını ve rekürrensi arttırdığını göstermiştir.

Sonuç: NLR'nin, NMIBC hastalarında tümör rekürrensi değerlendirmesinde kullanılabilecek, faydalı bir biyobelirteç gibi görünmektedir.

Anahtar kelimeler: Mesane kanseri, Rekürrens, Nötrofil-lenfosit oranı

How to cite / Atıf için: Çelen S, Günseren KÖ, Özlülerden Y, Mete A, Tuncay ÖL, Yavaşcaoğlu İ. Does neutrophil-lymphocyte ratio show recurrence in patients who underwent curative resection for non-muscle-invasive bladder cancer? J Surg Med. 2019;3(4):324-327.

Introduction

Clinical features of bladder cancer are heterogeneous, and 70% of cases are non-muscle-invasive bladder cancer (NMIBC) at the time of the diagnosis [1,2]. Despite appropriate treatment, these tumors develop recurrence rates ranging from 30% to 80% within 5 years, and progress to muscle-invasive disease up to 45%. The risk classification of NMIBC and its association with recurrence are determined according to the European Organization for Research and Treatment of Cancer (EORTC) tables [3]. To calculate the risk of recurrence and progression, NMIBC are divided into three groups: low, intermediate and high-risk. Number of tumor, tumor size, T category, World Health Organization (WHO) grade, and the presence of concurrent carcinoma in situ (CIS) are used to determine cancer risk [4]. However, despite the accurate calculation of risk analyzes, recurrence and progression is still unpredictable. In this case, it is necessary to investigate new clinical, molecular, biological, and environmental factors in order to make the risk calculation the most accurate. Inflammation is a critical component of tumor progression. The systemic inflammatory response (SIR) is associated with outcome in a variety of malignancies [5]. For example, as a SIR marker, incorporating C-reactive protein (CRP) and serum albumin, correlates with outcome in patients undergoing cancer treatment [6,7]. Elevated pre-operative or pre-treatment neutrophil to lymphocyte ratio (NLR) detected in peripheral blood are simple SIR markers, which have been identified in various malignancies [8,9]. Recent papers studied on NLR and recurrence showed that preoperative NLR was associated with the risk for disease recurrence, cancer-specific mortality in patients with NMIBC [10]. The aim of this study was to examine whether NLR could be useful inflammatory biomarkers for the risk of recurrence and progression with NMIBC.

Materials and methods

Data source and selection criteria

The medical records of 439 consecutive initially diagnosed NMIBC patients who underwent transurethral resection were obtained. Exclusion criteria in patient selection: Patients with hematological disorders, active infection, immune deficiency, history of additional cancer, with incomplete resections, patients with missing data in our electronic medical record system and patients undergoing intravesical treatment with Bacille Calmette-Guerin (BCG). After exclusion criteria, 178 patients were included in the study and data obtained from 178 patients, who underwent transurethral resection of bladder tumor (TURBT) (curative only and not diagnostic) for NMIBC between 2011 and 2016 in the urology department of Pamukkale University and Uludağ University were evaluated retrospectively in the study after approval for the study was granted by the Committees on Medical Ethics (PAU/Application Admission no: 60116787-020/29221). Data including; clinical characteristics, surgery, pathology, and follow-up were obtained from a retrospectively maintained database. To determine the clinical T stage of a bladder tumor according to the 2002 Union International Contre le Cancer (UICC) TNM classification, all patients was histologically confirmed by TURBT. The pathology reports, including carcinoma in-situ (CIS), were recorded and the patients were grouped as low-, intermediate- and high-risk. In the first and second year, the patients were followed-up every three months and in the third year patients were followed-up every six months in our institution. The number of white blood cells was determined by a hemocytometer from the peripheral blood obtained at the time of surgery prior to surgery, and the serum NLR values were calculated. Univariate and multivariate Cox regressions were performed to assess the predictive capability for recurrence, versus and in conjunction to the pathologically based EORTC score, among additional statistical analyses. This regression resulted in only NLR 2.5 as a significant variable (P=0.005). The patients were divided into 2 groups according to NLR values (NLR ≥2.5 (h-NLR) and <2.5 (l-NLR) before surgery. Recurrence rates of the patients were evaluated at the 1st year follow-up. For further analysis, all patients were grouped into low, medium and high groups according to recurrence risk groups by the EORTC tables. The cut off value was determined as 2.5 and the groups were evaluated within themselves.

Statistical analysis

All statistical analyses were carried out using Stat View 5.0 for Windows (SAS Institute, Cary, NC, USA). NLR values were compared using the Mann-Whitney U-test. Fisher's exact probability test was used to determine the significance of differences between two groups. Survival probabilities were calculated using the product limit method of Kaplan and Meier, considering overall cancer free survey. The influence of each significant predictor identified by univariate analysis was assessed by multivariate analysis using Cox's proportional hazards model. The influence of each clinicopathological variable on the risk of high NLR was assessed by logistic regression analysis. All P values less than 0.05 were considered statistically significant.

Results

l-NLR group included 79 patients, and l-NLR group consisted of 99 patients. There were no statistically significant differences between two groups in terms of age, height and BMI. The mean neutrophil lymphocyte ratio was 1.89 in l-NLR group and 3.58 in h-NLR group. No statistically significant difference was found between the groups in terms of gender, ASA, mitomycin, smoking history, BCG, Carcinoma in-situ, Ta0-Ta1 and risk categories (Table 1).

41 of the patients who had recurrence in the first year were in the l-NLR group and 71 of them were in the h-NLR group with, and this difference was significant (P=0.005) (Table 2).

When compared to the NLR of patients with tumor recurrence status; 10 patients (62.5%) with non-recurrence in the low-risk group were predominant in the l-NLR group and there was no statistically significant difference (P=0.05). In the medium-risk group; 8 patients (57.1%) with non-recurrence had a majority in the l-NLR group and 8 patients (61.5%) in the h-NLR group had recurrence and this was not statistically significant (P=0.050). In the high-risk group; twenty-nine patients (59.2%) in the l-NLR group and 54 patients (77.1%) in the h-NLR group were predominant in the presence of relapse,

and there was statistically significant difference between these data (P=0.029). Regarding the NLR of all patients without any risk category difference, 41 patients (51.9%) with recurrence were found in l-NLR group, while this number was 71 (77.1%) in h-NLR group. This difference was significant (P=0.005).

Table 1: Demographic data of the patients

		Groups l-NLR NLR <2.5	h-NLR NLR ≥2.5	*P*-value
n (%)		79 (44.4)	99 (55.6)	
		Mean (SD)	Mean (SD)	
Age		70.06 (12.45)	69.77 (10.39)	0.87
Weight		77.83 (11.21)	76.71 (14.58)	0.55
BMI (Body mass index)		27.35 (4.17)	27.12 (5.9)	0.77
NLR (Neutrophil-lymphocyte ratio)		1.89 (0.45)	3.58 (1.92)	
		n (%)	n (%)	
Sex	Female	8 (38.1)	13 (61.9)	0.35
	Male	71 (45.2)	86 (54.8)	
ASA	1	14 (53.8)	12 (46.2)	0.52
	2	57 (43.5)	74 (56.5)	
	3	8 (38.1)	13 (61.9)	
Mitomisin	No	69 (46.3)	80 (53.7)	0.21
	Yes	10 (35.7)	18 (64.3)	
Smoking	yes	28 (41.2)	40 (58.8)	0.33
BCG	No	47 (45.6)	56 (54.4)	0.41
	Yes	32 (42.7)	43 (57.3)	
Carcinoma in-situ	No	76 (45.8)	90 (54.2)	0.14
	Yes	3 (25)	9 (75)	
Ta 0- T 1	No	55 (46.6)	63 (53.4)	0.25
	Yes	24 (40)	36 (60)	
Risk Category	Low risk	16 (50)	16 (50)	0.47
	Medium Risk	14 (51.9)	13 (48.1)	
	High Risk	49 (41.2)	70 (58.8)	

SD: Standard deviation

Table 2: Recurrence rates of patients according to NLR

		l-NLR group n (%)	h-NLR group n (%)	*P*-value
Status	No recurrence	38 (57.6)	28 (42.4)	0.005
	Recurrence	41 (36.6)	71 (63.4)	

Table 3: Risk category and NLR evaluation

Risk category	Recurrence	Groups l-NLR	h-NLR	*P*-value
		n (%)	n (%)	
Low risk	No	10 (62.5)	7 (43.8)	0.24
	Yes	6 (37.5)	9 (56.3)	
Medium risk	No	8 (57.1)	5 (38.5)	0.28
	Yes	6 (42.9)	8 (61.5)	
High risk	No	20 (40.8)	16 (22.9)	0.03
	Yes	29 (59.2)	54 (77.1)	
Total	No	38 (48.1)	28 (28.3)	0.005
	Yes	41 (51.9)	71 (71.7)	

We observed that the recurrence rate of l-NLR group was less than h-NLR in the follow-up period of 36 months (Figure 1).

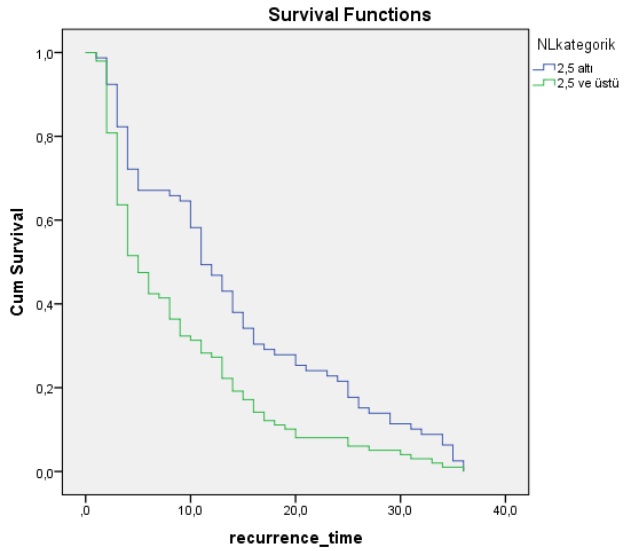

Figure 1: Kaplan-Meier survival curves, stratified by recurrence period neutrophil-lymphocyte ratio

Discussion

In order to predict recurrence and progression in NMIBC, EORTC tables were established; parameters such as tumor count, tumor size, previous recurrences, presence of T1 disease, presence of carcinoma in the site (CIS) and the degree of tumor were used. However, these evaluations are still lacking due to unpredictable factors. However, different biomarkers have been used to facilitate recurrence prediction in bladder cancer and to increase patient comfort by reducing the number of control cystoscopy. Urine cytology is a biomarker used for this purpose; ImmunoCyt (Diagnocure Inc., Quebec City, Canada) [11,12], the nuclear matrix protein-22 (Matritech, Newton, MA, USA) [13], fluorescence in situ hybridization (FISH) analysis (Urovysion Systems Vume Abbott Laboratories, Abbott Park IL, USA), urinary epidermal growth factor receptor and epithelial cell adhesion molecules were performed in many countries [14,15]. However, it is very important to use biomarkers in the methods to be used, to be cost effective and to use in practical use [16]. In addition, biomarkers should be able to be used at the same time in diagnosis and follow-up. The N/L ratio was a low prognostic indicator in colorectal cassettes, gastric carcinoma, renal cell cancers and ovarian cancer. [8,17,18]. In literature, it was reported that use of N/L ratio is effective in various conditions, e.g., cardiovascular problems [19,20]. In this study, our aim was to determine the predictive value of the preoperative N/L ratio for predictable tumor recurrences in NMIBC.

Systemic inflammation is known to increase in recurrence and progression in different types of cancer [2]. The prognostic value of leukocytosis and C-reactive protein (CRP) in cancer is poor [21]. The N/L ratio in the preoperative period is known to be used to predict recurrence in NMIBC [22,23]. Tachibana et al. [24] showed that bladder cancer cells produce granulocyte colony stimulating factor (G-CSF) receptors and this shows us that inflammation is important in the progression of bladder cancer. However, neutrophil vascular endothelial growth factor (VEGF) allows a proliferation of the tumor by secreting a proangiogenic factor [25]. The N/L ratio was determined as an independent prognostic factor in patients who underwent radical cystectomy (RC) between these inflammatory parameters [26]. In addition, the N/L ratio; it is an easy to detect biomarker that can be easily calculated by looking at cheap, peripheral blood. In this study, we evaluated whether the preoperative N/L ratio in 178 patients could predict recurrent disease based on the cut-off value of 2.5. In our study, we excluded all TURBT operations which were not completed (incomplete TURBT) in order to rule out all external factors.

Gondo et al. [26] reported that using the cut-off value of 2.5, and suggested that the N/L is an independent prognostic factor ratio for disease-related survival risk in bladder cancer patients treated with radical cystectomy. Krane et al. also reported the association of the high NLR value before the radical cystectomy has generally been associated with worse overall survival. Also they found that patients with a NLR >2.5 had a significantly higher likelihood of extravesical disease at radical cystectomy, suggesting that they may benefit from neoadjuvant chemotherapy [27]. In a recent study; Marchioni et al. [28] determined the cut-off value to be 2 and this value was

associated with upper urothelial cancer progression. Mano et al. [29] showed in their study, include 107 NMIBC patients, the value of NLR >2.41 is associated with disease progression; >2.43 was associated with disease recurrence. In our study, 2.5 cut-off value was associated with disease recurrence similarly to Mano's study. In addition, all risk groups were evaluated separately and the progression was statistically significant in the high risk group but not in other groups. Although the N/L ratios in the low and intermediate risk groups did not show statistical significance, they supported the numerical results of our study.

The most important aspect of this study is the separation of NMIBC patients according to the risk categorization and the high number of exclude criteria. In this way, the N/L ratio of all risk groups was evaluated based on the cut off value 2.5. In addition, the long-term follow-up of the patients in the Kaplan-Meier curve; when the cut-off value was 2.5, it was observed that the recurrence rate was significantly less in patients with N/L ratio <2.5 in 36 months follow-up. Cho et al. [18] patients with a high N/L ratio indicated relative lymphocytopenia. And as a result of this, it can cause an immune response and this allows potential tumor progression and worsens the prognosis.

This study has some limitations. The number of patients included in the study was low due to the design of the study retrospectively, and eligibility criteria for inclusion were comprehensive. In addition, because the follow-up times were relatively short and operator-dependent TURBT and pathologist-dependent pathological evaluations were affected by the results.

Conclusion

The present research shows that NLR is a prognostic indicator in NMIBC. It is found that the N/L ratio may be used as a predictor of recurrence patients with NMIBC, because it's easily accessible. However, randomized-controlled studies and prospective studies with a higher number of patients are needed for validation.

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The National Library of Medicine (NLM) citation style guide is used in this paper.
Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine