ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Predictive Value of Neutrophil-to-Lymphocyte Ratio before Transurethral Resection for Muscle Invasion in Bladder Cancer

Mesane Kanserinde Kas Invazyonunu Öngörmede Transüretral Rezeksiyon Öncesi Nötrofil-Lenfosit Oranının Prediktif Değeri

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ABSTRACT

Aim: *To evaluate the predictive value of the neutrophil-to-lymphocyte ratio (NLR) before transurethral resection in determining muscle invasion in patients diagnosed with bladder cancer.*

Materials and Methods: *This retrospective study included patients who underwent first-time transurethral resection of bladder tumors (TUR-B) for primary bladder cancer between January 2016 and December 2024. Patients with carcinoma in situ, preoperative infection, hematologic malignancies, or unexplained leukocytosis were excluded. Patients were divided into two groups based on pathological staging: Group 1 (pTa/pT1) and Group 2 (pT2). Demographic, clinical, and laboratory parameters, including leukocyte, neutrophil, and lymphocyte counts, were recorded. The optimal NLR cutoff for predicting muscle invasion was determined using ROC analysis. Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program software with a significance threshold of p <0.05.*

Results: *A total of 731 patients were included. Muscle invasion (pT2) was identified in 129 patients (17.6%). Group 2 had significantly higher age, proportion of female patients, high-grade tumors, and tumors larger than 3 cm. Lymphocyte counts were significantly lower in Group 2, while leukocyte, neutrophil counts, and NLR were significantly higher (p<0.001 for all). The optimal cutoff value of NLR was 2.96 (sensitivity: 42.6%, specificity: 89.5%, AUC: 0.701). Logistic regression revealed that female sex, high tumor grade, tumor size, and elevated NLR were independently associated with muscle invasion.*

Conclusion: *Preoperative neutrophil-to-lymphocyte ratio (NLR) is significantly associated with muscle-invasive bladder cancer. As a simple and accessible inflammatory marker, NLR may support preoperative staging and inform clinical decision-making in bladder cancer management.*

Key words: *bladder cancer; lymphocyte; muscle invasion; neutrophil*

ÖZET

Amaç: *Transüretral rezeksiyon (TUR) öncesi mesane kanseri tanısı almış hastalarda nötrofil/lenfosit oranının (NLR) kas invazyonunu öngörmedeki değerini değerlendirmektir.*

Gereç ve Yöntem: *Bu retrospektif çalışmada, Ocak 2016 ile Aralık 2024 tarihleri arasında primer mesane tümörü nedeniyle ilk kez TUR-B uygulanan hastalar incelendi. Karsinoma in situ tanısı, preoperatif enfeksiyon, hematolojik malignite öyküsü veya açıklanamayan lökositozu olan hastalar çalışma dışı bırakıldı. Hastalar patolojik evrelemeye göre Grup 1 (pTa/pT1) ve Grup 2 (pT2) olmak üzere iki gruba ayrıldı. Demografik, klinik ve laboratuvar verileri (lökosit, nötrofil ve lenfosit sayıları dâhil) kaydedildi. Kas invazyonunu öngörmede en uygun NLR eşik değeri ROC analizi ile belirlendi. İstatistiksel analizler IBM Sosyal Bilimlerde İstatistik Paket Program (SPSS) yazılımı ile yapıldı ve p <0,05 anlamlı kabul edildi.*

Bulgular: *Çalışmaya toplam 731 hasta dâhil edildi. Kas invazyonu (pT2) 129 hastada (%17,6) tespit edildi. Grup 2'de yaş, kadın hasta oranı, yüksek dereceli tümör ve 3 cm'den büyük tümör oranı anlamlı olarak yüksekti. Grup 2'de lenfosit sayısı anlamlı olarak daha düşük; lökosit, nötrofil sayıları ve NLR ise anlamlı olarak daha yüksekti (tüm karşılaştırmalarda p<0,001). Nötrofil/lenfosit oranı için en uygun eşik değeri 2,96 olarak saptandı (duyarlılık: %42,6; özgüllük: %89,5; AUC: 0,701). Lojistik regresyon analizinde kadın cinsiyet, yaş, tümör boyutu ve yüksek NLR değerleri, kas invazyonu ile bağımsız olarak ilişkili bulundu.*

Sonuç: *Preoperatif NLR değeri, kas invaziv mesane kanseri ile anlamlı şekilde ilişkilidir. Basit ve erişilebilir bir enflamasyon belirteci olan NLR, preoperatif evreleme sürecinde yardımcı olabilir ve klinik karar verme aşamasında yol gösterici bir biyobelirteç olarak kullanılabilir.*

Anahtar kelimeler: *kas invazyonu; lenfosit; mesane kanseri; nötrofil*

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Introduction

Bladder cancer (BC) is a major urologic malignancy, representing the most common cancer of the urinary system and the tenth most prevalent cancer overall worldwide (1). It exhibits a notable sex-related difference in incidence, with men being more frequently affected. At the time of diagnosis, around 20–25% of patients are found to have muscle-invasive disease (2). The therapeutic approach to muscle-invasive bladder cancer (MIBC) contrasts considerably with that for non–muscle-invasive bladder cancer (NMIBC), typically requiring comprehensive management strategies, including radical cystectomy, chemotherapy, and radiotherapy (3).

Therefore, accurate diagnosis of muscle invasion is critical and currently relies on findings from transurethral resection specimens. However, staging errors can still occur, and data obtained from radical cystectomy specimens have shown that many patients are understaged before surgery (4). In light of this, various studies have explored the predictive value of biochemical and genetic markers for muscle invasion. The neutrophil-to-lymphocyte ratio (NLR) has been identified as a potential marker of cancer progression and patient prognosis across various malignancies, including BC (5,6). Despite this, research directly examining the link between NLR and the presence of MIBC remains scarce and often relies on limited sample sizes. In this study, we aim to evaluate the diagnostic performance of NLR in identifying muscle-invasive disease among BC patients.

Material and Methods

Following approval by our institutional review board, we retrospectively examined cases of patients who had their initial transurethral resection of the bladder (TUR-B) for primary BC at our hospital between January 2016 and December 2024. Patients diagnosed with carcinoma in situ, those with signs of preoperative infection, individuals with a prior history of hematologic malignancy, or unexplained leukocytosis were excluded from the analysis. No patient was on antiplatelet or anti-inflammatory medications before the procedure. Based on pathological staging, participants were classified into two groups: Group 1 encompassed patients with NMIBC (pTa/pT1), while Group 2 comprised those with MIBC (pT2). Data collected included demographic and clinical characteristics such as sex, age, tumor grade, tumor size, number of tumors, and preoperative blood counts, including leukocytes, neutrophils, and lymphocytes.

The Kolmogorov-Smirnov test was used to assess whether continuous variables were normally distributed. These variables were summarized using medians and interquartile ranges (IQR), while categorical variables were presented as absolute numbers and percentages. Comparisons of continuous variables between groups were performed using the Mann-Whitney U test, whereas categorical variables were analyzed via the chi-square test. The discriminative ability of relevant parameters in detecting muscle invasion was evaluated using receiver operating characteristic (ROC) curve analysis. Univariate logistic regression was initially conducted to identify factors associated with muscle-invasive disease. Variables that reached statistical significance ($p < 0.05$) in univariate testing were then incorporated into a forward stepwise multivariate logistic regression model to determine independent predictors. All statistical analyses were carried out using IBM Statistical Package for Social Sciences (SPSS) program version 21.0 for Windows (IBM Corp., Armonk, NY, USA). A p-value below 0.05 was accepted as statistically significant.

Results

The study comprised 731 patients, with a median age of 67 years (IQR: 60–75), and a predominance of males (85.2%). According to pathological staging, 602 individuals were classified as having non-muscle-invasive disease (pTa/pT1, Group 1), while 129 were diagnosed with MIBC (pT2, Group 2). Group 2 had a higher median age and a greater proportion of female patients compared to Group 1 (Table 1). The prevalence of high-grade tumors (100% vs. 41.4%; $p < 0.001$) and tumors exceeding 3 cm in size (87.6% vs. 52%; $p < 0.001$) was significantly higher in Group 2. In contrast, tumor multiplicity did not differ significantly between the two groups. In preoperative blood parameters, lymphocyte count was significantly lower in Group 2 (2.00 vs. 2.17; $p<0.001$), while leukocyte and neutrophil counts were significantly higher (7.90 vs. 7.26; $p<0.001$ and 4.96 vs. 4.18; $p<0.001$, respectively). The NLR was also significantly higher in Group 2 (2.51 vs. 1.89; $p<0.001$). According to ROC analysis, the optimal cutoff value for NLR was determined to be 2.96, with a sensitivity of 42.6% and a specificity of 89.5% (area under the curve [AUC]: 0.701, 95% CI: 0.649–0.753) (Fig. 1). To identify factors correlated

Table 1. *Comparison of demographic, pathological and inflammatory data of the groups*

		Group 1 (pTa-pT1) (n=602)	Group 2 (pT2) (n=129)	P
Age (year), median (IQR)		66 (59–74)	73 (64–78)	**<0.001***
Gender (n)(%)	Male	521 (86.5)	102 (79.1)	**0.030****
	Female	81 (13.5)	27 (20.9)	
Pathological grade (n)(%)	PUNLMP	64 (10.6)	0 (0)	**<0.001****
	Low grade	289 (48.0)	0 (0)	
	High grade	249 (41.4)	129 (100)	
Tumor size (n)(%)	<3 cm	289 (48)	16 (12.4)	**<0.001****
	≥3 cm	313 (52)	113 (87.6)	
Tumor number (n)(%)	Single	346 (57.5)	66 (51.2)	0.190**
	Multipl	256 (42.5)	63 (48.8)	
Leucocyte count (10^3/uL), median (IQR)		7.26 (6.00–8.50)	7.90 (6.95–9.00)	**<0.001***
Neutrophil count (10^3/uL), median (IQR)		4.18 (3.40–4.99)	4.96 (4.10–6.11)	**<0.001***
Lymphocyte count (10^3/uL), median (IQR)		2.17 (1.73–2.65)	2.00 (1.46–2.43)	**<0.001***
NLR (median – IQR)		1.89 (1.49–2.47)	2.51 (1.86–3.67)	**<0.001***

IQR: inter quartile range; NLR: neutrophil/lymphocyte ratio; PUNLMP: papillary urothelial neoplasm of low malignant potential (PUNLMP); *: Mann-Whitney U test; **: Ki-square test.

Tablo 2. *Associations with the presence of muscle invasion in bladder cancer*

	Univariate analysis			Multivariate analysis		
Covariates	p	OR	95% CI	p	OR	95% CI
Age	<0.001	1.045	1.026–1.064	0.004	1.030	1.009–1.051
Female gender	0.031	1.703	1.049–2.764	0.023	1.890	1.092–3.274
Tumor size (>3 cm)	<0.001	6.521	3.772–11.273	<0.001	5.183	2.940–9.135
NLR (>2.96)	<0.001	6.359	4.113–9.831	<0.001	5.019	3.145–8.010

CI: Confidence interval; NLR: Neutrophil-lymphocyte ratio; OR: Odds ratio; covariates with p<0.05 in univariate analysis were entered in a multivariate logistic analysis model; method stepwise forward (LR).

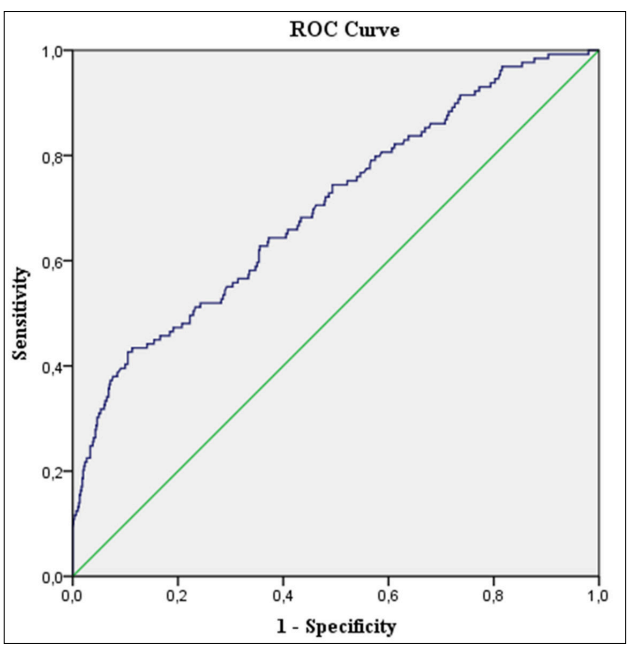

Figure 1. *Receiver operating characteristic (ROC) analysis of NLR for the presence of muscle invasion in bladder cancer.*

with muscle invasion in BC, logistic regression analysis was conducted. Female sex, age, tumor size and elevated NLR were found to be significantly associated with pT2 tumors (Table 2).

Discussion

While leukocytes have been known to exist in tumor tissues since the 19th century, only in the past decade has strong evidence emerged showing that Inflammation is fundamentally involved in both the initiation and progression of human cancers (7). Neutrophil-to-lymphocyte ratio is an easily obtainable marker from routine blood tests that indicates the body's systemic inflammatory state, based on disease-induced changes in key inflammatory cell populations. Recently, it has been suggested as a potential predictor for the development, progression, and outcome of various chronic inflammatory conditions and cancers (8). The accumulation of defective myeloid cells is associated with

increased neutrophil and decreased lymphocyte counts in the bloodstream, and the NLR holds predictive and prognostic significance across various tumor types (9).

In the present study, we demonstrated that the NLR was significantly higher in patients with T2 BC than in the NMIBC group. This is likely indicative of a heightened systemic inflammation in individuals afflicted with muscle-invasive disease, and therefore, a more advanced stage of BC. Numerous prior studies have established a positive association between higher NLR levels and more advanced tumor stages across urinary and other malignancies (10,11).

Management and surveillance strategies for patients with T2 BC differ significantly from those employed for individuals with NMIBC. The established standard of care for MIBC comprises radical cystectomy with pelvic lymph node dissection, administered with or without neoadjuvant chemotherapy. Current data indicate an overall five-year survival rate of approximately 60% (12).

The NLR, when assessed preoperatively in individuals with BC, may be a useful biomarker for assessing tumor invasiveness and disease progression, thereby aiding risk stratification and informing clinical decision-making related to patient management. Neutrophils are known to facilitate tumor progression via diverse mechanisms, notably by secreting cytokines (e.g., IL-6, IL-8), chemokines, matrix metalloproteinases, and reactive oxygen species, thereby promoting tumor invasion, angiogenesis, and metastasis. Conversely, lymphocytes are crucial mediators of anti-tumor immunity, particularly through cytotoxic T-cell activity. Therefore, an elevated NLR reflects both an enhanced pro-tumoral inflammatory state and an impaired immune response, potentially favoring tumor proliferation and invasion (13,14).

In the literature, high-grade urothelial neoplasms have been associated with increased neutrophil infiltration, as MIBC cases demonstrate significantly higher neutrophil counts and lower lymphocyte counts than NMIBC (15). In our study, similar results were found, in line with the literature: leukocytes and neutrophils were higher, and lymphocytes were lower, in the muscle-invasive group than in the non-muscle-invasive group.

The ROC analysis in our study yielded an AUC of 0.701, suggesting moderate discriminatory power. While the sensitivity was limited (42.6%), the high specificity (89.5%) indicates that an NLR above the determined cut-off may strongly suggest muscle invasion. In clinical practice, such a biomarker could be particularly valuable when combined with radiologic and cystoscopic findings to improve preoperative staging accuracy and assist in identifying candidates for early radical treatment.

This study has several limitations. As a retrospective analysis, it lacks sufficient follow-up data on patients after the initial surgery, which prevented us from evaluating the association between NLR and disease recurrence, progression, or overall survival. Additionally, NLR values were based on a single preoperative measurement per patient; averaging two or three preoperative measurements would likely have yielded more reliable and representative data. Future prospective studies incorporating serial NLR measurements, inflammatory cytokine profiles, and immune cell phenotyping are warranted to validate and further elucidate the prognostic role of systemic inflammation in BC. It is well established in the urologic pathology literature that interobserver variability can lead to discrepancies in the grading and staging of bladder tumors, particularly in challenging cases like high-grade pT1 lesions. Another limitation is that a single pathologist performed histopathological analyses in the present study.

Conclusion

This study underscored the role of inflammatory cells in the tumor microenvironment of urothelial carcinoma of the bladder. Neutrophil-to-lymphocyte ratio levels were associated with muscle invasion in patients with BC, suggesting their potential utility in guiding treatment decisions and identifying patients who may benefit from more aggressive therapeutic approaches.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492
2. Cumberbatch M, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, et al. Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018. Eur Urol. 2018;74(6):784–795. https://doi.org/10.1016/j.eururo.2018.09.001
3. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of nonmetastatic muscle-invasive bladder cancer: American Urological Association/American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Urologic Oncology clinical practice guideline summary. J Oncol Pract. 2017;13:621–625. https://doi.org/10.1200/JOP.2017.024919
4. Ark JT, Keegan KA, Barocas DA, Morgan TM, Resnick MJ, You C, et al. Incidence and predictors of understaging in patients with clinical T1 urothelial carcinoma undergoing radical cystectomy. BJU Int. 2014;113:894–899. https://doi.org/10.1111/bju.12245
5. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218–230. https://doi.org/10.1016/j.critrevonc.2013.03.010
6. 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(1):1–10. https://doi.org/10.1186/s12894-018-0404-x
7. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–899. https://doi.org/10.1016/j.cell.2010.01.025
8. Madonia M, Paliogiannis P, Solinas T, Mangoni AA, Carru C, Zinellu A. Neutrophil to lymphocyte ratio and muscular invasion in early-stage bladder cancer: a meta-analysis. Eur J Oncol. 2018;23:65–71.
9. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218–230. https://doi.org/10.1016/j.critrevonc.2013.03.010
10. Li X, Ma X, Tang L, Wang B, Chen L, Zhang F, et al. Prognostic value of neutrophil to-lymphocyte ratio in urothelial carcinoma of the upper urinary tract and bladder: a systematic review and meta analysis. Oncotarget. 2016;8:62681–62692. https://doi.org/10.18632/oncotarget.17467
11. Margetts J, Ogle LF, Chan SL, Chan AW, Chan KC, Jamieson D, et al. Neutrophils: driving progression and poor prognosis in hepatocellular carcinoma? Br J Cancer. 2018;118:248–257. https://doi.org/10.1038/bjc.2017.386
12. Mitra AP, Cai J, Miranda G, Bhanvadia S, Quinn DI, Schuckman AK, et al. Management trends and outcomes of patients undergoing radical cystectomy for urothelial carcinoma of the bladder: evolution of the University of Southern California Experience over 3,347 Cases. J Urol. 2022;207:302–313. https://doi.org/10.1097/JU.0000000000002242
13. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):124–135. https://doi.org/10.1093/jnci/dju124
14. Yi M, Li T, Niu M, Mei Q, Zhao B, Chu Q, et al. Exploiting innate immunity for cancer immunotherapy. Mol Cancer. 2023;22:187–242. https://doi.org/10.1186/s12943-023-01885-w
15. Hassan WA, ElBanna AK, Noufal N, El-Assmy M, Lotfy H, Ali RI. Significance of tumor-associated neutrophils, lymphocytes, and neutrophil-to-lymphocyte ratio in non-invasive and invasive bladder urothelial carcinoma. J Pathol Transl Med. 2023;57(2):88–94. https://doi.org/10.4132/jptm.2022.11.06