

Can the Preoperative Neutrophil-to-Lymphocyte Ratio Significantly Predict the Conditional Survival Probability in Muscle-invasive Bladder Cancer Patients Undergoing Radical Cystectomy?

Minyong Kang, Ulanbek J. Balpukov, Chang Wook Jeong, Cheol Kwak, Hyeon Hoe Kim, Ja Hyeon Ku

Abstract

Although the preoperative neutrophil-to-lymphocyte ratio (NLR) was identified as a significant predictive factor for the 5-year conditional survival at baseline and postoperative 1-year estimation, its significance was lost after 2 years postoperatively. Therefore, we suggest that the dynamic aspect of the preoperative NLR should be considered when assessing the prognosis of bladder cancer patients treated with radical cystectomy over time after the initial estimates, in particular, for patients who have already survived for additional years after surgery.

Introduction: The present study investigated the prognostic value of the preoperative neutrophil-to-lymphocyte ratio (NLR) in bladder cancer patients undergoing radical cystectomy (RC), with a focus on the conditional survival (CS) estimates over time after surgery. **Materials and Methods:** We analyzed 385 bladder cancer patients who underwent RC from 1999 to 2012. The patients were classified into 2 groups according to the preoperative NLR (< 2.5 vs. ≥ 2.5). The Kaplan-Meier survival analysis was used to calculate the conditional probabilities of cancer-specific survival and overall survival after surgery. Multivariate Cox regression models were used to identify the predictors of 5-year conditional cancer-specific survival and overall survival. **Results:** Patients with an elevated preoperative NLR (≥ 2.5) had a greater proportion of advanced-stage tumors ($\geq pT3$), high-grade tumors, and lymphovascular invasion. Patients with an elevated preoperative NLR (≥ 2.5) had poor CS estimates compared with those with a lower NLR (< 2.5) at baseline and 1 year after RC. However, no significant differences in CS probabilities were observed from 2 years after RC onward. In a multivariate Cox regression analysis, the preoperative NLR was identified as a significant predictive factor for 5-year CS at baseline and postoperative 1-year estimation; however, its significance was lost after 2 years postoperatively. **Conclusion:** Our study results suggest that the dynamic aspect of the NLR should be considered when assessing the prognosis of bladder cancer patients treated with RC over time after the initial estimates, in particular, in patients who have already survived for additional years after surgery.

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Introduction

Urothelial carcinoma of the urinary bladder has an aggressive behavior, with high rates of recurrence and progression to invasive cancer.^{1,2} Although patients with muscle-invasive bladder cancer

(MIBC) undergo radical cystectomy (RC) with pelvic lymph node dissection (PLND), many patients require adjuvant therapies to improve the oncologic outcomes.^{2,3} To determine the optimal therapeutic strategies, accurate preoperative risk stratification is important. Among several potential biomarkers, systemic inflammatory response (SIR) markers, such as the neutrophil-to-lymphocyte ratio (NLR), have received great attention in patients with various malignancies, such as lung, breast, gastric, and colorectal cancer.⁴⁻⁷ In bladder cancer, an elevated preoperative NLR was significantly associated with adverse pathologic outcomes and poor survival rates after surgical treatment.⁸⁻¹⁰ Accordingly, the preoperative serum NLR

Department of Urology, Seoul National University Hospital, Seoul, Republic of Korea

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Address for correspondence: Ja Hyeon Ku, MD, PhD, Department of Urology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea

E-mail contact: randyku@hanmail.net

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can be used for patient risk stratification to determine the use of neoadjuvant chemotherapy and enrollment in clinical trials.^{11,12}

However, the NLR can fluctuate according to the general condition of the patient or the time point for blood sampling; thus, its prognostic value could change over time after the initial estimation. Moreover, recent studies have revealed that the prognosis of bladder cancer patients changes over time after RC, indicating the importance of conditional survival (CS) estimates.^{13,14} In this context, we hypothesized that the preoperative NLR measured at a single time point cannot accurately predict CS over time after surgery.

In the present study, we sought to elucidate the prognostic significance of the preoperative NLR in bladder cancer patients undergoing RC with PLND, with a particular focus on the CS estimates over time after surgery.

Materials and Methods

Study Population

The institutional review board at our hospital approved the present study (approval no. 1604-047-753). The medical records of 432 bladder cancer patients who had undergone RC and PLND from 1999 to 2012 were retrospectively reviewed from the electronic database of the Seoul National University Hospital. We acknowledge that the present study population overlapped with patients included in a previous report by Moon et al.¹⁵ We excluded patients if the pathologic diagnosis was nonurothelial cell carcinoma and preoperative distant metastasis. These patients received neoadjuvant systemic chemotherapy, and had incomplete medical records, such as no data recorded of the complete blood cell count. We also excluded the patients with definitive evidence of systemic inflammation at peripheral blood sampling. The Consolidated Standards of Reporting Trials diagram illustrating the inclusion and exclusion criteria for the present study is shown in [Supplemental Figure 1](#) (available in the online version).

Study Design

We checked the baseline complete blood cell count with differential within the 3 to 4 weeks before surgery and calculated the NLR using the following formula: NLR equaled the absolute neutrophil count divided by the absolute lymphocyte count.¹⁶ To choose the optimal cutoff value for the pretreatment NLR, receiver operating characteristic curve analysis was used. We determined the cutoff value for NLR to maximize the specificity and/or sensitivity in predicting the oncologic outcomes. The patients were finally classified into 2 groups according to the preoperative NLR (< 2.5 vs. ≥ 2.5).

RC with bilateral PLND was performed in patients with MIBC, as described in a previous report.¹⁷ After the surgical tissue samples were processed and placed on glass slides, 2 pathologists with experience in the genitourinary system reviewed the slides and determined the pathologic TMN stage and tumor grade according to the 2010 American Joint Committee on Cancer staging system and the 2004 World Health Organization/International Society of Urological Pathology consensus classification, respectively. To assess the oncologic outcomes, the patients routinely attended outpatient clinics every 3 months for the first 2 years after surgery. After this initial period, the patients were examined every 6 months for 3 to 4 years postoperatively and annually thereafter.

Table 1 Comparison of Clinicopathologic Features Stratified by Preoperative NLR

Variable	Preoperative NLR		P Value
	NLR <2.5	NLR ≥2.5	
Patients (n)	237 (61.6)	148 (38.4)	
Age at surgery (y)	65 (59-70)	67 (59-73)	.059
Gender			.878
Male	204 (86.1)	129 (87.2)	
Female	33 (13.9)	19 (12.8)	
BMI (kg/m ²)	23.60 (21.40-25.30)	22.60 (20.90-24.75)	.027
SIR markers			
Neutrophil count	3039 (2401-3773)	5056 (3977-6947)	<.001
Lymphocyte count	1927 (1626-2250)	1363 (1097-1773)	<.001
NLR	1.69 (1.30-1.98)	3.35 (2.82-4.23)	<.001
Pathologic T stage			<.001
≤pT2	168 (70.9)	78 (52.7)	
≥pT3	69 (29.1)	70 (47.3)	
Tumor grade			.020
Low grade	51 (21.6)	18 (12.2)	
High grade	185 (78.4)	130 (87.8)	
Lymphovascular invasion			.040
Absent	170 (71.7)	89 (60.1)	
Present	67 (28.3)	59 (39.9)	
Carcinoma in situ			.309
Absent	159 (67.1)	107 (72.3)	
Present	78 (32.9)	41 (27.7)	
Resection margin			.269
Negative	234 (98.7)	143 (96.6)	
Positive	3 (1.3)	5 (3.4)	
Pathologic N stage			.130
pN0	191 (80.6)	107 (72.3)	
pN1-N3	46 (19.4)	41 (27.7)	
LN's removed			.069
≤19	156 (66.1)	111 (75.0)	
≥20	80 (33.9)	37 (25.0)	
Adjuvant chemotherapy			.091
Yes	185 (78.1)	104 (70.3)	
No	52 (21.9)	44 (29.7)	

Data presented as n (%) or median (interquartile range).

Abbreviations: BMI = body mass index; LN's = lymph nodes; NLR = neutrophil-to-lymphocyte ratio; SIR = systemic inflammatory response.

Cancer-specific survival (CSS) and overall survival (OS) after RC with PLND were the primary endpoints in the present study. We assessed the conditional CSS and OS probabilities after RC using the concept proposed by Henson and Ries.¹⁸ CS (a|b) is defined as the probability of more “a” years of survivorship in those who have previously survived for “b” years after the baseline estimation such as the initial diagnosis or treatment. “S (a)” denotes the proportion of actual survivors after the baseline

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