

# Neutrophil-to-lymphocyte ratio as a predictor of overall survival and cancer advancement in patients undergoing radical cystectomy for bladder cancer

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**Introduction** Neutrophil-to-lymphocyte ratio (NLR) has proven to be promising as a prognostic factor in many malignancies. We investigated the prognostic significance of NLR in patients undergoing radical cystectomy (RC) for bladder cancer (BC).

**Material and methods** We retrospectively evaluated the data of 134 consecutive patients with BC who underwent RC between 2011 and 2017 at a single center. Overall survival (OS) was assessed using the Kaplan-Meier method and compared between NLR subpopulations using the log-rank test. Univariate and multivariate Cox proportional hazard models were used to identify the variables affecting OS.

**Results** At a median follow-up of 2.2 years, high NLR (>2.7) correlated with worse a survival outcome ( $p = 0.0345$  in log-rank test), higher tumor stage ( $p = 0.0047$ ), and higher frequency of positive lymph nodes ( $p = 0.0285$ ). The univariate model showed that a high NLR ( $p = 0.038528$ ), advanced pathological tumor stage ( $p = 0.000763$ ), lymph node involvement ( $p = 0.013384$ ), a high grade of cancer ( $p = 0.015611$ ), lymphovascular invasion (LVI) ( $p = 0.001530$ ), positive margins ( $p = 0.000890$ ) and ureterocutaneostomy as urinary diversion ( $p = 0.038854$ ) had a negative impact on OS. Tumor extending beyond the submucosa (>pT1) (hazard ratio 2.161, confidence interval 1058–4411,  $p = 0.0345$ ) and lymphatic infiltration (hazard ratio 1.599, confidence interval 1028–2482,  $p = 0.037$ ) have been recognized as independent risk factors of poor prognosis in multivariate Cox regression analysis.

**Conclusions** In our cohort, an elevated NLR is associated with worse OS and adverse histopathological findings. Consequently, the NLR is an easily acquired biomarker, which may be useful in pretreatment patient risk stratification.

**Key Words:** bladder cancer <> inflammation <> neutrophil-lymphocyte ratio

## INTRODUCTION

Bladder cancer (BC) is the ninth most commonly diagnosed cancer and the 13<sup>th</sup> leading cause of cancer death. The incidence of BC is higher in developed regions such as North America, Europe, and parts of Western Asia, and has remained stable since the 1990s with slight fluctuations [1, 2, 3]. However, the mortality rate has shown a downward trend in recent years [1].

It is estimated that 75% of patients with BC will not progress to muscle invasive bladder cancer (MIBC), while the remaining 25% will develop MIBC [4, 5]. Radical cystectomy (RC) with pelvic lymph node dissection preceded by cisplatin-based neoadjuvant chemotherapy is the current gold-standard treatment for MIBC [6]. The survival rate of patients with BC has not significantly changed in the last 30 years, and in the case of locally advanced disease (T2–T4), the survival rate is nearly 50% [6, 7].

A number of prognostic factors have been identified for BC. Clinical and tissue parameters have been associated with the risk of recurrence, progression, and shorter survival time [8, 9]. However, prognostic techniques for precise risk stratification and biomarkers that more accurately predict the clinical outcomes of MIBC treatment are still needed. According to recent research, inflammation is one of the most important factors in tumor development and inflammatory cells are key participants in the neoplastic process, promoting proliferation, survival, and migration in the tumor environment [10, 11, 12].

Inflammatory markers, such as elevated C-reactive protein level, white blood cell number, platelet count, and neutrophil-to-lymphocyte ratio (NLR), have shown promise in the prognosis of different medical conditions, including cardiovascular diseases and various types of malignancies such as pancreatic cancer, epithelial ovarian cancer, gastric cancer, colorectal cancer, and BC [13, 14]. Elevated NLR may indicate poor antitumor immune response, more advanced condition, and worse prognosis [15]. Further, the prognostic value of NLR is still being utilized in diagnosing a wide range of neoplastic diseases at different stages. NLR has also been identified as a potential prognostic factor in patients with MIBC undergoing RC [16, 17]. Reports have revealed that NLR can be associated with overall survival (OS), tumor progression, and recurrence after treatment [8, 16, 17, 18]. Therefore, the aim of our study was to evaluate the prognostic significance of preoperative NLR in patients undergoing RC for BC.

## MATERIAL AND METHODS

The study protocol was approved by the institutional bioethics committee. The data of urothelial carcinoma patients undergoing RC were collected from the Department of Urology. Our retrospective cohort study included 136 patients who underwent treatment between 2011 and 2017. Patients who received neoadjuvant chemotherapy (NAC) ( $n = 2$ ) were excluded from the study.

The following clinicopathological data were obtained from the medical records: age, sex, preoperative neutrophil and lymphocyte levels, type of urinary diversion, length of hospital stay after surgery, blood transfusion, need for reoperation, need for postoperative parenteral nutrition, pathological tumor and lymph node stages, histology, total lymph nodes removed, lymphovascular invasion (LVI), and surgical margin status. The preoperative blood counts were performed 1–8 days before surgery.

Due to the retrospective nature of the study, data on the time of death from any cause were obtained

from the state institution's registry. The registry provides data on whether or not a person is alive as well as the date of death.

The OS was the endpoint of the study and was calculated from the date of surgery to the date of registry verification. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Based on the optimal sensitivity and specificity of NLR for selected patient outcomes, a cutoff value of 2.7 was determined using a receiver operating characteristic (ROC) curve.

The clinicopathological data included in the study were categorized into continuous or categorical data and analyzed in the context of low- or high-NLR subgroups. Chi-square, Fisher's exact, and Mann-Whitney U tests were used according to the variable type. The Kaplan-Meier method was used to estimate OS, and the log-rank test was used

to compare the OS between low- and high-NLR subpopulations. Univariate and multivariate Cox proportional hazard models were used to identify the variables affecting OS. All statistical analyses were performed using STATA software version 13.  $p < 0.05$  was considered to be statistically significant. All  $p$  values were two-sided.

This research was approved by the Ethics Committee of the affiliated hospital of Lublin Medical University (Trial registration number: KE-0254/178/2020). All methods were performed in accordance with relevant guidelines and regulations.

## RESULTS

The study group consisted of 134 people with high-risk noninvasive or infiltrating BC, including 115 men and 19 women. The median age of all of the patients was 66 years, and the median neutrophil and lymphocyte levels were  $5.12 \times 10^9/l$  and  $1.73 \times 10^9/l$ , respectively. The patients' stay in the hospital after cystectomy lasted from 2 to 59 days, with a median of 9 days. Sixty patients required blood transfusions (44.8%), and 12 (9%) were reoperated during the hospital stay. Parenteral nutrition was used in 16 (12%) patients. Ureterocutaneostomy and Bicker's ileal conduit were used as urinary diversion in 57 (42.5%) and 77 (57.5%) of cases, respectively. There was a clear distinction between the low- and high-NLR groups, with ureterocutaneostomy being more frequently performed in the high-NLR subpopulation ( $p = 0.0157$ ).

Further stratification of clinicopathological factors based on NLR levels (high versus low) revealed that the high-NLR group was characterized by unfavorable features in terms of tumor stage or lymph node involvement. According to postoperative pathology

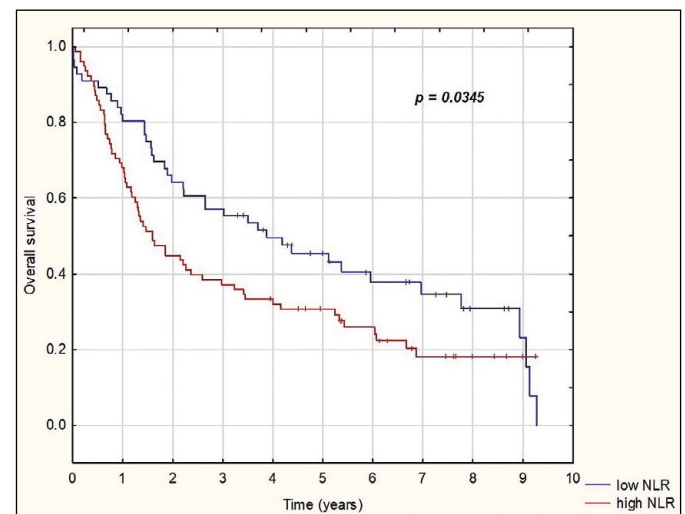
reports, patients with an NLR >2.7 were more likely to have extravesical extension of the tumor ( $p = 0.0047$ ) and positive lymph nodes ( $p = 0.0285$ ). No statistical difference was found after positive lymph node cases were classified into TNM staging groups (Nx–N3) ( $p = 0.1269$ ). Furthermore, no significant difference was observed between groups with

**Table 1.** Clinicopathologic characteristics of the cohort stratified by preoperative NLR

	Total	NLR ≤2.7	NLR >2.7	p
Age, year, median (IQR)	66	64.5 (59–71)	67.50 (60–72)	0.1083
Sex, number (%)				
Female	19 (14.2)	7 (12.5)	12 (15.4)	0.8027
Male	115 (85.8)	49 (87.5)	66 (84.6)	
Neutrophil $\times 10^9/l$ , median (IQR)	5.12 (4.25–6.85)	4.27 (3.38–5.01)	6.35 (4.99–8.39)	<0.0001
Lymphocyte $\times 10^9/l$ , median (IQR)	1.73 (1.4–2.24)	2.16 (1.69–2.57)	1.52 (1.18–1.85)	<0.0001
Length of stay, days, median (IQR)	9 (7–12)	9 (7–12)	8.5 (7–13)	
Urinary diversion, number (%)				
Ureterocutaneostomy	57 (42.5)	17 (30.4)	40 (51.3)	0.0157
Bricker ileal conduit	77 (57.5)	39 (69.6)	38 (48.7)	
Blood transfusions, number (%)	60 (44.8)	21 (37.5)	39 (50)	0.1512
Reoperations within stay, number (%)	12 (9)	3 (5.5)	9 (11.5)	0.3578
Parenteral nutrition, number (%)	16 (12%)	6 (10.7)	10 (12.9)	0.7911
Pathologic T stage, number (%)				
≤T1	25 (19.1)	16 (29.1)	9 (11.8)	0.0047
T2	24 (18.3)	11 (20)	13 (17.1)	
T3	58 (44.3)	23 (41.8)	35 (46.1)	
T4	24 (18.3)	5 (9.1)	19 (25)	
Pathologic N stage, number (%)				
Nx	12 (9.1)	4 (7.1)	8 (10.5)	0.1269
N0	74 (56.1)	38 (67.9)	36 (47.4)	
N1	24 (18.2)	10 (17.9)	14 (18.4)	
N2	18 (13.6)	2 (3.6)	16 (21.1)	
N3	4 (3)	2 (3.6)	2 (2.6)	
Grade				
Low	10 (7.7)	5 (8.9)	5 (6.8)	0.74459
High	120 (92.3)	51 (91.1)	69 (93.2)	
pN+, number (%)	46 (37)	14 (26)	32 (46)	0.0285
Lymph node count, median (IQR)	6 (4–9)	7 (4–9)	6 (3–9)	0.5440
Lymphovascular invasion, number (%)	50 (37.3)	18 (32.1)	32 (41)	0.2944
CIS (%)	35 (25.1)	16 (28.6)	19 (24.4)	0.5840
Positive radial margin, number (%)	13 (9.7)	3 (5.4)	10 (12.8)	0.23649

IQR – interquartile range; NLR – neutrophil to lymphocyte ratio; CIS – carcinoma in situ

regard to tumor grade ( $p = 0.745$ ), number of lymph nodes removed during cystectomy ( $p = 0.544$ ), concomitant carcinoma in situ (CIS) ( $p = 0.584$ ), or positive surgical margins (PSM) ( $p = 0.237$ ) (Table 1). The total median follow-up time was 2.2 years (interquartile range [IQR] 1–5.4), and a total of 100 deaths from all causes occurred throughout the period. The median OS of the cohort was 2.2 years (IQR 1–6.9). The Kaplan-Meier analysis showed a difference in survival between the high- (median 1.6 years; IQR 0.7–5.7) and low-NLR (median 3.8 years; IQR 1.5–8.6) groups (Figure 1), which was confirmed to be statistically significant using the log-rank test ( $p = 0.0345$ ). A Cox proportional hazard analysis was performed to investigate the effect of various clinicopathological factors and NLR on OS. The univariate model showed that age ( $p = 0.007372$ ), high NLR ( $p = 0.038528$ ), advanced pathological tumor stage ( $p = 0.000763$ ), lymph node involvement ( $p = 0.013384$ ), high grade of cancer ( $p = 0.015611$ ), LVI ( $p = 0.001530$ ), positive margins ( $p = 0.000890$ ), prostatic involvement of urothelial cancer ( $p = 0.012344$ ), and ureterocutaneostomy as urinary diversion ( $p = 0.038854$ ) had a negative impact on OS (Table 2). A multivariate Cox regression analysis that took into consideration the effects of multiple factors showed that a tumor extending beyond the submucosa (>pT1) was associated with a twofold higher risk of death from any cause (hazard ratio 2.161 confidence interval 1058–4411,  $p = 0.0345$ ) and hence, in addition to lymphatic infiltration (hazard ratio 1.599 confidence interval 1028–2482,  $p = 0.037$ ), an independent risk factor of poor prognosis (Table 3).



**Figure 1.** Kaplan-Meier curves for overall survival of cystectomy patients categorized by the neutrophil to lymphocyte ratio (low NLR ≤2.7; high NLR >2.7); \*the log-rank test.

NLR – neutrophil-to-lymphocyte ratio

**Table 2.** Univariate analysis of clinicopathological parameters for the prediction of overall survival following radical cystectomy

	All-cause mortality		
	HR	95% CI	p
Age	1.033	1.009–1.058	0.007372
Sex	1.077	0.610–1.900	0.798758
NLR (>2.7 compared to ≤2.7)	1.538	1.023–2.313	0.038528
Pathologic tumor stage (pT2–4 compared to pT1)	2.955	1.572–5.553	0.000763
pN+	1.696	1.116–2.578	0.013384
Grade (high compared to low)	4.145	1.309–13.123	0.015611
CIS	0.821	0.523–1.289	0.391303
Lymphovascular invasion	1.924	1.284–2.884	0.001530
Positive radial margin	2.854	1.538–5.296	0.000890
Prostatic TCC involvement	2.049	1.173–3.580	0.012344
Urinary diversion (ureterocutaneostomy compared to Bricker ileal conduit)	1.527	1.022–2.282	0.038854

HR – hazard ratio; NLR – neutrophil to lymphocyte ratio; CIS – carcinoma in situ; TCC – transitional cell carcinoma

**Table 3.** Multivariate analysis of clinicopathological parameters for the prediction of overall survival following radical cystectomy

	HR	95% CI	p
Age	1.016	0.988–1.044	0.268242
NLR (>2.7 compared to ≤2.7)	1.362	0.882–2.102	0.162988
Pathologic tumor stage (pT2–4 compared to pT1)	2.160	1.058–4.411	0.034486
Lymphovascular invasion	1.598	1.028–2.482	0.037131
Positive radial margin	1.694	0.848–3.387	0.135696
Urinary diversion (ureterocutaneostomy compared to Bricker ileal conduit)	1.033	0.663–1.608	0.887578

HR – hazard ratio; CI – confidence interval; NLR – neutrophil to lymphocyte ratio

## DISCUSSION

In our cohort of 134 consecutive patients with BC who underwent RC in 2011–2017, we found that preoperative NLR >2.7 was associated with a more advanced pathological stage of the tumor, lymph node involvement at the time of cystectomy, worse OS, and a higher frequency of ureterocutaneostomy as urine diversion.

No recognized markers are available for routine laboratory testing to stratify and assess preoperative risk among patients with BC; therefore, further research is needed to identify simple and accurate tools. Pre-

treatment measurements of inflammatory markers such as lymphocytes, neutrophils, high-density lipoprotein (HDL), albumin, C-reactive protein (CRP), NLR and modified Glasgow Predictive Scale (mGPS) proved to be useful as prognostic indicators [19].

Attempts to elucidate the relationship between NLR and prognosis on a pathophysiological basis led to the study of the role of inflammation. Cancer-related inflammation induces the regulation of the innate immune response. It is manifested by an increased reaction dependent on neutrophils, and increased infiltration of tumor macrophages with simultaneous suppression of lymphocytes [20, 21]. Neutrophils, depending on microenvironmental factors, can promote tumor growth through remodeling of the extracellular matrix, angiogenesis, controlling of tumor cell proliferation, and suppression of anti-tumor immune surveillance [22].

The prognostic value of NLR, a widely used marker of the systemic inflammatory response, is being utilized in diagnosing various diseases at different stages. NLR is a potentially cost-effective and time-saving parameter that can be easily estimated from blood counts, which makes it an attractive tool with a potential prognostic value deserving further investigation. It is important to note that increased tumor burden, which is linked to cancer immune system response, may be reflected in the NLR value [18].

Recent studies recommended an NLR cut-off value of 3, but the method for selecting the NLR cut-off value remained unclear [23]. The NLR cut-off value of 2.7, which we assumed in this study, based on the optimal sensitivity and specificity of NLR for selected patient outcomes, was determined using the receiver operating characteristic curve (ROC). This value was similar and proportional to the values adopted in the research from previous years.

Various studies in the fields of oncology and cardiovascular diseases have recently demonstrated the usefulness of NLR [19]. Previous works have shown an association between NLR, postoperative survival, and tumor progression in patients with various types of cancers [13, 14, 20, 21]. Increased NLR was considered an unfavorable prognostic factor of colorectal, gastric, hematological, esophageal, pancreatic, liver, urological, and gynecological cancers [22]. In their meta-analysis comprising of more than 40,000 patients with multiple types of solid tumors, Templeton et al. reported that NLR >4 was associated with poor OS [23].

In a meta-analysis in the field of urology, Luo showed that patients with renal cell carcinoma, upper tract urothelial carcinoma, BC, and prostate cancer had a higher NLR and therefore a higher risk of death from all causes than those with a low NLR [24].

In a study of 68 patients, Krane et al. found that a high NLR was associated with poor OS and cancer-specific survival (CSS) in patients undergoing RC for muscle-invasive BC. [30] Moreover, similar results were also obtained by Viers et al. [16]. Based on multivariate analysis, NLR was considered as an independent prognostic factor for overall survival in these studies. In our study an NLR >2.7 was also associated with poor OS, with a mean of 19.2 months vs 45.6 months (log rank test 0.03). Similar results were obtained by Tan et al. (22.3 months vs 64.8 months) [31]. However, we could not define NLR as an independent prognostic factor for overall survival, as we obtained statistical significance only in univariate analysis.

In addition, Viers et al. found that NLR was associated with lymph node involvement and extravesical extension during RC [16]. We also obtained similar results in our study with regard to lymph node involvement, which was confirmed only by univariate analysis.

In our study, we also found, using multivariate analysis, that LVI observed during the histopathological examination was an independent prognostic factor for OS. This result is consistent with those of previous studies, for example the one by Mathieu et al., which proved the statistically significant effect of LVI on OS [26].

The percentage of PSM in previous studies varied considerably ranging from 2.5 to 26% [27]. In our study, we found PSM in 13 patients (9.7%), which is comparable to previous results. Using univariate analysis, we confirmed that PSM was a predictor of OS.

In addition, univariate analysis revealed that ureterocutaneostomy as urinary diversion was a statistically significant factor affecting OS. This is due to the fact that the aforementioned method is often utilized in patients with more advanced cancer, in those with a single kidney, or in general, in patients at risk [28].

The strength of our research is that this is the first and only cohort study in this field in Central and Eastern Europe.

Our results are consistent with those of previous studies that demonstrate an association between NLR and oncologic outcomes and suggest a role for NLR in prognostication for patients with BC undergoing RC.

Our study also has several limitations. First, data were obtained from a single referral institution, the cohort was historical and nonrandomized. Second, different interfering conditions, such as chronic diseases, could affect NLR. Third, CSS was not reported because no data on the cause of death were available. Other limitations of the study are the relatively long inclusion period and the small sample size. Finally, the range of lymphadenectomy was not clearly defined in all cases.

## CONCLUSIONS

Despite the limitations, our results suggest that NLR has a role in predicting OS and that elevated NLR could be considered as a biomarker of adverse histopathological findings. Our study showed that preoperative NLR could be useful in patient risk stratification prior to surgical treatment. NLR should be included in nomograms that determine the risk of surgical failure and, furthermore, it should be utilized to identify patients who require therapy intensification and closer follow-up. Interestingly, there are reports of the role of NLR in predicting responses to NACT that may be helpful in better planning of the treatment process. Further prospective, multicenter studies are needed to establish the most accurate target for utilizing NLR.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ETHICS APPROVAL

This research was approved by the Ethics Committee of the affiliated hospital of Lublin Medical University (Trial registration number: KE-0254/178/2020, Date of registration: 24.09.2020).

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