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Original Article

# Association between early change in neutrophil-to-lymphocyte ratio after radical cystectomy and treatment outcomes

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## Objectives

To evaluate the associations of peri-operative neutrophil-to-lymphocyte ratio (NLR) and change in NLR with survival after radical cystectomy.

## Patients and Methods

We retrospectively reviewed a multicentre cohort of patients with bladder cancer who underwent radical cystectomy between 2010 and 2020. Preoperative NLR, postoperative NLR, delta-NLR (postoperative minus preoperative NLR) and NLR change (postoperative divided by preoperative NLR) were calculated. Patients were stratified based on elevation of preoperative and/ or postoperative NLR above the median values. Multivariable Cox regression models were used to evaluate the associations of peri-operative NLR and NLR change with survival.

## Results

The study cohort included 346 patients with a median age of 69 years. The median (interquartile range) preoperative NLR, postoperative NLR, delta-NLR and NLR change were 2.55 (1.83, 3.90), 3.33 (2.21, 5.20), 0.43 (−0.50, 2.08) and 1.2 (0.82, 1.96), respectively. Both preoperative and postoperative NLR were elevated in 110 patients (32%), 126 patients (36%) had an elevated preoperative or postoperative NLR, and 110 patients (32%) did not have an elevated NLR. On multivariable analysis, increased preoperative and postoperative NLR were significantly associated with decreased survival. While delta-NLR and NLR change were not associated with outcome, patients with elevations in both preoperative and postoperative NLR had the worst overall (hazard ratio [HR] 2.97, 95% confidence interval [CI] 1.78, 4.95; $P < 0.001$) and cancer-specific survival rates (HR 2.41, 95% CI 1.3, 4.4; $P = 0.004$).

## Conclusions

Preoperative and postoperative NLR are significant predictors of survival after radical cystectomy; patients in whom both NLR measures were elevated had the worst outcomes. Future studies should evaluate whether an increase in NLR during long-term follow-up may precede disease recurrence.

## Keywords

bladder cancer, neutrophil-lymphocyte-ratio, prognosis, radical cystectomy, survival, #BladderCancer, #blcsm, #uroonc

## Introduction

Peripheral blood neutrophil-to-lymphocyte ratio (NLR) is an increasingly studied cancer-related biomarker, and elevated NLR values are often associated with poor prognosis in various malignancies [1]. In non-muscle-invasive and muscle-invasive bladder cancer, elevated pre-treatment NLR has been associated with adverse pathology and a poor prognosis

[1–9]. A large meta-analysis conducted by Lucca et al., in a cohort of patients who underwent radical cystectomy, found that elevated pre-treatment NLR had a hazard ratio (HR) of 1.5 for overall mortality [6]. Two additional large meta-analyses evaluating the same patient population that included more recent studies showed similar results [4,5].

Change in NLR has been hypothesized to predict treatment outcome; treatment-related effects include reduction in disease burden and activation of the tumour-associated immune response, which may lead to changes in various biomarkers including NLR [10]. Consistent with this hypothesis, change in NLR was associated with survival in metastatic RCC after immune checkpoint blockade [11]. Similar results were found in advanced pancreatic tumours treated with chemotherapy [12]. In a large series of patients who underwent curative intent surgery for colonic cancer, delta-NLR, defined as postoperative minus preoperative NLR, has proven to be a valuable predictor of prognosis [13]. Similar studies evaluating the prognostic role of postoperative NLR and change in NLR among patients treated for bladder cancer are less common and report conflicting results [14–16].

In this study, we aimed to evaluate the associations between peri-operative changes in NLR and outcomes in patients with bladder cancer undergoing radical cystectomy.

## Patients and Methods

After obtaining institutional review board approval, we reviewed the medical records of 392 patients who underwent radical cystectomy, pelvic lymph node dissection and urinary diversion in five different medical centres between the years 2010 and 2020. We excluded three patients without pre- and postoperative blood counts available for review, as well as 34 patients who had their preoperative blood tests performed >30 days before surgery, eight patients who had their postoperative blood tests performed >90 days after surgery and one patient with a known haematological disorder, leaving a total of 346 patients for further analyses.

Clinical characteristics evaluated prior to surgery included patient age, sex, non-age-adjusted Charlson Comorbidity Index, and clinical stage categorized as muscle-invasive and non-muscle-invasive. All patients underwent radical cystectomy and urinary diversion. The surgical approach and the type of urinary diversion were recorded. All surgical specimens were reviewed by genitourinary pathologists and tumour T-stage and N-stage were assigned. Surgical margin status and the presence of variant histology including sarcomatoid features, squamous de-differentiation or micropapillary features were also evaluated. Neoadjuvant and adjuvant therapies were given at the discretion of the treating physicians to patients who were eligible for systemic treatment. After radical cystectomy, patients were followed with serial physical examinations and imaging studies.

Preoperative complete blood counts (CBCs) were evaluated using the last CBC obtained prior to surgery. Postoperative CBCs were evaluated at the first follow-up for patients without concomitant infection; in cases of a concomitant inflammatory process, CBC evaluation was deferred until resolution. All CBCs were obtained within 30 days prior to surgery and up to 90 days after surgery. The NLR was calculated as the ratio between the absolute number of neutrophils and the absolute number of lymphocytes. The median preoperative and postoperative NLR values were evaluated and patients with an NLR above the median values were defined as having increased preoperative and postoperative NLR, respectively. The change between preoperative and postoperative NLR values was evaluated using delta-NLR, defined as postoperative NLR minus preoperative NLR, and NLR change was defined as postoperative NLR divided by preoperative NLR. Finally, patients were classified into three groups based on whether they had both an elevated preoperative NLR and elevated postoperative NLR (both NLRs elevated), whether they had either an elevated preoperative NLR or postoperative NLR (single NLR elevated), or whether neither the preoperative nor the postoperative NLR were elevated (NLR not elevated).

The study endpoints were death from any cause and cancer-related death. Descriptive statistics were used to report baseline patient and tumour characteristics. Median and interquartile range (IQR) values were used to report continuous variables and number and percent were used to report categorical variables. Clinical characteristics were compared between patients when grouped based on an increase in preoperative and/ or postoperative NLR values. Chi-squared and Mann–Whitney *U*-tests were used to compare categorical and continuous variables, respectively. *P* values were adjusted using the Benjamini–Hochberg method to account for multiple testing. The Kaplan–Meier method was used to evaluate overall and cancer-specific survivals. Patients were followed from the time of surgery to the time of death or last follow-up. Patients who did not die were censored at their last follow-up. Multivariable Cox regression models were used to evaluate the associations between preoperative NLR, postoperative NLR, delta-NLR, NLR change and NLR group category and survival, while adjusting for known predictors of outcome after radical cystectomy including patient age, Charlson Comorbidity Index (categorized as <3 vs ≥3), clinical stage (categorized as non-muscle-invasive vs muscle-invasive), tumour T-stage (categorized as T0–1, T2 and T3–4), lymph node involvement, surgical margin status, neoadjuvant and adjuvant chemotherapy treatment.

## Results

The study cohort consisted of 346 patients with a median (IQR) age of 69 (64, 76) years. Clinical and pathological

characteristics of the study cohort are reported in Table 1. Most patients (294/344, 85%) had evidence of muscle-invasive disease before cystectomy. Over half of the patients (185 patients, 53%) had pathological stage T2 or lower disease and 86 patients (25%) had lymph node involvement on final pathology. Neoadjuvant treatment was given to 143 patients (41%), and 75 patients (22%) received adjuvant treatment after surgery. Most patients (79%) received cisplatin-based neoadjuvant treatment, and 51% received cisplatin-based adjuvant treatment.

**Table 1** Clinical and pathological characteristics of the study cohort ($n$ = 346).

| Characteristic | |
|---|---|
| Age, median (IQR), years | 69 (64, 76) |
| Sex, *n* (%) | |
| Female | 78 (22.5) |
| Male | 268 (77.5) |
| Charlson Comorbidity Index, *n* (%) | |
| <3 | 252 (73) |
| ≥3 | 94 (27) |
| Local clinical stage, *n* (%) | |
| Non-muscle-invasive | 50 (14) |
| Muscle-invasive | 294 (85) |
| NA | 2 (1) |
| Surgical approach, *n* (%) | |
| Open | 270 (78) |
| Robotic | 76 (22) |
| Diversion type, *n* (%) | |
| Ileal conduit | 280 (81) |
| Orthotopic neobladder | 60 (17) |
| Indiana pouch | 2 (1) |
| NA | 4 (1) |
| Pathological T-stage, *n* (%) | |
| T0–T1 | 126 (36) |
| T2 | 59 (17) |
| T3–T4 | 161 (47) |
| Pathological lymph node involvement, *n* (%) | |
| Negative | 260 (75) |
| Positive | 86 (25) |
| Surgical margin status, *n* (%) | |
| Negative | 317 (92) |
| Positive | 29 (8) |
| Neoadjuvant treatment, *n* (%) | |
| Gemcitabine-cisplatin | 94 (27) |
| MVAC | 14 (4) |
| Gemcitabine-carboplatin | 18 (5) |
| Immunotherapy | 5 (1) |
| Other | 9 (3) |
| No treatment | 203 (59) |
| NA | 3 (1) |
| Adjuvant treatment, *n* (%) | |
| Gemcitabine-cisplatin | 32 (9) |
| MVAC | 2 (1) |
| Gemcitabine-carboplatin | 17 (5) |
| Immunotherapy | 9 (3) |
| Other | 8 (2) |
| No treatment | 271 (78) |
| NA | 7 (2) |
| Preoperative NLR, median (IQR) | 2.55 (1.83, 3.9) |
| Postoperative NLR, median (IQR) | 3.33 (2.21, 5.2) |
| Delta-NLR, median (IQR) | 0.43 (−0.50, 2.08) |
| NLR change, median (IQR) | 1.2 (0.82, 1.96) |
| NLR increase group, *n* (%) | |
| None | 110 (32) |
| Preoperative or postoperative | 126 (36) |
| Preoperative and postoperative | 110 (32) |

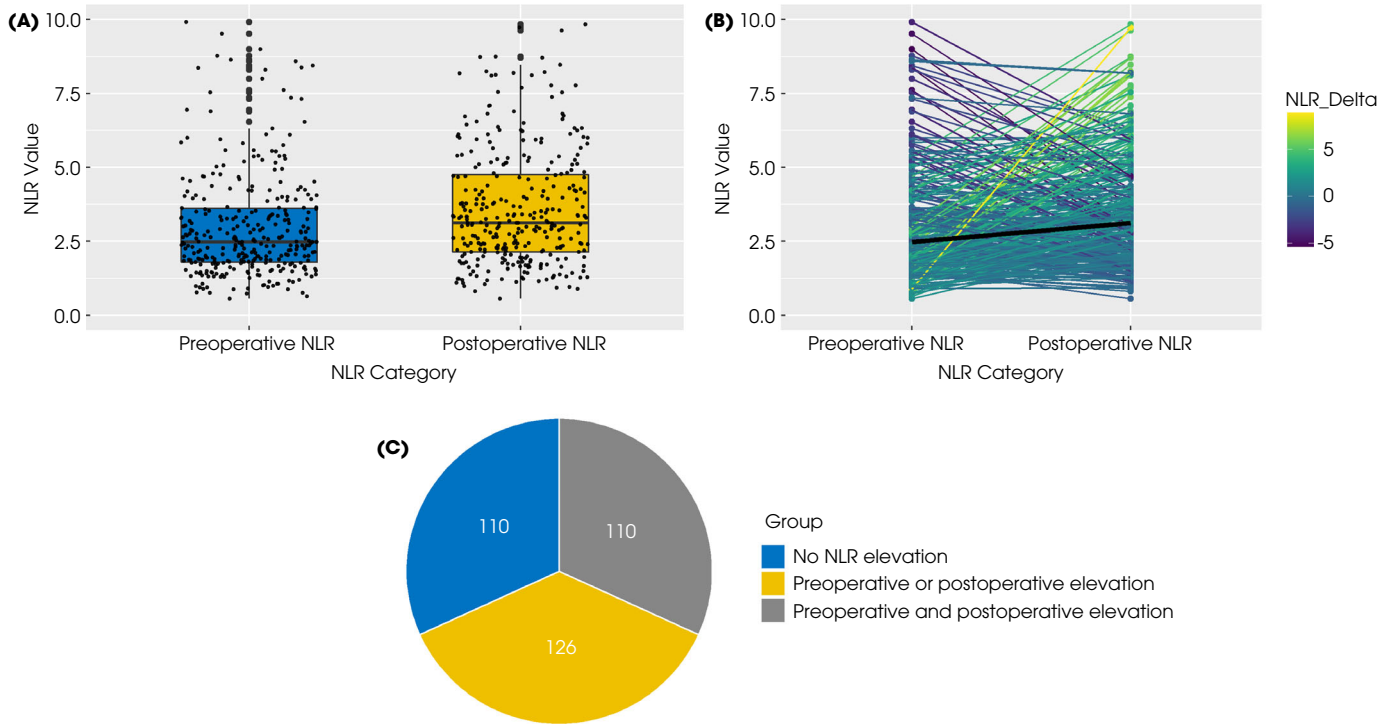
*IQR, interquartile range; MVAC, methotrexate, vinblastine, adriamycin, and cisplatin; NA, not available; NLR, neutrophil-to-lymphocyte ratio.*

The median (IQR) time between obtaining a preoperative CBC and surgery was 1 (1, 7) days. The median (IQR) time until a postoperative CBC was obtained at the first follow-up visit after discharge was 32 (21, 50) days. The median (IQR) preoperative NLR was 2.55 (1.83, 3.9) and the median (IQR) postoperative NLR was 3.33 (2.21, 5.2). The median (IQR) delta-NLR was 0.43 (−0.50, 2.08), and the median (IQR) NLR change was 1.20 (0.82, 1.96). In 110 patients (32%) both preoperative and postoperative NLR were elevated compared to the corresponding median NLR; 126 patients (36%) had either an elevated preoperative or an elevated postoperative NLR and 110 patients (32%) did not have an elevated NLR in either the preoperative or the postoperative assessments (Table 1, Fig. 1). Age, Charlson Comorbidity Index and pathological T-stage significantly differed among the three groups, with a higher rate of patients with an elevated comorbidity index and higher T-stage apparent in the group with both elevated preoperative and elevated postoperative NLR, while patients without NLR elevation were younger (Table S1).

The median (IQR) follow-up for survivors was 44 (32, 60) months. During the follow-up period a total of 131 patients died at a median time of 12 (7, 26) months. Cause of death was documented for 116 patients, 91 of whom (78%) died from bladder cancer at a median (IQR) time of 10 (6, 23) months. The 2-year and 5-year estimated overall survival rates for the whole cohort were 73% (95% CI 69%, 78%) and 57% (95% CI 51%, 63%), respectively. Similarly, the 2-year and 5-year estimated cancer-specific survival rates were 79% (95% CI 75%, 84%) and 68% (95% CI 63%, 74%), respectively. On univariable analyses, patients with an elevated preoperative and postoperative NLR value had significantly decreased rates of overall and cancer-specific survival (Fig. 2). The estimated 5-year overall and cancer-specific survival rates for patients with elevated preoperative and elevated postoperative NLR were 32% (95% CI 22%, 46%) and 52% (42%, 64%), respectively. The corresponding rates for patients with either an elevated preoperative or an elevated postoperative NLR were 60% (95% CI 51%, 71%) and 70% (95% CI 61%, 80%), and those of patients who did not have an elevation in either NLR value were 77% (95% CI 69%, 87%) and 81% (95% CI 73%, 91%), respectively.

On multivariable analyses adjusted for age, Charlson Comorbidity Index, clinical stage, pathological T-stage, N-stage, surgical margin status, and neoadjuvant and adjuvant chemotherapy treatment, both elevated preoperative (HR 1.09, 95% CI 1.04, 1.14; $P < 0.001$) and elevated postoperative NLR (HR 1.1, 95% CI 1.06, 1.14; $P < 0.001$) were associated with a

**Fig. 1** (**A**) Boxplot of preoperative and postoperative neutrophil-to-lymphocyte ratio (NLR) values. (**B**) Plot depicting individual patient changes in NLR values; colour lines represent delta-NLR and black line represents change between the median values. (**C**) Pie chart of peri-operative NLR status. For parts (**A**) and (**B**) 27 patients with preoperative and/or postoperative NLR values >10 were excluded.




significantly worse overall survival. Delta-NLR and NLR change were not associated with overall survival. Patients with both an elevated preoperative and an elevated postoperative NLR had significantly worse overall survival when compared to patients who had neither an elevated preoperative nor an elevated postoperative NLR (HR 2.97, 95% CI 1.78, 4.95; $P < 0.001$ [Table 2]). Results of the multivariable analyses for cancer-specific survival were similar, aside from a significant association between elevated delta-NLR and a worse outcome (HR 1.05, 95% CI 1, 1.1; $P = 0.04$ [Table 2]).

The use of neoadjuvant and adjuvant chemotherapy may have affected the peri-operative blood counts, therefore, we performed post hoc subgroup analyses on 158 patients who did not receive peri-operative systemic therapy. The results were similar to those of the full cohort, showing an association between overall survival and preoperative NLR (HR 1.11, 95% CI 0.99, 1.25; $P = 0.06$), postoperative NLR (HR 1.07, 95% CI 1.02, 1.13; $P = 0.01$) and patients with both elevated preoperative and elevated postoperative NLR (HR 2.64, 95% CI 1.12, 6.24; $P = 0.027$ [Fig. S1A]) when adjusting for age, T-stage and N-stage. Additionally, there remained no association between delta-NLR and NLR change and outcome. We performed additional post hoc analyses on a subgroup of 159 patients with localized disease at radical cystectomy (T0–T2, N0). On multivariable analyses adjusted for age, preoperative NLR (HR 1.12, 95% CI 1.04, 1.2; $P = 0.003$) and elevations in both preoperative and postoperative NLR (HR 4.02, 95% CI 1.53, 10.6; $P = 0.005$ [Fig. S1B]) were associated with worse overall survival.

## Discussion

This study assessed the prognostic value of peri-operative changes in NLR in patients with bladder cancer who underwent radical cystectomy. Our multicentre cohort had similar patient characteristics, disease characteristics and overall survival when compared to previously published cohorts of radical cystectomy [4–6]. On multivariable analysis both elevated preoperative and elevated postoperative NLR were associated with a significantly worse outcome. Delta-NLR and NLR change were not associated with overall survival; however, patients with both an elevated preoperative and an elevated postoperative NLR had significantly worse cancer-specific and overall survival when compared to patients who had neither an elevated preoperative nor an elevated postoperative NLR.

Reports on the association of pre-treatment NLR and poor prognosis have been published with regard to various malignancies and disease stages [1]. For patients undergoing radical cystectomy for bladder cancer, Viers et al. reported an

**Fig. 2** Kaplan–Meier curves of (**A**) cancer-specific survival and (**B**) overall survival after radical cystectomy, stratified by peri-operative NLR status: NLR not elevated vs preoperative or postoperative NLR elevated vs preoperative and postoperative NLR elevated. *P* <0.001 on log-rank test for both.

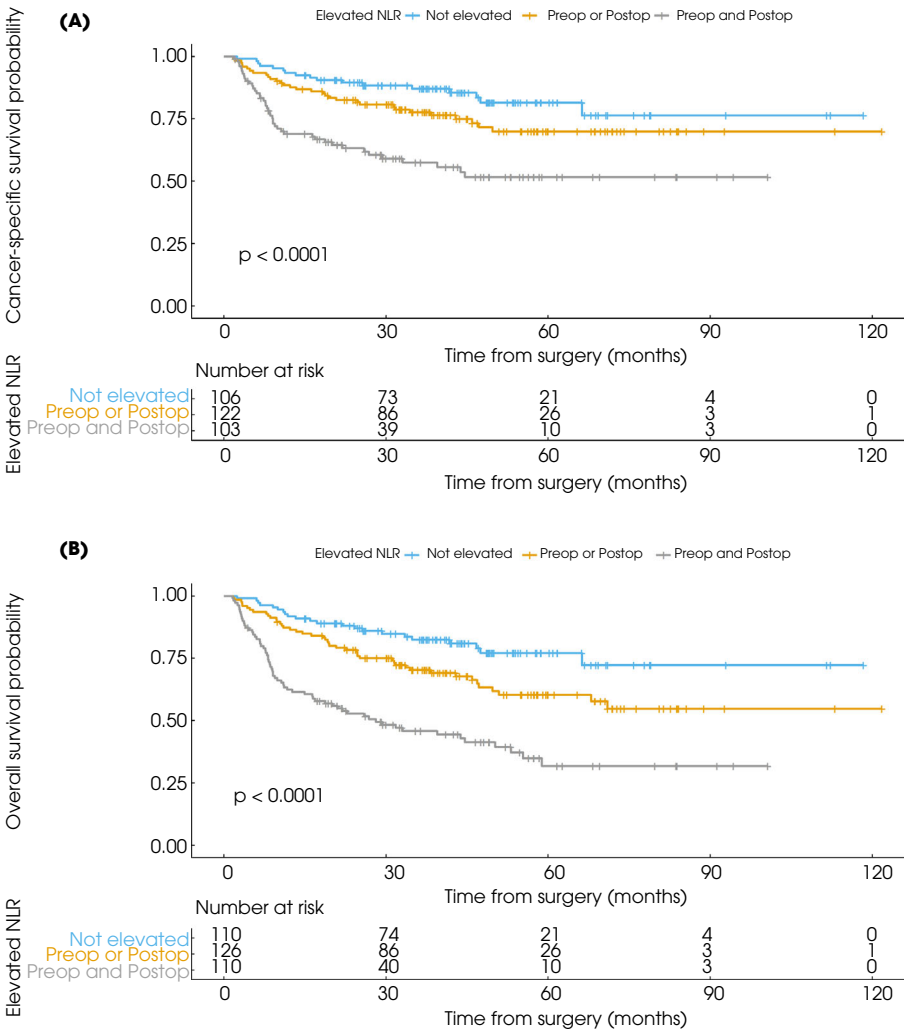



**Table 2** Multivariable Cox regression models evaluating the association between peri-operative neutrophil-to-lymphocyte ratio and overall and cancer-specific survival after radical cystectomy.

| Variable | Overall survival | | Cancer-specific survival | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Preoperative NLR | 1.09 (1.04, 1.14) | <0.001 | 1.09 (1.03, 1.15) | 0.002 |
| Postoperative NLR | 1.1 (1.06, 1.14) | <0.001 | 1.1 (1.05, 1.14) | <0.001 |
| Delta-NLR* | 1.04 (0.99, 1.09) | 0.08 | 1.05 (1, 1.1) | 0.04 |
| NLR change† | 1.02 (0.99, 1.05) | 0.22 | 1.03 (0.99, 1.06) | 0.08 |
| Elevated NLR | | | | |
| Not elevated | Reference | Reference | | |
| Preoperative or postoperative | 1.5 (0.87, 2.53) | 0.14 | 1.31 (0.7, 2.4) | 0.4 |
| Preoperative and postoperative | 2.97 (1.78, 4.95) | <0.001 | 2.41 (1.3, 4.4) | 0.004 |

*Each line represents a separate model, all models were adjusted for patient age at surgery, Charlson Comorbidity index (categorized as <3 vs ≥3), clinical stage (categorized as non-muscle invasive vs muscle invasive), tumour T-stage (categorized as T0–1, T2 and T3–4), lymph node involvement, surgical margin status, neoadjuvant and adjuvant chemotherapy treatment. CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio. *Calculated as postoperative NLR minus preoperative NLR. †Calculated as postoperative NLR divided by preoperative NLR.*

association between pre-treatment NLR and advanced pathological disease stage and disease-specific mortality [3]. In a meta-analysis summarizing clinical outcomes of more than 11 000 patients with bladder cancer treated with radical cystectomy with or without neoadjuvant chemotherapy, Hu et al. [5] demonstrated an association between pre-treatment NLR and decreased progression-free and overall survival. In a study evaluating different pre-treatment blood-based biomarkers in a similar cohort, Bhindi et al. showed that NLR was the only biomarker that was significantly associated with progression-free, disease-specific and overall survival [7]. To date, there is no definitive pre-treatment NLR cut-off, and most large bladder cancer-related studies use the median values as cut-offs, with a range of 2.4–3 [2–8]. Similarly to previous reports, patients in our cohort had a median pre-treatment NLR of 2.54, and pre-treatment NLR was significantly associated with outcome.

The mechanism underlying the association between NLR and outcome is yet to be elucidated and probably involves multiple pathways. Previous reports support a close relationship between cancer and the inflammatory cascade [17,18]. Elevated peripheral blood neutrophil levels are thought to reflect the inflammatory microenvironment within the tumour, that in turn has tumour-promoting activity. This pro-tumoural effect can be mediated through a variety of signals that include chemokines, lipid mediators and pathogen signals. These mediators can promote vascular cell permeability, cell invasion, extracellular matrix remodelling, angiogenesis, cancer cell proliferation and inhibition of anti-tumoural immune surveillance. Decreased level of lymphocytes, on the other hand, reflect decreased cell-mediated host immunity and a decrease in their anti-tumour activity, which may enable cancer progression. Thus, it is likely that the combination of neutrophilia and lymphocytopenia (i.e., high NLR) promotes a pro-tumoural environment which eventually leads to tumour progression and a poor oncological outcome [17–19].

Change in NLR after treatment has been evaluated in several malignancies. Wu et al. assessed peri-operative NLR changes after partial hepatectomy for hepatocellular carcinoma and found an association between the sum of preoperative NLR and postoperative NLR and overall survival [20]. Shibutani et al. assessed patients who underwent curative-intent surgery for colorectal cancer, reporting an association between elevated postoperative NLR and survival. Moreover, after stratifying the patients into four groups based on high vs low pre- and post-treatment NLR values, the group with low pre-treatment and low post-treatment NLR were found to have the best prognosis [21]. Li et al. assessed patients treated for stage 1–3 colon cancer, failing to show an association between postoperative NLR and survival; however, delta-NLR (subtracting postoperative from preoperative NLR) showed a significant association with survival, suggesting that when the NLR value increases after treatment, prognosis becomes poorer [13]. Finally, Lalani et al. showed that the NLR value 6 weeks after initiation of immune checkpoint blockade was associated with outcome in metastatic RCC. In these patients, an NLR increase of ≥25% at 6 weeks was significantly correlated with a reduced overall response rate and an independent predictor of decreased overall and progression-free survival, while a decrease in NLR by ≥25% was associated with improved outcome [11]. When evaluating the association between NLR change and outcome in bladder cancer, Albisinni et al. demonstrated that increased postoperative NLR was associated with reduced recurrence-free survival [14]. In a large cohort, Kang et al. showed an association between elevated postoperative NLR and poor oncological outcomes among patients with advanced pathological tumour stage. Patients with both elevated pre-treatment and elevated post-treatment NLR had worse oncological outcomes than patients with other changes in pre-treatment and post-treatment NLR [15]. Yoshida et al. demonstrated the prognostic ability of both pre- and post-treatment NLR. Furthermore, when stratifying patients into four groups based on their NLR values (high vs low, pre- and post-treatment), patients with high NLR before and after surgery had the worst survival rate [16]. Morizawa et al. [8], demonstrated that during follow-up after radical cystectomy, NLR increased significantly in the last visit before recurrence was detected radiographically. The present study supports an association between NLR values before and after treatment and survival, an association that was evident as early as 1 month after surgery.

In the studies mentioned above, post-treatment NLR was evaluated 3 months after surgery, in comparison to our study, where values were evaluated approximately 1 month after surgery. Trials of adjuvant chemotherapy after radical cystectomy generally require chemotherapy to start within 90 days postoperatively [22]. Similarly, most patients in the CheckMate274 trial were randomized to receive adjuvant immunotherapy or placebo within 90 days from cystectomy [23]. Data from a retrospective study reported a median interval of 57 days between cystectomy and initiation of adjuvant chemotherapy, with 87% of patients starting chemotherapy within 90 days. In addition, shorter surgery to adjuvant chemotherapy interval was associated with better outcomes; however, the association did not reach statistical significance, possibly due to the small number of patients (13%) with a delay beyond 3 months [22]. Therefore, the association between early peri-operative NLR and outcome, as seen in our study, may be important within the context of adjuvant treatment.

Refinement of the selection criteria for adjuvant therapy administration through individualized risk estimation could optimize treatment while decreasing toxicity. Pederzoli et al.

reported that, when using a nomogram that accounted for surgical margin status, pathological tumour and nodal stage, and previous neoadjuvant chemotherapy administration, adjuvant chemotherapy was beneficial for patients with a calculated recurrence risk of >40% and did not impact cancer recurrence in lower-risk disease [24]. In the present study, we report a significant association between elevation of both preoperative and postoperative NLR and worse outcome when adjusting for known predictors of outcome after radical cystectomy. This association was also apparent among a subgroup of patients with localized pathology at cystectomy. Our findings may prompt the incorporation of NLR group in future nomograms aimed at selecting patients for adjuvant treatment, especially among patients who are not typical candidates for adjuvant therapy according to the inclusion criteria used in current adjuvant trials which are based on pathological stage alone. Given the latest advancement in adjuvant treatment for bladder cancer and the proven benefit of nivolumab given after radical surgery to patients with high-risk muscle-invasive urothelial carcinoma [23], early peri-operative NLR is a readily available tool that can aid in patient selection for adjuvant therapy, either using standard chemotherapy or novel immunotherapeutic agents to maximize oncological outcomes.

This study has several limitations, mainly related to its retrospective nature. The study population included both patients treated with and without peri-operative chemotherapy, which may have influenced blood counts and bone marrow response. However, a subgroup analysis of patients who did not receive neoadjuvant or adjuvant treatment showed similar results to those of the full cohort. Postoperative NLR values were collected in the early recovery phase after surgery, possibly influencing NLR values. While our multicentre cohort captures overall and disease-specific death events, we did not collect accurate data regarding disease recurrence during follow-up. Finally, we were unable to adjust for all clinical variables in the post hoc multivariable regression models, due to a limited number of events within the evaluated subgroups. Nevertheless, our study includes a multicentre cohort representing a real-life setting. In the emerging era of immunotherapy for bladder cancer, biomarkers that reflect the immune system function and response to treatment can have a substantial effect on patient management.

In conclusion, the findings of this study support the prognostic ability of NLR values, both in the preoperative and in the early postoperative phases. Patients with both measures elevated had the worst outcome. These findings could have a substantial effect on patient selection for adjuvant immunotherapy. Future studies should evaluate whether an increase in NLR during long-term follow-up may precede disease recurrence.

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## Disclosures of Interest

The authors declare no disclosures of interest.

## References

1 **Templeton AJ, McNamara MG, Šeruga B et al.** Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014; 106: dju124. https://doi.org/10.1093/jnci/dju124

2 **Black AJ, Zargar H, Zargar-Shoshtari K et al.** The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy. *Urol Oncol* 2020; 38: 3.e17–27

3 **Viers BR, Boorjian SA, Frank I et al.** 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: 1157–64

4 **Tang X, Du P, Yang Y.** The clinical use of neutrophil-to-lymphocyte ratio in bladder cancer patients: a systematic review and meta-analysis. *Int J Clin Oncol* 2017; 22: 817–25

5 **Hu G, Xu F, Zhong K et al.** The prognostic role of preoperative circulating neutrophil-lymphocyte ratio in primary bladder cancer patients undergoing radical cystectomy: a meta-analysis. *World J Urol* 2019; 37: 1817–25

6 **Lucca I, Jichlinski P, Shariat SF et al.** The neutrophil-to-lymphocyte ratio as a prognostic factor for patients with urothelial carcinoma of the bladder following radical cystectomy: validation and meta-analysis. *Eur Urol Focus* 2016; 2: 79–85

7 **Bhindi B, Hermanns T, Wei Y et al.** Identification of the best complete blood count-based predictors for bladder cancer outcomes in patients undergoing radical cystectomy. *Br J Cancer* 2016; 114: 207–12

8 **Morizawa Y, Miyake M, Shimada K et al.** Neutrophil-to-lymphocyte ratio as a detection marker of tumor recurrence in patients with muscle-invasive bladder cancer after radical cystectomy. *Urol Oncol* 2016; 34: 257.e11–7

9 **Mano R, Baniel J, Shoshany O et al.** Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non-muscle-invasive bladder cancer. *Urol Oncol* 2015; 33: 67.e1–7

10 **Ashizawa N, Furuya S, Katsutoshi S et al.** Clinical significance of dynamic neutrophil-lymphocyte ratio changes in patients with colorectal cancer. *Anticancer Res* 2020; 40: 2311–7

11 **Lalani AKA, Xie W, Martini DJ et al.** Change in neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. *J Immuno Ther Cancer* 2018; 6: 1–9

12 **Luo G, Guo M, Liu Z et al.** Blood neutrophil-lymphocyte ratio predicts survival in patients with advanced pancreatic cancer treated with chemotherapy. *Ann Surg Oncol* 2015; 22: 670–6

13 **Li Z, Zhao R, Cui Y, Zhou Y, Wu X.** The dynamic change of neutrophil to lymphocyte ratio can predict clinical outcome in stage I–III colon cancer. *Sci Rep* 2018; 8: 1–8

14 **Albisinni S, Moussa I, Aoun F et al.** The impact of postoperative inflammatory biomarkers on oncologic outcomes of bladder cancer. *Prog Urol* 2019; 29: 270–81

15 **Kang M, Jeong CW, Kwak C, Kim HH, Ku JH.** The prognostic significance of the early postoperative neutrophil-to-lymphocyte ratio in patients with urothelial carcinoma of the bladder undergoing radical cystectomy. *Ann Surg Oncol* 2016; 23: 335–42

16 **Yoshida T, Kinoshita H, Yoshida K et al.** Perioperative change in neutrophil-lymphocyte ratio predicts the overall survival of patients with bladder cancer undergoing radical cystectomy. *Jpn J Clin Oncol* 2016; 46: 1162–7

17 **Fridlender ZG, Sun J, Kim S et al.** Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. *Cancer Cell* 2009; 16: 183–94

18 **Mantovani A, Cassatella MA, Costantini C, Jaillon S.** Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat Rev Immunol* 2011; 11: 519–31

19 **Gooden MJM, de Bock GH, Leffers N, Daemen T, Nijman HW.** The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. *Br J Cancer* 2011; 105: 93–103

20 **Wu M, Yang S, Feng X, Yu F, Liu X, Dong J.** Preoperative plus postoperative neutrophil-lymphocyte ratio for predicting overall survival following partial hepatectomy for hepatocellular carcinoma. *Oncol Lett* 2020; 20: 1

21 **Shibutani M, Maeda K, Nagahara H et al.** The prognostic significance of a postoperative systemic inflammatory response in patients with colorectal cancer. *World J Surg Oncol* 2015; 13: 1–8

22 **Grunewald CM, Henn A, Galsky MD et al.** Impact of timing of adjuvant chemotherapy following radical cystectomy for bladder cancer on patient survival. *Urol Oncol* 2020; 38: 934.e1–9

23 **Bajorin DF, Witjes JA, Gschwend JE et al.** Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med* 2021; 384: 2102–14

24 **Pederzoli F, Bandini M, Briganti A et al.** Incremental utility of adjuvant chemotherapy in muscle-invasive bladder cancer: quantifying the relapse risk associated with therapeutic effect. *Eur Urol* 2019; 76: 425–9

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Fig. S1.** Kaplan–Meier curves for overall survival after radical cystectomy for (**A**) 158 patients who did not receive perioperative systemic therapy and (**B**) 159 patients with localized pathological disease (stage ≤T2,N0), stratified by perioperative neutrophil-to-lymphocyte ratio (NLR) status: NLR not elevated vs preoperative or postoperative NLR elevated vs preoperative and postoperative NLR elevated. *P* value <0.001 on log-rank test for both.

**Table S1.** Clinical and pathological characteristics of the study cohort, stratified by preoperative and postoperative neutrophil-to-lymphocyte ratio (NLR) status (no elevation, preoperative or postoperative NLR elevated, both preoperative and postoperative NLR elevated, $n = 346$).

 