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Urologic Oncology: Seminars and Original Investigations 38 (2020) 3.e17–3.e27

UROLOGIC ONCOLOGY

Clinical-Bladder cancer

The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy

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Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.urolonc.2019.09.023

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Received 22 March 2019; received in revised form 2 September 2019; accepted 25 September 2019

Abstract

Introduction: The neutrophil-to-lymphocyte ratio (NLR) is an attractive marker because it is derived from routine bloodwork. NLR has shown promise as a prognostic factor in muscle invasive bladder cancer (MIBC) but its value in patients receiving neoadjuvant chemotherapy (NAC) before radical cystectomy (RC) is not yet established. Since NLR is related to an oncogenic environment and poor antitumor host response, we hypothesized that a high NLR would be associated with a poor response to NAC and would remain a poor prognostic indicator in patients receiving NAC.

Methods: A retrospective analysis was performed on patients with nonmetastatic MIBC (cT2-4aN0M0) who received NAC prior to RC between 2000 and 2013 at 1 of 19 centers across Europe and North America. The pre-NAC NLR was used to split patients into a low (NLR $\leq$ 3) and high (NLR $>$ 3) group. Demographic and clinical parameters were compared between the groups using Student's *t* test, chi-squared, or Fisher's exact test. Putative risk factors for disease-specific and overall survival were analyzed using Cox regression, while predictors of response to NAC (defined as absence of MIBC in RC specimen) were investigated using logistic regression.

Results: Data were available for 340 patients (199 NLR $\leq$ 3, 141 NLR $>$ 3). Other than age and rate of lymphovascular invasion, demographic and pretreatment characteristics did not differ significantly. More patients in the NLR $>$ 3 group had residual MIBC after NAC than the NLR $\leq$ 3 group (70.8% vs. 58.3%, $P = 0.049$). NLR was the only significant predictor of response (odds ratio: 0.36, $P = 0.003$) in logistic regression. NLR was a significant risk factor for both disease-specific (hazard ratio (HR): 2.4, $P = 0.006$) and overall survival (HR:1.8, $P = 0.02$).

Conclusion: NLR $>$ 3 was associated with a decreased response to NAC and shorter disease-specific and overall survival. This suggests that NLR is a simple tool that can aid in MIBC risk stratification in clinical practice.

Keywords: MIBC; NLR; Neoadjuvant chemotherapy; Urothelial carcinoma; Radical cystectomy

1. Introduction

Standard therapy for nonmetastatic muscle invasive bladder cancer (MIBC) includes neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC). Even with optimal multidisciplinary care, however, the 5-year overall survival (OS) is only approximately 50% [1-3]. The uptake of NAC has been slow, as many physicians are not convinced that the magnitude of the benefit (5% improved OS at 5 years) justifies the risks to the patient, including potential adverse effects of chemotherapy and a delay in definitive surgery in patients who do not respond to NAC [1]. Prognostic tools to stratify risk and predictive biomarkers that allow selection of patients likely to respond to NAC, are therefore essential to advance the field and optimize individual treatment choices.

Prognostic factors are associated with risk of recurrence, progression, and survival [2]. A variety of prognostic tools have been described in MIBC, including clinical parameters and tissue markers [3-5]. A blood-based marker, the neutrophil-to-lymphocyte ratio (NLR), has demonstrated potential as a prognostic marker in many cancers including MIBC [6]. NLR is thought to reflect both systemic inflammation and antitumor immune response. The inflammatory environment, measured as an elevated neutrophil count, purportedly promotes oncogenesis and progression [7,8]. A low lymphocyte count, on the other hand, may indicate an inability of the host to mount a targeted immune response towards tumor cells [1]. A high NLR therefore may indicate increased inflammation and a poor antitumor immune response, and is related to more advanced cancer as well as worse prognosis [1,8].

NLR has shown promise as a prognostic factor in patients with MIBC undergoing RC [9,10]. An increased NLR before treatment can be associated with upstaging to nonorgan confined disease and recurrence after treatment [9,11-14]. A multitude of studies also relate a high NLR in MIBC to worse disease-specific survival (DSS) and OS [1,7,9,10,15]. Only 3 small studies with a total of 224 patients have investigated the impact of pretreatment NLR on outcome in patients receiving NAC. Two studies showed no significant association between NLR and response to NAC, while the third demonstrated a significant

relationship between NLR and both pathological response and survival in MIBC patients receiving NAC before RC [1,8,16]. Based on this data, the value of NLR as a prognostic marker in patients receiving NAC before RC remains uncertain.

The objective of this study was to use a large multicenter cohort to elucidate how NLR relates to tumor response to NAC and evaluate whether NLR has potential value as a prognostic tool in patients receiving NAC prior to RC. We hypothesized that a high NLR would correlate to lower response to NAC and shorter survival compared to low NLR.

2. Methods

2.1. Patients

Demographic, clinicopathological, and outcome data were retrospectively collected from the medical records of 1,865 consecutive patients who underwent RC after NAC between 2000 and 2013 at 19 centers across Europe and North America, as previously described [17]. Data were collected with the approval of each institution's clinical research ethics board and deidentified data were shared with the use of data transfer agreements. This analysis included 340 patients who had nonmetastatic, muscle invasive (cT2-T4aN0M0) urothelial carcinoma, received at least 3 cycles of cisplatin-based NAC, and had blood count data available within 30 days before starting NAC to calculate NLR.

2.2. Statistical analysis

Using a receiver operating characteristic curve we determined that a NLR cut-off of 3.56 provided the optimal balance between sensitivity and specificity in our cohort (Supplemental Fig. 1). Since this was very close to the commonly used cut-off of 3, we decided to use the same cut-off in our study to allow easier comparison to other studies [7,18-20]. Patients were classified into a low and high NLR group (NLR $\leq$ 3 or NLR > 3).

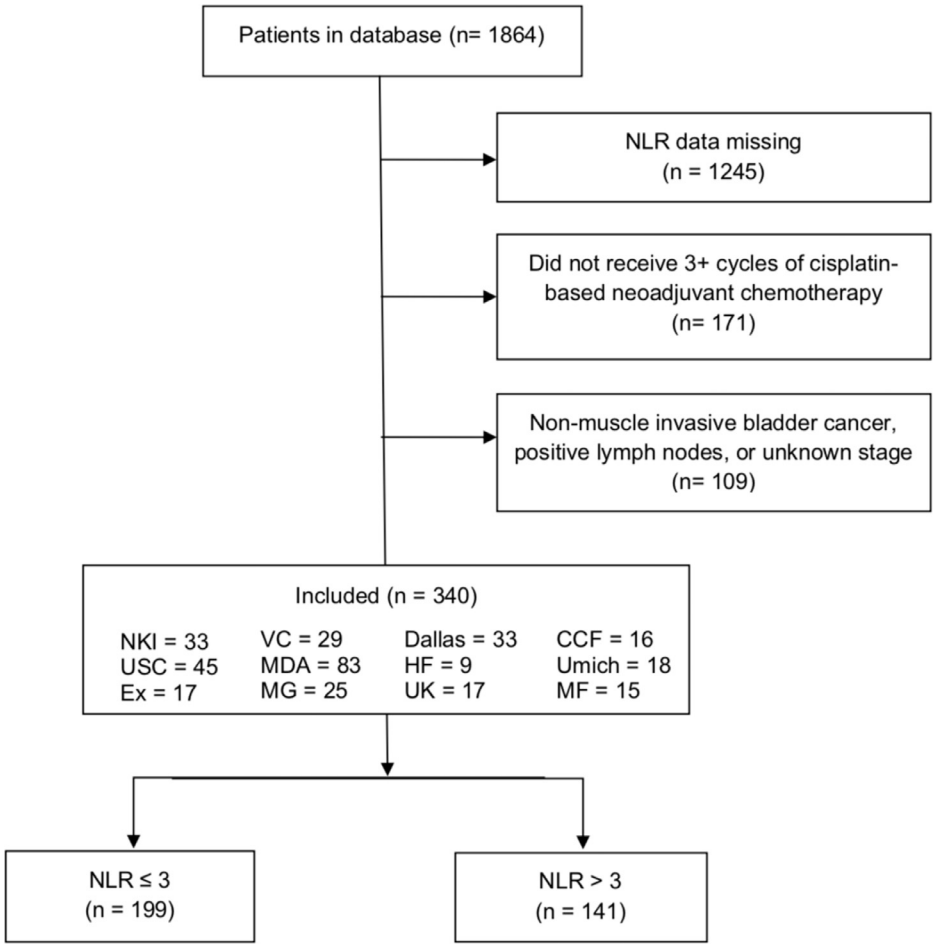


Fig. 1. Consort flow diagram. Of the 1,864 patients in our database, 1,245 were excluded due to missing NLR data and 280 because they did not meet the inclusion criteria listed on the right of the diagram. This resulted in a total of 340 patients for the analysis, 199 of whom had an NLR $\leq$ 3 while the other 141 had an NLR > 3. The breakdown of patients from each center is shown. CCF = Cleveland Clinic; Dallas = University of Texas, Southwestern; Ex = Exeter; HF = Freeman Hospital; MDA = MD Anderson Cancer Center; MF = Moffitt Cancer Center; MG = McGill University; NKI = Netherlands Cancer Institute; NLR = neutrophil-to-lymphocyte ratio; UK = University of Kansas; UMich = University of Michigan; USC = University of Southern California; VC = Vancouver Prostate Center.

Demographics and preoperative clinicopathological characteristics (age, sex, race, BMI, smoking, Eastern cooperative oncology group (ECOG) performance status, hydronephrosis, clinical T-stage, histology, lymphovascular invasion in transurethral resection of bladder tumor (TURBT) tissue, hemoglobin, and platelet count) were compared between these 2 groups using Mann Whitney-*U* test for continuous variables and chi-squared or Fisher's exact for categorical variables. These methods were also used to compare treatment and pathological parameters (NAC regimen, number of NAC cycles, pathological T-stage, pathological N-stage, pathological response to NAC, lymphovascular invasion in RC tissue, and surgical margin status) between the two groups. The Kaplan-Meier method was used to estimate DSS and OS stratified by NLR ≤ 3 and NLR > 3, and the log-rank method was used to determine significance.

Multivariable analysis was performed based on these survival endpoints using a Cox regression. Finally, a logistic regression was used to look for predictors of pathological response to NAC. All multivariable analyses included the relevant preoperative characteristics (age, sex, hydronephrosis, clinical T-stage, histology, lymphovascular invasion, hemoglobin, and platelets). ECOG performance status was excluded due to the large number of patients with missing data. Patients with missing data were excluded from the multivariable analysis so that the data of 216 patients was analyzed. All statistical analysis was performed using SPSS-v.25 (IBM Corp., Armonk, NY, USA). A P value <0.05 was considered significant.

3. Results

A total of 340 patients were included in the analysis, of which 199 patients had a NLR ≤ 3 and 141 had a NLR > 3 (Fig. 1). The majority of patients included in this study were male (77.4%) and Caucasian (68.5%), with clinical stage T2 (57.1%) pure urothelial carcinoma (81.5%). The average age was 62.8 ± 9.4 years, and the

Table 1
Patient demographics and preoperative characteristics

		NLR ≤ 3	NLR > 3	Total	*P* value
Age (mean, STD) (*n* = 338)		61.5 ± 9.3	64.5 ± 9.2	62.8 ± 9.4	0.002
Sex (*n*, %)	Male	150 (75.4%)	113 (80.1%)	263 (77.4%)	0.301
	Female	49 (24.6%)	28 (19.9%)	77 (22.6%)	
Race (*n*, %)	Caucasian	131 (65.8%)	102 (72.3%)	233 (68.5%)	0.882
	Black	16 (8.0%)	9 (6.3%)	25 (7.4%)	
	Asian	5 (2.5%)	4 (2.8%)	9 (2.6%)	
	Hispanic	3 (1.5%)	3 (2.1%)	6 (1.8%)	
	Unknown	44 (22.1%)	23 (16.3%)	67 (19.7%)	
Smoker (*n*, %)	Never	56 (28.1%)	47 (33.3%)	103 (30.2%)	0.741
	Prior	91 (45.7%)	64 (45.4%)	155 (45.6%)	
	Current	36 (18.1%)	30 (21.3%)	66 (19.4%)	
	Unknown	16 (8.0%)	-	16 (4.7%)	
ECOG (*n*, %)	0	99 (49.7%)	63 (44.7%)	162 (47.6%)	0.057
	1	32 (16.1%)	28 (19.9%)	60 (17.6%)	
	2	1 (0.5%)	5 (3.5%)	6 (1.8%)	
	3	-	1 (0.7%)	1 (0.3%)	
	Unknown	67 (33.7%)	44 (31.2%)	111 (32.6%)	
Hydronephrosis (*n*, %)	No	129 (64.8%)	76 (53.9%)	205 (60.3%)	0.110
	Unilateral	55 (27.6%)	49 (34.8%)	104 (30.6%)	
	Bilateral	6 (3.0%)	8 (5.7%)	14 (4.1%)	
	Unknown	9 (4.5%)	8 (5.7%)	17 (5.0%)	
Clinical T-Stage (*n*, %)	T2	119 (59.8%)	75 (53.2%)	194 (57.1%)	0.376
	T3	61 (30.7%)	47 (33.3%)	108 (31.8%)	
	T4a	19 (9.5%)	19 (13.5%)	38 (11.2%)	
Histology (*n*, %)	Pure UC	164 (82.4%)	113 (80.1%)	277 (81.5%)	0.682
	UC with squamous differentiation	12 (6.0%)	14 (9.9%)	26 (7.6%)	
	UC with glandular differentiation	5 (2.5%)	3 (2.1%)	8 (2.4%)	
	Micropapillary	3 (1.5%)	-	3 (0.9%)	
	Sarcomatoid	1 (0.5%)	1 (0.7%)	2 (0.6%)	
	Small cell	3 (1.5%)	3 (2.1%)	6 (1.8%)	
	Unknown	11 (5.5%)	7 (5.0%)	18 (5.3%)	
Lymphovascular invasion (TURBT) (*n*, %)	Present	120 (60.3%)	68 (48.2%)	188 (55.3%)	0.030
	Absent	43 (21.6%)	43 (30.5%)	86 (25.3%)	
	Unknown	36 (18.1%)	30 (21.3%)	66 (19.4%)	
Hemoglobin (mean, STD)		12.6 ± 2.6	12.9 ± 1.9	12.7 ± 2.3	0.790
Platelets (mean, STD)		279.5±115.9	297.2±118.1	286.7±116.8	0.208

ECOG = Eastern cooperative oncology group; NLR = neutrophil-to-lymphocyte ratio; TURBT = transurethral resection of bladder tumor; UC = urothelial carcinoma.

patients with NLR > 3 were slightly older than those in the NLR ≤ 3 group (64.5 vs. 61.5 years, respectively, $P = 0.002$). The performance status was commensurate with a population undergoing NAC and RC (ECOG = 0 in 47.6%). Lymphovascular invasion was present in 55.3% of tumors at the time of TURBT, but in a higher proportion of patients in the NLR ≤ 3 group (60.3% vs. 48.2%, $P = 0.03$). None of the other patient demographics or preoperative characteristics varied significantly between groups (Table 1).

Table 2 shows that treatment parameters and pathological outcomes were not significantly different between groups. However, while 24.1% of NLR ≤ 3 patients had pathologic complete response (ypT0N0) to NAC and 17.6% had a partial response (ypTa/Tis/T1N0), these rates were only 16.3% and 14.9%, respectively, in patients with NLR > 3. Residual muscle invasive and/or node-positive disease (ypT2-4Nany or ypTanyN1-3) was found in 68.1% of NLR > 3 patients and 55.3% of NLR ≤ 3 patients ($P = 0.071$).

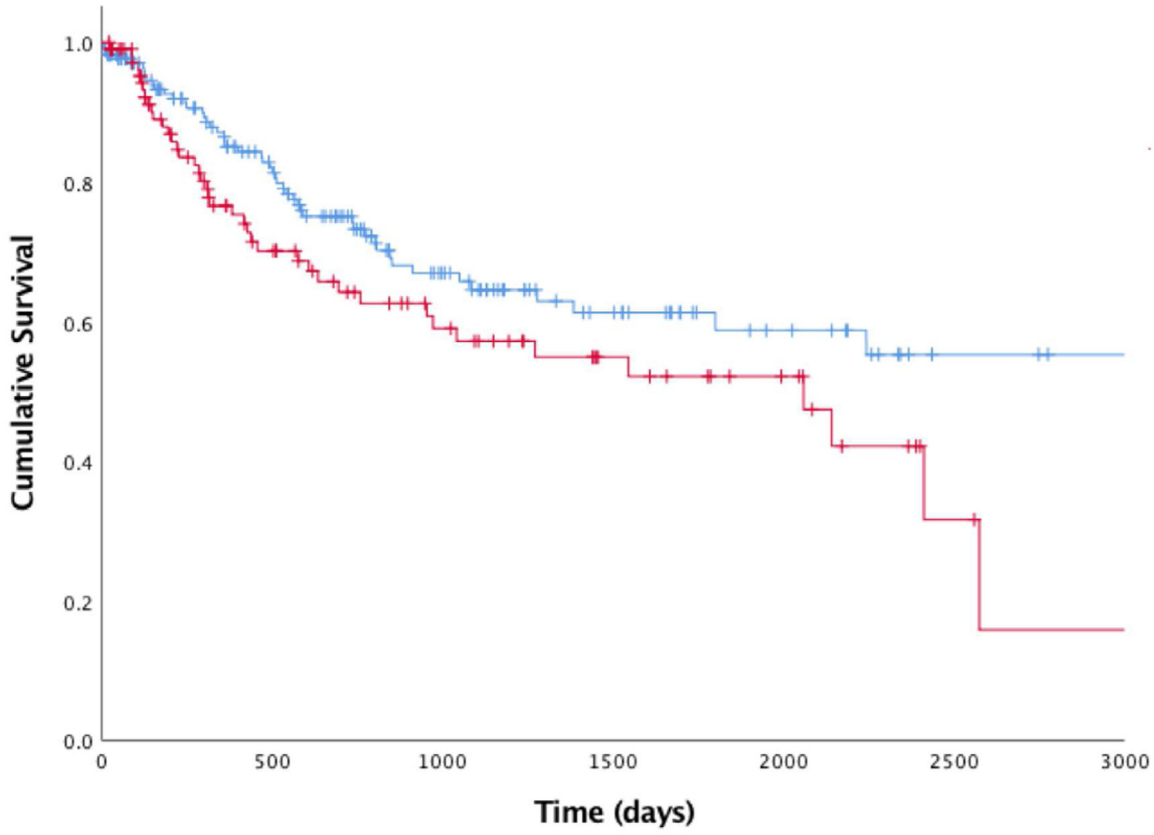
Patients with a NLR > 3 had worse OS than patients with NLR ≤ 3 (Fig. 2), and there was a statistically nonsignificant trend towards worse DSS (Fig. 3). In the univariable Cox regression no variables were significant risk factors for DSS, but smoking was protective (hazard ratio (HR): 0.44, $P < 0.01$, Supplemental Table 1). In the multivariable analysis, a NLR > 3 was the only significant risk factor independently prognostic for DSS (HR: 2.4, $P = 0.006$; Table 3). NLR > 3 (HR: 1.8, $P = 0.02$) and age were independent predictors of OS in both the univariable and multivariable Cox regressions ($P < 0.05$, Table 4 and Supplemental Table 2). Furthermore, NLR > 3 predicted a lower pathological response rate to NAC in multivariable analysis (OR: 0.43, $P = 0.01$). None of the other variables significantly correlated with pathological response to NAC (Table 5). Secondary multivariable analyses that included treatment center as a variable identified that it was not a risk factor for survival or response to NAC ($P > 0.05$). Multivariable analysis with NLR as a continuous variable identified a statistically significant linear relationship between NLR and OS (HR: 1.07, 1.001-1.14; $P = 0.048$). However, the relationship between DSS and NLR as well as response to NAC and NLR were not significant (DSS HR: 1.06, 0.98-1.14; $P = 0.16$ and response OR: 0.97, 0.90-1.04; $P = 0.37$).

Table 2
Treatment and pathological outcomes

		NLR ≤ 3	NLR > 3	Total	*P* value
NAC regimen (*n*, %)	DDMVAC	47 (23.6%)	48 (34.0%)	95 (27.9%)	0.079
	MVAC	55 (27.6%)	26 (18.4%)	81 (23.8%)	
	GC	95 (47.7%)	66 (46.8%)	161 (47.4%)	
	Other cis containing	2 (1.0%)	1 (0.7%)	3 (0.9%)	
NAC number of cycles (*n*, %)	3	71 (35.7%)	53 (37.6%)	124 (36.5%)	0.060
	4	113 (56.8%)	67 (47.5%)	180 (52.9%)	
	>4	15 (7.5%)	21 (14.9%)	36 (10.6%)	
Pathological T-Stage (*n*, %)	ypT0	53 (26.6%)	25 (17.7%)	78 (22.9%)	0.074
	ypTa	5 (2.5%)	2 (1.4%)	7 (2.1%)	
	ypTis	26 (13.1%)	10 (7.1%)	36 (10.6%)	
	ypT1	11 (5.5%)	9 (6.4%)	20 (5.9%)	
	ypT2	36 (18.1%)	34 (24.1%)	70 (20.6%)	
	ypT3	49 (24.6%)	38 (27.0%)	87 (25.6%)	
	ypT4	17 (8.5%)	22 (15.6%)	39 (11.5%)	
	ypTx	2 (1.0%)	1 (0.7%)	3 (0.9%)	
Pathological N-Stage (*n*, %)	ypN0	148 (74.4%)	99 (70.2%)	247 (72.6%)	0.148
	ypN1	19 (9.5%)	11 (7.8%)	30 (8.8%)	
	ypN2	18 (9.0%)	24 (17.0%)	42 (12.4%)	
	ypN3	4 (2.0%)	5 (3.5%)	9 (2.6%)	
	ypNx	10 (5.0%)	2 (1.4%)	12 (3.5%)	
Response to NAC (*n*, %)	ypT0N0	48 (24.1%)	23 (16.3%)	71 (20.9%)	0.071
	ypTa/Tis/T1N0	35 (17.6%)	21 (14.9%)	56 (16.5%)	
	ypT2-T4Nany or ypTanyN1-3	110 (55.3%)	96 (68.1%)	206 (60.6%)	
	Unknown[a]	6 (3.0%)	1 (0.7%)	7 (2.1%)	
Lymphovascular invasion (RC) (*n*, %)	Absent	34 (17.1%)	27 (19.1%)	61 (17.9%)	0.831
	Present	18 (9.0%)	13 (9.2%)	31 (9.1%)	
	Unknown	147 (73.9%)	101 (71.6%)	248 (72.9%)	
Surgical margin (*n*, %)	Positive	5 (2.5%)	10 (7.1%)	15 (4.4%)	0.053
	Negative	183 (92.0%)	129 (91.5%)	312 (91.8%)	
	Unknown	11 (5.5%)	2 (1.4%)	13 (3.8%)	

NAC = neoadjuvant chemotherapy; NLR = neutrophil-to-lymphocyte ratio; RC = radical cystectomy; MVAC = methotrexate (M), vinblastine (V), adriamycin (A), and cisplatin (C); DDMVAC = dose dense MVAC; GC = gemcitabine-cisplatin.

[a] In 8 patients with pTx or ypTNx the lack of response was evident from the corresponding ypT or ypN stage, which indicated residual muscle invasive or nodal disease in each case.



Number at Risk	NLR ≤ 3	199	108	58	35	21	10	8
	NLR > 3	141	53	33	20	13	4	1

Fig. 2. Kaplan-Meier Curve comparing overall survival for NLR ≤ 3 (blue) and NLR > 3 (red). Vertical ticks represent censored patients, while numbers below the x-axis represent the number of patients at risk in each group in 500 day intervals. ($P = 0.048$). NLR = neutrophil-to-lymphocyte ratio.

4. Discussion

There is growing evidence that inflammation not only plays an important role in carcinogenesis, but also tumor progression [6]. An inflammatory microenvironment promotes the proliferation of malignant cells, angiogenesis, and metastasis, and interferes with the host immune response [21]. There is evidence to suggest that inflammation may even contribute to the genetic instability of cancer [22]. As a consequence, inflammatory indices such as NLR, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio have been evaluated as prognostic or predictive factors. Elevated NLR has been shown to have prognostic implications for various cancers including colorectal, ovarian, pancreatic, and gastric cancers [6]. A review of NLR in urothelial cancers found it to be a prognostic biomarker in 87.5%, 80%, and 60% of the studies on upper tract urothelial cancer, urothelial bladder cancer, and metastatic and advanced disease, respectively [6]. In this study, we used a large multicenter cohort to evaluate NLR in patients undergoing NAC prior to RC and found that an elevated NLR (>3) was independently associated with shorter DSS and OS. There was a statistically non-significant association with downstaging at time of cystectomy as well.

In the context of MIBC, prognostic factors could potentially be used to identify a subpopulation with a particularly high risk of progression and death after standard treatment, with a resultant need for alternative or more intensive treatment options [4]. Clinical stage is a prognostic parameter that is sometimes used to guide NAC, because the relative benefit has been shown to be larger in patients with cT3-4N0 disease compared to patients with cT2N0 disease [23,24]. However, prognostic biomarkers do not necessarily inform whether the treatment will be effective in high risk patients. In order to select the treatment to which a patient is likely to respond, a predictive biomarker is required. Predictive biomarkers to guide patient selection for NAC are under development, but none are yet validated for routine clinical use [25-27].

This study supports the role for NLR as a prognostic marker but a randomized trial including patients with and without NAC would be required to determine if it has a role as a predictive marker as well. Since 31% of patients with

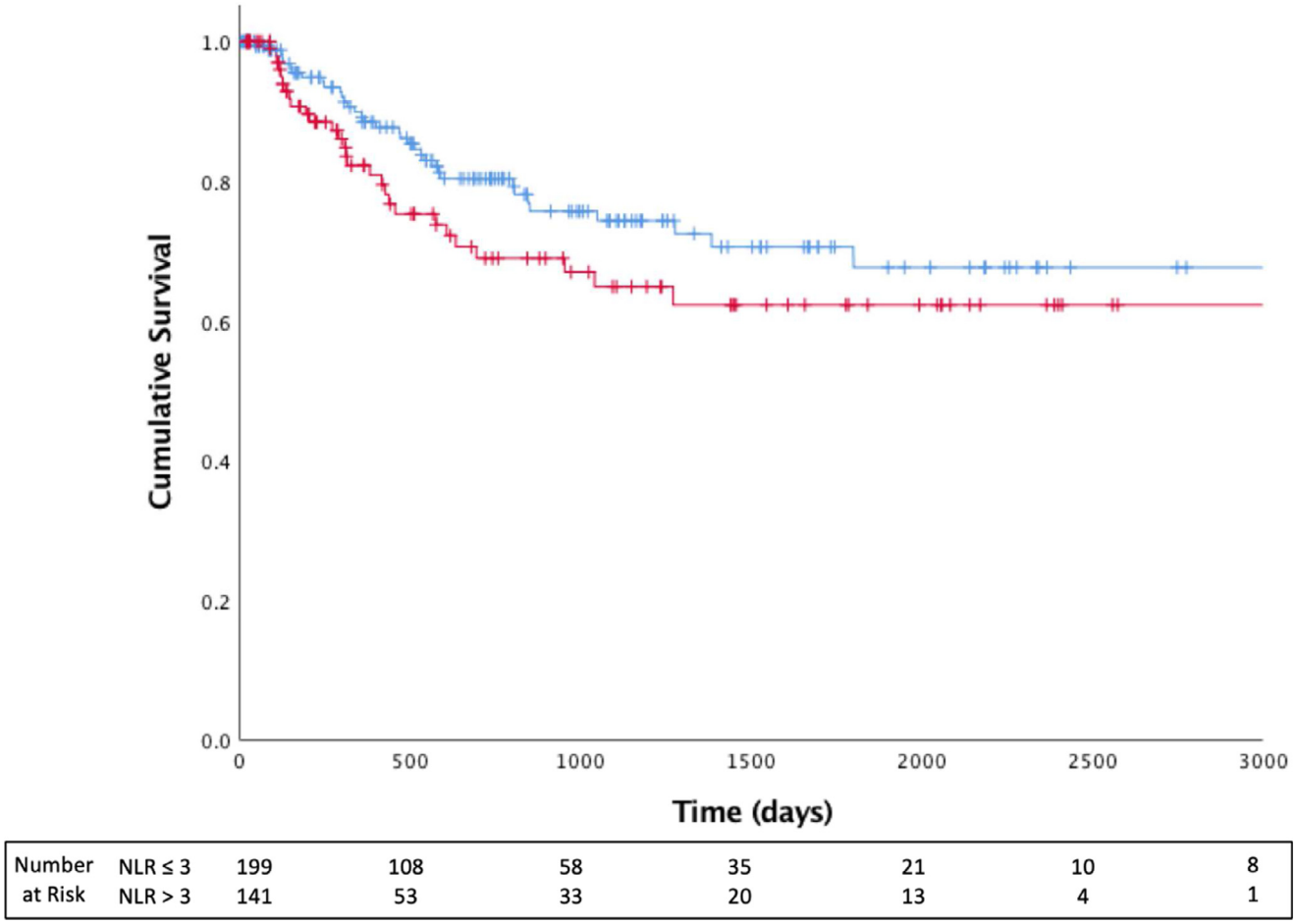


Fig. 3. Kaplan-Meier Curve comparing disease-specific survival stratified by NLR ≤ 3 (blue) and NLR > 3 (red). Vertical ticks represent censored patients, while numbers below the x-axis represent the number of patients at risk in each group in 500 day intervals. ($P = 0.113$). NLR = neutrophil-to-lymphocyte ratio.

NLR > 3 were down-staged at cystectomy, which far exceeds the rate expected from TURBT alone (10-15%), there is still a role for NAC in patients with elevated NLR. One can consider this to be a low cost marker that may help provide additional information for patients regarding prognosis and may assist in clinical trial stratification. It may also serve as a part of a panel of markers in the future. There is a potential role to evaluate the predictive value of NLR especially with use of immune therapies [28].

NLR has been clearly linked to a decreased recurrence-free survival and OS in patients with MIBC treated by RC [29]. The utility of NLR has, however, not yet been thoroughly examined in patients receiving NAC prior to RC. Seah et al. and van Kessel et al. proposed that a low NLR is related to better response to NAC but neither study showed statistically significant differences [8,16]. Buisan et al. found a significant relationship between NLR and both pathological response and survival, but only had a sample size of 75 patients [1]. Our results reinforce the results of Buisan et al. with a much larger samples size of 340 patients from European and North American centers [1].

When including NLR, previously identified prognostic factors such as clinical T stage did not significantly impact response to NAC, DSS, or OS in the multivariable analysis, although the trend for T stage was in the expected direction [15,30]. This may be due to our moderate sample size and relatively large number of variables in our multivariable analyses. Past or current smoking appeared to be protective in the multivariable analysis for DSS (HR: 0.43, $P = 0.006$). Although an explanation for this result is not obvious and may be random, smoking increases mortality due to a number of causes that may compete with DSS but not in OS.

Our study is limited by its retrospective nature and moderate sample size. Furthermore, ECOG performance status data, which almost certainly impacts patient survival, was excluded from our multivariable analysis due to a large proportion of missing data. However, ECOG performance status did not differ significantly between the low and high NLR groups, and a multivariable analysis including ECOG performance status only in patients with this parameter available showed a similar impact of NLR on patient survival and response to NAC, although statistical significance was lost due to the reduced sample

Table 3
Multivariable analysis (Cox regression) for predictors of disease-specific survival (number of events = 60)

	HR	95% confidence interval		*P* value
NLR (pre-NAC)				
Ref: ≤3				
>3	2.40	1.29	4.47	0.006
Age				
Continuous	1.01	0.98	1.04	0.566
Sex				
Ref: Male				
Female	0.96	0.45	2.06	0.923
Smoker				
Ref: No				
Ever smoker	0.43	0.23	0.79	0.006
Hydronephrosis				
Ref: No				
Yes	0.62	0.32	1.23	0.17
Histology				
Ref: Pure UC				
Other	1.60	0.82	3.12	0.17
cT stage				
Ref: T2				
T3	1.68	0.63	4.52	0.30
T4	2.00	0.70	5.69	0.19
Lymphovascular invasion				
Ref: Absent				
Present	0.76	0.39	1.46	0.41
Hemoglobin				
Continuous	0.91	0.79	1.04	0.18
Platelets				
Continuous	1.00	0.997	1.003	0.96

NAC = neoadjuvant chemotherapy; NLR = neutrophil-to-lymphocyte ratio.

Table 4
Multivariable analysis (Cox regression) for predictors of overall survival (number of events = 86)

	HR	95% confidence interval		*P* value
NLR (pre-NAC)				
Ref: ≤3				
>3	1.83	1.10	3.03	0.02
Age				
Continuous	1.03	1.00	1.06	0.03
Sex				
Ref: Male				
Female	1.12	0.60	2.05	0.75
Smoker				
Ref: No				
Ever smoker	0.69	0.41	1.18	0.18
Hydronephrosis				
Ref: No				
Yes	0.61	0.35	1.09	0.10
Histology				
Ref: Pure UC				
Other	1.169	0.640	2.137	0.28

(*continued*)

Table 4 (***Continued***)

	HR	95% confidence interval		*P* value
cT stage				
Ref: T2				
T3	T3: 1.08	0.52	2.26	0.84
T4	T4: 1.41	0.64	3.10	0.40
Lymphovascular invasion				
Ref: Absent				
Present	0.82	0.48	1.39	0.46
Hemoglobin				
Continuous	0.93	0.83	1.05	0.23
Platelets				
Continuous	1.00	0.998	1.002	0.96

NAC = neoadjuvant chemotherapy; NLR = neutrophil-to-lymphocyte ratio.

Table 5
Multivariable analysis (logistic regression) for predictors of response (ypT0/Tis/Ta/T1N0 vs. ypT2-4N0-3) to neoadjuvant chemotherapy (number of events = 106)

	OR	95% confidence interval		*P* value
NLR (pre-NAC)				
Ref: ≤3				
>3	0.43	0.22	0.82	0.01
Age				
Continuous	0.99	0.96	1.02	0.45
Sex				
Ref: Male				
Female	0.45	0.20	1.04	0.06
Smoker				
Ref: No				
Ever smoker	1.24	0.63	2.40	0.54
Hydronephrosis				
Ref: No				
Yes	0.59	0.30	1.16	0.13
cT stage				
Ref: T2				
T3	1.35	0.45	4.09	0.59
T4	1.66	0.52	5.26	0.39
Histology				
Ref: Pure UC				
Other	0.56	0.23	1.35	0.20
Lymphovascular invasion				
Ref: Absent				
Present	1.50	0.78	2.85	0.22
Hemoglobin				
Continuous	1.07	0.92	1.25	0.40
Platelets				
Continuous	1.00	0.997	1.004	0.73

NAC = neoadjuvant chemotherapy; NLR = neutrophil-to-lymphocyte ratio.

size. We also do not have a comparison cohort that was not treated with NAC, so we are unable to speculate whether NAC should be prioritized more or less in patients based on NLR. Further research would need to be done to answer this question. Our results together with those of prior reports in the literature suggest that NLR is a valid prognostic factor for patients with nonmetastatic MIBC undergoing RC, regardless of whether they receive NAC. Since NLR is derived from routine bloodwork, making it both inexpensive and accessible, it has the potential to be a useful tool to aid in patient risk stratification.

5. Conclusion

We have determined that NLR is a prognostic marker in patients with MIBC receiving NAC followed by RC. Patients with NLR > 3 have worse DSS and OS. Without a comparison cohort of patients who did not receive NAC, it is impossible to determine if NLR is predictive of response to NAC and whether there is a differential benefit of NAC in patients with high and low NLR. Nonetheless, NLR is a simple and inexpensive risk factor that can be used to assess prognosis in patients with MIBC.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.09.023.

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