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Bladder Cancer

Role of Serum Lymphocyte-derived Biomarkers in Nonmetastatic Muscle-invasive Bladder Cancer Patients Treated with Trimodal Therapy

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Article info

Abstract

Background: The role of serum lymphocyte-based biomarkers, such as the neutrophil-to-lymphocyte (NLR), lymphocyte-to-monocyte (LMR), and platelet-to-lymphocyte (PLR) ratios, was previously studied in patients with muscle-invasive bladder cancer (MIBC) treated with radical cystectomy but remains underexplored in patients treated with trimodal therapy (TMT).

Objective: To analyze the impact of serum lymphocyte-based biomarkers on main oncological outcomes after TMT for MIBC.

Design, setting, and participants: A retrospective study, including 176 patients treated with TMT for nonmetastatic MIBC (cT2–4/cN0–2) between 2001 and 2017 at a tertiary academic center, was conducted.

Intervention: TMT, consisting of initial maximal transurethral resection of the bladder tumor, followed by radiotherapy with concurrent chemotherapy.

Outcome measurements and statistical analysis: Clinicopathological characteristics, serum laboratory tests, and imaging reports were collected. NLR, LMR, and PLR were calculated before and at the end of TMT. Dynamic patterns of NLR, LMR, and PLR during TMT were studied. Multivariable regression models were performed to estimate the effect of these biomarkers on complete response (CR) to TMT and survival.

Results and limitations: The median age was 75 yr (interquartile range 66–82). Staging was cT2 in 156 (89%) and cN0 in 159 (90%) patients. A pretreatment NLR (pre-NLR) of ≥ 4.0 was independently associated with lower CR rates (odds ratio 0.32; $p = 0.013$). In addition, a pre-NLR of ≥ 4.0 was associated with worse cancer-specific survival (hazard ratio [HR] 1.88; $p = 0.032$) and overall survival

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(OS; HR 1.61; *p* = 0.033) together with other factors such as hydronephrosis, Eastern Cooperative Oncology Group performance status, and cT stage 3-4a. When both pre- and post-treatment variables were considered, an increase in NLR beyond 75% during TMT (HR 1.63; *p* = 0.035) was associated with worse OS. This study was limited by its retrospective design.

Conclusions: A high pre-NLR value was independently associated with lower rates of CR and worse survival in MIBC patients undergoing TMT. Prospective validation is needed to implement NLR into clinical practice.

Patient summary: In this study, we reported the oncological outcomes of patients with muscle-invasive bladder cancer treated with trimodal therapy. We found that the neutrophil-to-lymphocyte ratio, a cheap and available blood-derived biomarker, was associated with response to trimodal therapy and survival outcomes.

1. Introduction

Among serum-derived inflammatory biomarkers, the neutrophil-to-lymphocyte ratio (NLR) has extensively been explored as a potential predictor of prognosis in many malignancies [1–3]. A meta-analysis with 100 studies and >40 000 patients with solid tumors, including urothelial carcinoma, showed that a pretreatment NLR (pre-NLR) was independently associated with recurrence-free survival, progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) [2]. Theoretically, a higher number of neutrophils in the bloodstream reflect a proinflammatory state associated with disease progression and worse outcomes [4]. Meanwhile, a lower number of lymphocytes are associated with decreased antitumor immune response, also favoring tumor progression [4]. In addition, studies exploring the lymphocyte-to-monocyte (LMR) and platelet-to-lymphocyte (PLR) ratios suggested a similar role of serum levels of monocytes and platelets in inflammation and carcinogenesis [5].

Trimodal therapy (TMT) is a suitable organ-preserving alternative to radical cystectomy (RC) in patients with muscle-invasive bladder cancer (MIBC), as it has shown comparable outcomes when patients are carefully selected according to pretreatment clinicopathological features (eg, clinical tumor stage, presence of carcinoma in situ, and presence of hydronephrosis) [6–8]. Identifying novel predictors of response and prognostic factors associated with oncological outcomes after TMT is an unmet need. Particularly, the role of serum lymphocyte-derived biomarkers in oncological outcomes after TMT remains underexplored, with two reports on the topic suggesting a significant association of NLR with both complete response (CR) and survival [9,10].

In this study, we sought to analyze the role of pretreatment, post-treatment, and dynamic patterns of NLR, LMR, and PLR in CR and survival in MIBC patients undergoing TMT.

2. Patients and methods

This retrospective, single-center study included patients treated with curative-intent radiation therapy (RT) and concurrent chemotherapy for nonmetastatic MIBC (cT2-4aN0-2M0) from 2001 to 2017. Patients treated with palliative RT dose, those who did not receive concurrent chemotherapy, and those with invasion beyond the prostate or uterus (cT4b), adenopathy above the bifurcation of the common-iliac vessels (cN3), or distant metastasis (cM1) were excluded [11]. To avoid potential confounding values of NLR, LMR, and PLR, patients with previously known inflammatory or autoimmune diseases, and those diagnosed with infections within 6 mo of TMT (eg, urinary tract infection) were also excluded.

Demographics, clinicopathological data, laboratory tests, and imaging reports were collected. Response to TMT was assessed by urine cytology, white-light cystoscopy, tumor bed biopsy, and cross-sectional imaging within 3 mo from the last day of RT. A CR was defined by a negative tumor bed biopsy, or the combination of negative urine cytology and normal cystoscopy, with no signs of locoregional disease on cross-sectional imaging. Patients were followed according to current guideline recommendations, with urine cytology, white light cystoscopy, and imaging every 3–4 mo in the first 2 yr, every 6 mo in years 3–5, and yearly thereafter.

2.1. Statistical analysis

Median values with interquartile ranges (IQRs) were determined for quantitative variables and absolute numbers with the respective percentages for qualitative variables. Comparisons were performed using Student *t* or chi-square test. Pre-NLR, pretreatment LMR (pre-LMR), and pretreatment PLR (pre-PLR) were determined by dividing the absolute neutrophil, monocyte, and platelet serum counts, respectively, by the absolute lymphocyte count before RT. Similarly, post-treatment NLR, LMR, and PLR (post-NLR, post-LMR, and post-PLR, respectively) were based on blood tests collected during the last week of RT. Dynamic changes in NLR, LMR, and PLR were explored by calculating the percentage of increase (or decrease) in these biomarkers during treatment.

To identify factors associated with CR, pretreatment variables were analyzed with a univariable logistic regression test. Variables with a *p* value of <0.2 were included in a stepwise multivariable model. If significantly associated with CR ($p < 0.05$), a cutoff for the pretreatment serum biomarker was defined using the receiver operating characteristic (ROC) curve and the point with the highest sensitivity and specificity (Youden index).

Surveillance started on the last day of RT. For survival analysis, patients were censored at the last follow-up date, and deaths due to bladder cancer and any cause were counted as events for CSS and OS, respectively. Kaplan-Meier curves and log-rank test were used to estimate CSS and OS. A Cox multivariable regression model including pretreatment variables with a *p* value of <0.2 in a univariable analysis

was performed. Log linearity was verified for quantitative variables, and the proportional hazard assumptions were verified for all variables. To avoid a potential interaction between NLR, LMR, and PLR, pretreatment parameters were tested separately into consecutive multivariable models together with other clinicopathological variables. Furthermore, the dynamic changes in NLR, LMR, and PLR were studied in a separate multivariable model, now including both pre- and post-treatment variables. For this purpose, the median percentage of increase (or decrease) during TMT was used as a cutoff. Statistical significance was set at a p value of <0.05. Statistical analysis and plots were performed using SAS software (version 9.2; SAS Institute, Cary, NC, USA) and RStudio (version 1.4.1717, © 2009–2021; RStudio, Inc., Integrated Development Environment for R, PBC, Boston, MA, USA).

3. Results

A total of 176 patients were included. Clinicopathological characteristics are listed in Table 1. All patients had urothelial carcinoma as their primary histology, and secondary differentiation was present in 24 (14%) patients; squamous-cell (5%) and glandular (5%) carcinomas were most common. RT was delivered at a median dose of 50 Gy (range 44.0–66.6 Gy), in a median of 20 fractions (range 16–42). Cisplatin-based neoadjuvant chemotherapy (NAC) was given to 29 (16%) patients. Concurrent chemotherapy was administered to all patients during the RT course. Gemcitabine alone (63.1%, at a weekly dose of 100 mg/m^2) and cisplatin alone (11.4%, at a weekly dose of 40 mg/m^2) were the most common regimens.

3.1. Pre- and post-treatment serum-derived biomarkers

The median values of pre- and post-treatment serum biomarkers for the entire cohort are shown in Table 1. Patients with a low pre-LMR were slightly older ($p = 0.02$) and had worse Eastern Cooperative Oncology Group performance status (ECOG PS; $p = 0.03$) than those with a high pre-LMR. Patients with a high pre-PLR were older than those with a low pre-PLR ($p = 0.04$). Patients with low post-LMR and high post-PLR values were more likely treated with gemcitabine-based concurrent chemotherapy ($p = 0.032$ and 0.012, respectively) compared with other regimens (Supplementary Tables 1–3). Considering pre- and post-treatment values, NLR and PLR increased at a median of 75.8% (IQR 14.1–164.4) and 122.8% (IQR 43.1–236.1), respectively, while LMR decreased at a median of 53.4% (IQR 27.1–71.7) during TMT.

3.2. CR to TMT

A CR was confirmed in 127 (72.2%) patients. Pre-NLR was the only significant pretreatment serum biomarker associated with CR in the univariable analysis (Table 2 and Supplementary Table 4). In a multivariable analysis, pre-NLR (odds ratio [OR] 0.79, 95% confidence interval [CI] 0.65–0.96; $p = 0.015$) and the use of NAC (OR 0.22, 95% CI 0.08–0.58; $p = 0.002$) were independent predictors of a lower rate of CR. A cutoff of the pre-NLR was established at 4.0. In the multivariable analysis, a pre-NLR of ≥4.0 remained associated with lower rates of CR (OR 0.32, 95% CI 0.13–0.79; $p = 0.013$; Table 3).

Table 1 – Demographic and clinicopathological information for the total cohort

Characteristic	Total ($n = 176$)	
	n or Median	% or IQR
Age (yr)	75	66–82
Gender		
Male	134	76.1
Female	42	23.9
ECOG PS		
0–1	153	86.9
2–3	23	13.1
Tumor stage		
cT2	156	88.6
cT3–4a	26	11.4
Nodal stage		
cN0	159	90.3
cN1–2	17	9.7
CIS		
Yes	56	31.8
No	120	68.2
LVI		
Yes	50	28.4
No	125	71.0
Missing	1	0.6
Hydronephrosis		
Yes	33	18.7
No	142	80.7
Missing	1	0.6
Neoadjuvant chemotherapy		
Yes	29	16.5
No	147	83.5
Complete TURBT		
Yes	137	77.8
No	37	21.0
Missing	2	1.2
CR to TMT		
Yes	127	72.2
No	31	17.6
Missing	18	10.2
Salvage RC		
Yes	16	9.1
No	160	90.9
Pre-NLR	2.8	1.9–2.9
Post-NLR	4.7	3.3–7.5
NLR increase (%)	75.8	14.1–164.4
Pre-LMR	2.7	2.0–3.7
Post-LMR	1.3	0.8–2.0
LMR decrease (%)	53.4	27.1–71.7
Pre-PLR	136	105–182
Post-PLR	312	215–439
PLR increase (%)	122.8	43.1–236.1

CIS = carcinoma in situ; CR = complete response; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LMR = lymphocyte-to-monocyte ratio; LVI = lymphovascular invasion; n = number; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; PS = performance status; RC = radical cystectomy; TMT = trimodal therapy; TURBT = transurethral resection of bladder tumor.

3.3. Survival analysis

The median follow-up for survivors was 46 mo (95% CI 31–62). Estimated 5-yr CSS and OS rates were 61% (95% CI 52–71) and 47% (95% CI 39–55), respectively. Patients with a pre-NLR of ≥4.0 experienced worse median CSS (129 vs 55 mo; $p = 0.059$) and OS (64 vs 24 mo; $p = 0.007$) compared with patients with a pre-NLR of <4.0 (Fig. 1).

Univariable Cox regression analyses for CSS and OS are shown in Table 2 and Supplementary Table 4. Including only pretreatment variables in a multivariable analysis, pre-NLR ≥4.0 was independently associated with worse CSS (hazard ratio [HR] 1.88, 95% CI 1.04–3.43; $p = 0.038$) together with hydronephrosis (HR 2.66, 95% CI 1.43–4.95;

Table 2 – Univariable logistic regression analysis of the effect of pre-treatment NLR, LMR, and PLR on CR, and univariable Cox regression analysis of pre- and post-treatment, and dynamic patterns of NLR, LMR, and PLR on CSS and OS

Total cohort	Univariable analysis								
	Logistic regression			Cox regression—CSS			Cox regression—OS		
	OR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Pre-NLR	0.82	0.68–0.99	**0.035**	1.09	0.98–1.21	0.121	1.09	1.01–1.18	**0.033**
Pre-LMR	1.03	0.87–1.22	0.698	0.97	0.84–1.12	0.657	0.88	0.73–1.05	0.155
Pre-PLR	1.00	0.99–1.00	0.130	1.00	1.00–1.01	**0.013**	1.00	1.00–1.01	**0.008**
Post-NLR	–	–	–	1.05	1.01–1.10	**0.031**	1.06	1.02–1.10	**0.002**
Post-LMR	–	–	–	0.90	0.71–1.14	0.379	0.85	0.69–1.05	0.126
Post-PLR	–	–	–	1.00	1.00–1.00	**<0.001**	1.00	1.00–1.00	**<0.001**
NLR increase									
<75%	–	–	–	REF			REF		
≥75%	–	–	–	1.00	0.99–1.01	0.810	1.35	0.90–2.03	0.149
LMR decrease									
<50%	–	–	–	REF			REF		
≥50%	–	–	–	2.28	0.32–16.6	0.414	1.41	0.45–4.47	0.555
PLR increase									
<120%	–	–	–	REF			REF		
≥120%	–	–	–	1.84	1.05–3.22	**0.034**	1.45	0.98–2.16	0.063

CI = confidence interval; CR = complete response; CSS = cancer-specific survival; HR = hazard ratio; LMR = lymphocyte-to-monocyte ratio; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio; OS = overall survival; PLR = platelet-to-lymphocyte ratio; REF = reference.[a]
[a] Significant p-values (<0.05) are represented in bold.

Table 3 – Multivariable logistic regression analysis for CR to TMT and multivariable Cox regression analysis for CSS and OS including pre-TMT baseline variables

Total cohort	Multivariable analysis								
	Logistic regression			Cox regression—CSS			Cox regression—OS [a]		
	OR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
ECOG PS									
0–1	–	–	–	–	–	–	REF		
2–3	–	–	–	–	–	–	2.32	1.39–3.88	**0.001**
Tumor stage									
cT2	–	–	–	–	–	–	REF		
cT3-4a	–	–	–	–	–	–	2.07	1.18–3.63	**0.011**
Hydronephrosis									
No	–	–	–	REF			–	–	–
Yes	–	–	–	2.66	1.43–4.95	**0.002**	–	–	–
NAC									
No	REF			–	–	–	–	–	–
Yes	0.22	0.08–0.58	**0.002**	–	–	–	–	–	–
Pre-NLR									
<4.0	REF			REF			REF		
≥4.0	0.32	0.13–0.79	**0.013**	1.88	1.04–3.43	**0.038**	1.61	1.04–2.48	**0.033**

CI = confidence interval; CR = complete response; CSS = cancer-specific survival; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NAC = neoadjuvant chemotherapy; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio; OS = overall survival; PS = performance status; REF = reference.[b]
[a] Multivariable Cox regression analysis for OS considering pre- and post-TMT variables: age (HR = 1.03, 95% CI 1.00–1.06; *p* = 0.022), ECOG PS (HR = 2.08, 95% CI 1.14–3.81; *p* = 0.018), CR (HR = 0.34, 95% CI 0.20–0.57; *p* < 0.001), and increase in NLR ≥75% (HR = 1.63, 95% CI 1.04–2.56; *p* = 0.035).
[b] Significant p-values (<0.05) are represented in bold.

p = 0.002). A pre-NLR of ≥4.0 was also associated with worse OS (HR 1.61, 95% CI 1.04–2.48; *p* = 0.033), together with ECOG PS (HR 2.32, 95% CI 1.39–3.88; *p* = 0.001) and cT stage (HR 2.07, 95% CI 1.18–3.63; *p* = 0.011; Table 3). When both pre- and post-treatment variables were included, an increase in NLR of ≥75% (HR 1.63, 95% CI 1.04–2.56; *p* = 0.035), together with age (HR 1.03, 95% CI 1.00–1.06; *p* = 0.022), ECOG PS (HR 2.08, 95% CI 1.14–3.81; *p* = 0.018), and CR (HR 0.34, 95% CI 0.20–0.57; *p* < 0.001) were associated with OS. We also evaluated the role of pre-NLR only among a subset of patients (*n* = 127) who achieved a CR after TMT. Pre-NLR was independently associated with worse OS (but not CSS) in the multivariable analysis (HR = 1.68, 95% CI 1.02–2.78; *p* = 0.042) based on this subset of patients.

4. Discussion

We demonstrated that a pre-NLR of ≥4.0 was associated with lower rates of CR and worse survival outcomes (CSS and OS). Furthermore, an increase in NLR of ≥75% during TMT (post-NLR being ≥1.75 times than pre-NLR) was found to be prognostic for worse OS.

4.1. NLR and bladder cancer

Previous meta-analyses on retrospective data have consistently shown the prognostic value of the NLR in both the non–muscle-invasive and the metastatic setting [3,12–15]. Specifically for nonmetastatic MIBC, most studies on NLR included patients treated with RC [16–18]. In a multicenter
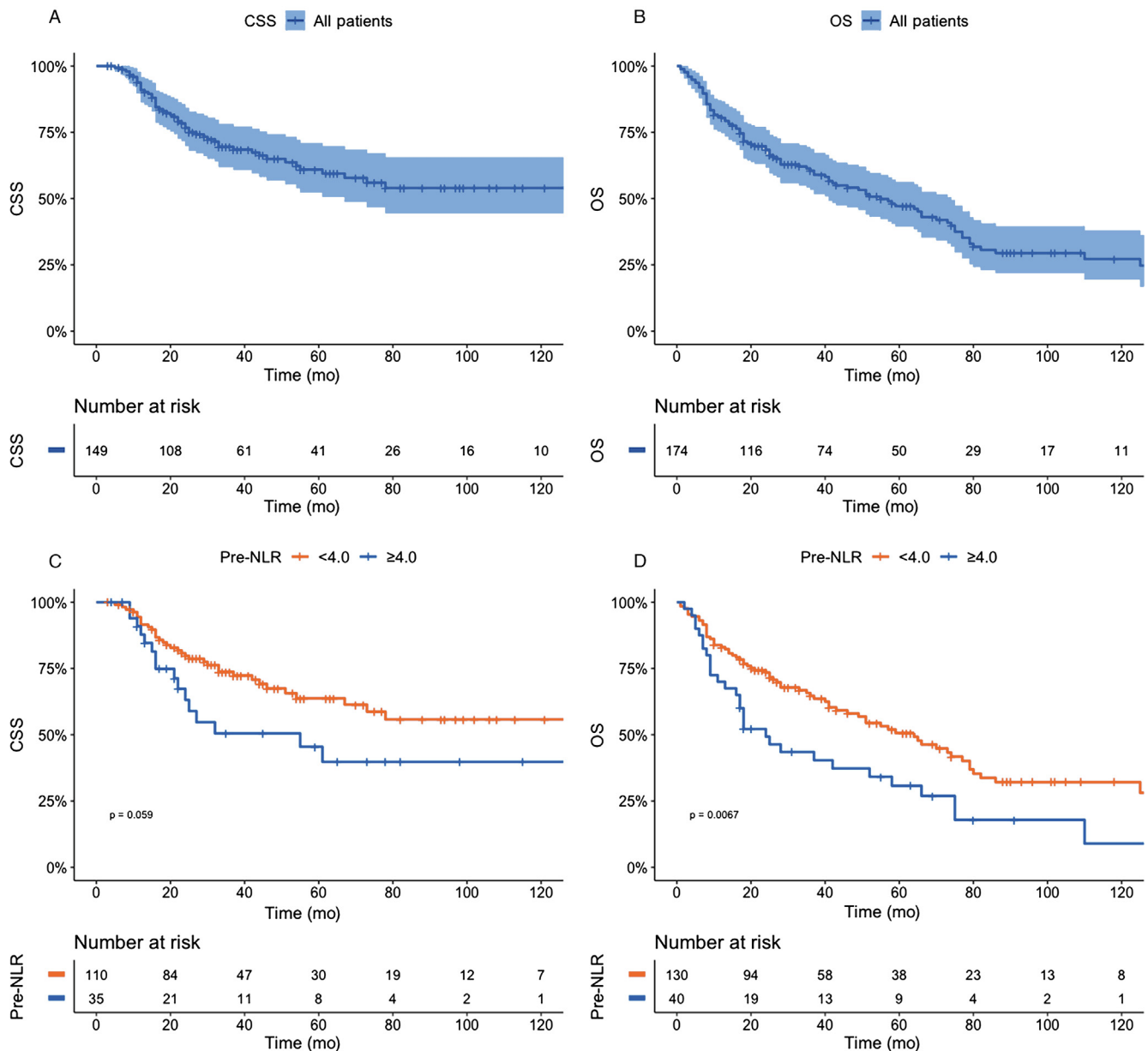
Fig. 1 – (A and B) Cancer-specific and overall survival Kaplan-Meier plots for all patients and (C and D) stratified by pre-NLR status. CSS = cancer-specific survival; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival.

study including ten academic institutions and >4000 patients treated with RC (without NAC), Lucca et al [19] evaluated and validated NLR as a prognostic factor associated with worse survival outcomes. In their analysis, an NLR of ≥2.7 (cutoff based on visual assessment of a functional form associated with patients' outcomes) correlated with advanced-stage disease and was independently associated with CSS and OS [19].

Two recent studies have explored pre-NLR in patients with MIBC undergoing RT-based therapy. Hurmuz et al [9] analyzed 44 patients treated with TMT, and pre-NLR was significantly associated with worse CSS (HR = 3.15; p = 0.043). In their study, complete transurethral resection of the bladder tumor (TURBT) was achieved in 55% of patients, 23% had stage cT3–4, and 27% had hydronephrosis [9]. Sim-

ilarly, another retrospective study by Wu et al [10] analyzed 193 MIBC patients treated with RT-based therapy. They showed that a pre-NLR higher than the median was significantly associated with shorter survival (PFS and bladder-preservation survival) and lower rates of CR to TMT [10]. In that study, 31% of patients had locally advanced T3–4 disease and 41% were treated with only one cycle of concurrent chemotherapy [10]. Our study corroborates with these previous findings where a high pre-NLR was associated with CR, CSS, and OS. Importantly, our cohort was possibly more homogenous, consisted of patients with more favorable disease (complete TURBT was performed in 78%; stage cT3–4 and hydronephrosis were reported in 11% and 18%, respectively), and was treated with strict contemporary TMT protocols. In addition, the cutoff of 4.0 was defined

by the ROC curve for predicting CR (a strong predictor of OS), rather than a median value that is dependent on a particular studied population.

4.2. Dynamics of serum-derived biomarkers during TMT

The dynamic patterns of serum biomarkers seem to correlate with oncological outcomes, and we observed shorter OS among patients with an increase of $\geq$75% in NLR during TMT. In the multivariable analysis, this increase in NLR had an independent impact on OS when included with pre- and post-treatment endpoints. A study by Kaiser et al [20] evaluated the impact of changes in NLR during NAC in 296 patients with MIBC who subsequently underwent curative-intent RC (73%) or RT-based therapy (13%). Patients were stratified into four categories based on pre- and post-NAC NLR, resulting in the "low-low", "low-high", "high-low", and "high-high" subgroups. They showed that patients with a sustained high NLR during NAC experienced worse disease-free survival and OS than those with a sustained low NLR [20]. Another study in patients with metastatic urothelial carcinoma treated with immunotherapy (pembrolizumab) demonstrated that those with a reduction of $\geq$25% in the values of NLR during treatment had improved PFS and CSS [21].

During the first weeks of treatment, RT induces a series of biological responses in the irradiated tissue, which are followed by a systemic release of proinflammatory mediators, resulting in the recruitment of neutrophils to the tumor site and a decreased absolute number of intratumoral lymphocytes [22,23]. As verified in our cohort, the NLR most commonly increases during TMT due to RT-induced local inflammatory reaction. The role of neutrophils in cancer growth and response to RT, however, remains controversial as both pro- and antitumor mechanisms have been proposed in the literature [24,25]. Recently, Morizawa et al [26] investigated the correlation between NLR and the tumor microenvironment using immunohistochemistry in 58 bladder cancer specimens after RC. They showed that pre-TURBT NLR correlated with the expression of Foxp3, a known marker for Treg cells, which are considered critical suppressors of antitumor responses that maintain immunological tolerance to host tissues [26]. No association was observed between serum pre-NLR and the concentration of neutrophils within the local tumor microenvironment in that study [26].

Whether RT-induced inflammation results in pro- or antitumor function is also controversial in the literature [27], and further studies are needed to define how changes in NLR during RT-based therapy correlate with carcinogenesis and survival. Additionally, studies on the role of molecular signatures and patterns of tumor cell infiltration in MIBC treated with TMT are warranted to determine how serum and tumor inflammatory mediators interact.

4.3. LMR and PLR

To the best of our knowledge, this is the first study evaluating the role of LMR or PLR in MIBC patients managed with TMT. In a study by Zhang et al [5] assessing LMR and PLR in 124 patients undergoing RC for MIBC, LMR was the only independent marker associated with OS. Yoshida et al [28] reviewing 323 patients after RC also demonstrated that sustained low levels of LMR resulted in worse OS and CSS compared with a sustained high LMR. A meta-analysis including eight studies and 3303 patients with bladder cancer undergoing RC confirmed the role of pre-PLR in predicting OS (HR 1.26, p = 0.026) [29]. Another study even suggested that pre-PLR might be a superior biomarker than pre-NLR in predicting oncological outcomes of patients undergoing RC [30]. In the multivariable analysis of our cohort, LMR and PLR were independent predictors of neither CR nor OS. Whether the lack of an independent association of LMR and PLR with the outcomes after TMT was particular to our cohort or might specifically be related to chemoradiation for MIBC requires further investigation.

4.4. Limitations

Besides the retrospective single-center design, other limitations should be noted in our study. Whether variation in the RT volume, dose, and the different radiosensitizing agents used to treat our patients may have impacted the biomarker ratios remains to be determined. NAC was administered to 16.5% of our patients. Not only the median levels of pre-NLR among patients who underwent and those who did not undergo NAC were comparable (2.56 [IQR 1.97–3.46] and 2.85 [IQR 1.95–3.97], respectively; p = 0.074), but also the proportion of patients undergoing NAC was similar across subgroups of high versus low pre-NLR (17.1% vs 16.9%; p = 1.0). Moreover, although we did not observe any confounding role in survival outcomes, NAC was associated with lower rates of CR most likely as a result of a selection bias, as patients receiving NAC were those harboring more advanced disease, with a higher proportion of cT3–4 stage (34.5% vs 6.8%; p < 0.001), cN+ (44.8% vs 2.7%; p < 0.001), and incomplete initial TURBT (44.8% vs 16.3%; p = 0.001).

Finally, whether inflammatory biomarkers might be useful in predicting response to TMT and selecting ideal patients for bladder preservation versus RC requires further evaluation with studies designed to compare both strategies. Our study did not compare TMT versus RC based on the use of serum biomarkers; thus, whether patients with a high pre-NLR should be counseled toward one therapeutic strategy to the detriment of the other remains unanswered. Nevertheless, serum-derived biomarkers are inexpensive, noninvasive, and readily accessible through routine blood tests during chemoradiation. Although prospective validation is needed, these biomarkers may be integrated into clinical practice, aiming for rational counseling and tailored follow-up of MIBC patients undergoing RT-based bladder preservation.

5. Conclusions

A pre-NLR of $\geq$4.0 was independently associated with lower rates of CR to TMT and worse CSS and OS after TMT. Depending on prospective validation, this serum lymphocyte-based biomarker may be integrated into clinical practice for counseling MIBC patients undergoing

curative-intent TMT and may prove to be a useful tool for a tailored follow-up. Further studies are needed to determine whether these biomarkers may also aid in refining the selection of patients for RC versus TMT.

Author contributions: Wassim Kassouf had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kool, Kassouf.
Acquisition of data: Kool, Kassouf.
Analysis and interpretation of data: Kool, Marcq, Mansure, Kassouf.
Drafting of the manuscript: Kool, Marcq, Kassouf.
Critical revision of the manuscript for important intellectual content: Shinde-Jadhav, Mansure, Saleh, Rajan, Aprikian, Tanguay, Cury, Brimo, Souhami, Kassouf.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2021.11.011.

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