CANCER DIAGNOSIS & PROGNOSIS
3: 706-715 (2023) doi: 10.21873/cdp.10275

Pretreatment PLR Is Preferable to NLR and LMR as a Predictor in Locally Advanced and Metastatic Bladder Cancer

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Abstract. *Background/Aim: Advanced bladder cancer (BC) is associated with an inflammatory nature and poor prognosis Inflammatory biomarkers are potential predictors in BC. We conducted a study to assess the prognostic value of the pretreatment neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) in advanced bladder cancer. Patients and Methods: A total of 226-patients with muscle-invasive BC (MIBC) were included. Overall (OS) and progression-free survival were estimated using the Kaplan–Meier method and the log-rank test was used for comparison. Univariate and multivariate Cox proportional hazard models were used to determine NLR, PLR, and LMR association with OS. Results: Our patients' median progression-free survival and OS were 12.18 and 15.54 months, respectively. Receiver operating characteristic analysis revealed cut-off values for our chosen inflammatory markers. The patients with high NLR or PLR had inferior median OS compared to their counterparts with lower ratios for both (NLR: 22.51 vs. 9.84 months, respectively, p≤0.001; PLR: 17.68 vs. 14.08 months, respectively, p=0.08). Meanwhile, patients with low LMR had inferior median OS compared to patients with higher LMR (LMR: 20.14 months vs. 10.55 months, respectively, p<0.001). The multivariate Cox regression analysis identified a high PLR as an independent predictive factor of worse OS (hazard ratio=2.774, 95% confidence interval=1.486-5.178, p=0.001) but not NLR or LMR. Conclusion: PLR, C-reactive protein-to-albumin ratio, and serum LDH levels, but not NLR and LMR, may function as independent predictors in patients with advanced BC prior to systemic treatment.*

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Key Words: Bladder cancer, inflammation markers, LMR, NLR, overall survival, PLR, prognostic factors.

Bladder cancer (BC) ranks as the ninth most common cancer worldwide (1) and its incidence has increased over the past few decades. Clinically, histology classifies it into two significant groups: non-muscle-invasive BC and muscle-invasive BC (MIBC) (2, 3). While urologists adopt local therapy approaches for non-MIBC, MIBC is managed systemically in medical oncology clinics. MIBC is invasive and can progress to metastatic disease, usually by local invasion of surrounding pelvic structures. Patients with MIBC represent 25% of newly diagnosed cases, and approximately 90% have urothelial cell histology, also known as transitional cell carcinoma (TCC) (4). Their 5-year survival rate ranges from 38% for the population with extension through the bladder to surrounding tissue, or spread to lymph nodes or nearby organs, to 6% for patients with distant metastasis (4).

This makes MIBC, especially stage IV cases, a treatment-resistant disease, and the only benefit of systemic therapy is palliation. Platinum-based therapy constitutes the first line of treatment (5). The most effective platinum agent is believed to be cisplatin and challenging as it is, using cisplatin may not be feasible in all patients due to their poor kidney

function and poor performance status (6). These patients routinely receive a carboplatin-based regimen to overcome toxicities associated with cisplatin. However, it has inferior outcomes compared to cisplatin (7). Whether TCC is resistant to therapy or responsive is unclear; some tests, such as circulating tumor DNA, radiological imaging, and inflammatory marker-driven pathogenesis can indicate this. Additionally, inflammatory marker-based assays have been proposed as a predictive tool for identifying these patients (8). Further research has considered cellular inflammatory indices as determinants of systemic response, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). They have been found to affect tumor recurrence and progression, but the results reported so far are contradictory. While Bambury *et al*. (9) found a significant correlation between lower NLR and improved overall survival (OS), Kuwada *et al*. (10) did not demonstrate it to be a significant indicator in patients diagnosed with BC. PLR has been studied as another marker of inflammation. In a meta-analysis, an increased PLR was not found to be a significant indicator for OS [hazard ratio (HR)=1.23, 95% confidence interval (CI)=0.95-1.59, p=0.124] of patients with BC (11).

In this study, we report our results based on our experience with our patients, aiming to provide further insight into the clinical value of the impact of systemic inflammatory markers NLR, PLR and LMR on OS in patients with advanced MIBC receiving first-line chemotherapy.

Patients and Methods

Patients. The files of patients admitted to the Department of Medical Oncology, Pamukkale University, Turkey, with a diagnosis of MIBC from 2008 until 2020 were retrospectively analyzed. Two hundred and twenty-six consecutive patients with advanced BC treated with chemotherapy with or without definitive/palliative radiotherapy were identified after 56 patients were excluded from the total population. All patients had pathologically confirmed advanced urothelial MIBC. A few cases with squamous and sarcomatous differentiation were also included in our cohort. These patients received first-line standard-of-care treatment with chemotherapy (platin plus gemcitabine, methotrexate with vinblastine, doxorubicin and cisplatin or single-agent gemcitabine) until progression, death, or toxicity. Patients with acute or chronic infection, autoimmune or hematological diseases, patients with chronic liver and renal diseases, patients receiving drugs that had a potential effect on the measured parameters, and patients ineligible for chemotherapy were considered ineligible and excluded from our analyses. According to our institutional guidelines, patients had a complete blood count within a median of 3 days (range=0-7 days) before the initiation of chemotherapy. TNM classification was according to the eighth edition of the American Joint Committee on Cancer (2017) (12), and patients were divided into two risk groups according to the TNM classification: Stage 3 (locally advanced disease) and stage 4 (metastatic disease). Demographics and clinicopathological characteristics were collected from the patient's electronic records. Institutional Review Board approval was obtained from the local Ethics Committee prior to all studies (Pamukkale University Ethical Comittee: 22.06.2021; Number 12) and all procedures were performed according to the Helsinki Declaration and its subsequent amendments.

Predictor variables. Three variables were hypothesized as possible predictors of death with prognostic significance: NLR, PLR, and LMR. They were calculated as the absolute neutrophil count divided by the absolute lymphocyte count for NLR, the absolute platelet count divided by the absolute lymphocyte count for PLR, and the absolute lymphocyte count divided by the absolute monocyte count for LMR. Progression-free survival was measured from the initiation of chemotherapy to progression or death. OS was measured from the initiation of chemotherapy until to the last follow-up or death.

Statistical analysis. Continuous variables are presented as the median with interquartile range, and dichotomous variables as percentages. Mann–Whitney U-tests and chi-square tests were used to compare continuous and categorical variables in independent groups. Kaplan–Meier method was used for survival analyses, and a log-rank test was performed to compare the differences between sub-groups. Receiver operator characteristics curves with Youden's J index were plotted to determine the optimal cut-off values for NLR, PLR, LMR, and other factors, such as C-reactive protein-to-albumin ratio (CAR), lactate dehydrogenase enzyme (LDH), and hemoglobin for predicting OS. Univariate and multivariate analyses were performed using Cox proportional-hazards regression models to define risk factors for OS. Multivariate analyses were performed using variables with a value of $p<0.05$ in univariate analyses and the backward elimination method. The statistical analyses in the present study were performed using SPSS v25 (IBM Inc., Armonk, NY, USA) software, and value of $p<0.05$ were considered statistically significant.

Results

Patient characteristics. The male/female ratio was 10.8 (n=207/19) and the median age was 67 years. Histological subtype results were available for 97% of the cases and tumor grade for 90%. Demographic and clinical parameters of all cases were complete and well-documented. The second and third lines of therapy included chemotherapy, vinflunine, and atezolizumab/pembrolizumab/nivolumab. Histologically, our study population comprised patients with urothelial MIBC (TCC) (n=226). According to the TNM scoring system, the percentage of patients with locally advanced and metastatic disease was 48.2% and 51.8%, respectively.

By performing the receiver operating characteristics analysis, an NLR value of 3.29 was found to be the optimal cut-off for predicting OS [area under the curve (AUC)=0.64; sensitivity=59%; specificity=68%; p=0.001]. The optimal PLR cut-off for predicting OS was 169.38 (AUC=0.68; sensitivity=65%; specificity=71%; $p<0.0001$) and that for LMR was 2.73 (AUC=0.68; sensitivity=47%; specificity=81%; $p<0.0001$) (Figure 1).

The patients' baseline demographic, clinical, and histopathological characteristics were stratified according to

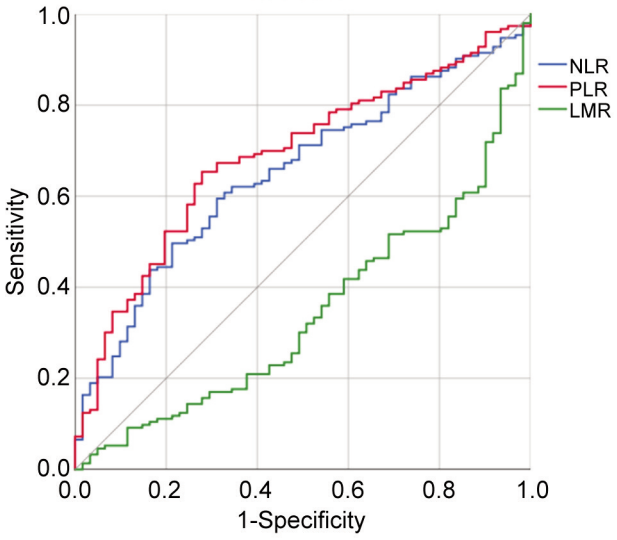


Figure 1. *Cut-off values for neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) as risk factors affecting overall survival by receiver operating characteristic analysis.*

NLR, PLR, and LMR. The values are summarized in Table I. Patients with an elevated PLR exhibited a higher incidence of metastatic stage (p=0.014), elevated CAR levels (p<0.001), and lower hemoglobin levels (p<0.001) before chemotherapy. Additionally, patients with elevated NLR demonstrated a higher incidence of extensive stage (p<0.001) and liver metastasis (p=0.018), absence of cystectomy (p=0.004), elevated CAR levels (p<0.001) and LDH levels (p=0.040), and lower hemoglobin levels (p<0.001). Furthermore, patients with a lower LMR displayed a higher incidence of metastatic stage (p<0.001), absence of cystectomy (p=0.026), elevated CAR levels (p<0.001), and lower hemoglobin levels (p<0.001). No significant differences were observed among the three groups when examining additional characteristics, such as age, sex, smoking history, intravesical BCG therapy history, bone metastasis, lung metastasis, and brain metastasis.

The prognostic significance of NLR, PLR, and LMR for OS. The median progression-free survival of our patient cohort was 12.18 months, and the median OS was 15.54 months. Seventy-one percent (n=162) of our patients died within a median follow-up period of ≈15 months (range=0.13-147.55 months). Patients with a high NLR or PLR had inferior median OS compared to their counterparts with lower values for these (NLR: 22.51 *vs*. 9.84 months, respectively, p≤0.001; PLR: 17.68 *vs*. 14.08 months, respectively, p=0.08). Meanwhile, patients with a low LMR had significantly inferior median OS compared to those with a high LMR (20.14 *vs*. 10.55 months, respectively, p<0.001) (Figure 2). The 3-year survival rates of patients with high and low NLR were 17.2% and 47.6%, respectively; whilst those for PLR were 24.3% and 41.7%, and for LMR were 41.3% and 16.0%, respectively.

In the univariate Cox analysis, older age (p=0.008), male sex (p=0.032), no previous history of BCG treatment (p=0.017), distant metastasis (p<0.001), bone metastasis (p<0.001), lung metastasis (p=0.007), liver metastasis (p=0.001), history of cystectomy (p=0.008), LMR ≤2.73 (p<0.001), NLR >3.29 (p<0.001), PLR >169.38 (p<0.001), CAR >0.33 (p<0.001), LDH >194 U/l (p<0.001), hemoglobin ≤12.3 g/dl (p<0.001) were determined to be significant prognostic factors for shortened median OS (Table II). However, in multivariate Cox analyses, as shown in Table II, PLR >169.38, not NLR and LMR, was an independent indicator of median OS (HR=1.634 95% CI=1.108-2.410, p=0.013). In addition to PLR, five other independent factors identified as conferring poorer median OS were no previous history of BCG treatment (HR=2.716, 95% CI=1.708-4.319, p<0.001), bone metastasis (HR=1.447, 95% CI=0.979-2.139, p=0.064), lung metastasis (HR=1.579, 95% CI=1.064-2.345, p=0.023), CAR >0.33 (HR=2.337, 95% CI=1.083-2.325, p<0.001), and LDH >194 U/l (HR=1.587, 95% CI=1.083-2.325, p=0.018).

Discussion

Our study investigated markers of inflammation in MIBC and their impact on survival. This report shows results for 226 patients with stage III and IV invasive MIBC who presented to the Department of Medical Oncology, Pamukkale University, Turkey. All patients received the standard treatment of chemotherapy (mostly platinum-based) with/without local surgery or radiotherapy, according to the institutional guidelines and as per the National Comprehensive Cancer Network guidelines (13). Although chemotherapy improves the survival rates of chemotherapy-eligible patients with BC (stage III and IV), heterogeneity exists among patient groups.

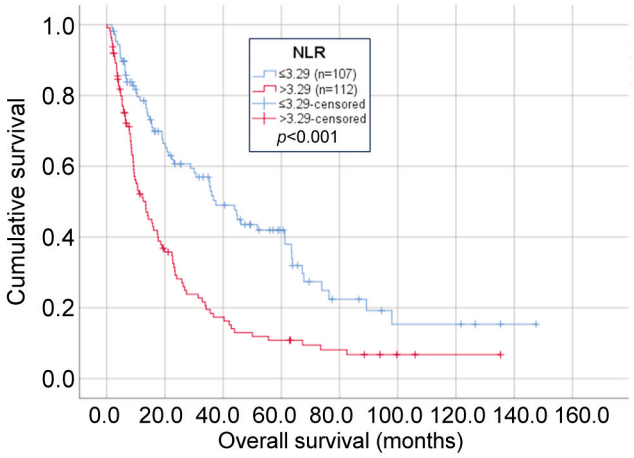
We selected NLR, PLR and LMR as novel inflammatory biomarkers to evaluate their predictive and prognostic value in late-stage BC. They have the advantages of convenience of access, being blood-based biomarkers, and being readily available from routine blood work on patients with cancer, particularly in retrospective cohorts. Previously, some studies investigated scoring systems for the prognosis of patients receiving chemotherapy as first-line treatment for metastatic BC and their relation to responses and survival outcomes. Significant indicators in these scoring systems were normal alkaline phosphatase, normal hemoglobin, high Karnofsky prognostic score, and older age (>60 years) (14). One study identified Karnofsky performance score of less than 80% and visceral metastasis as predictive factors for both response and

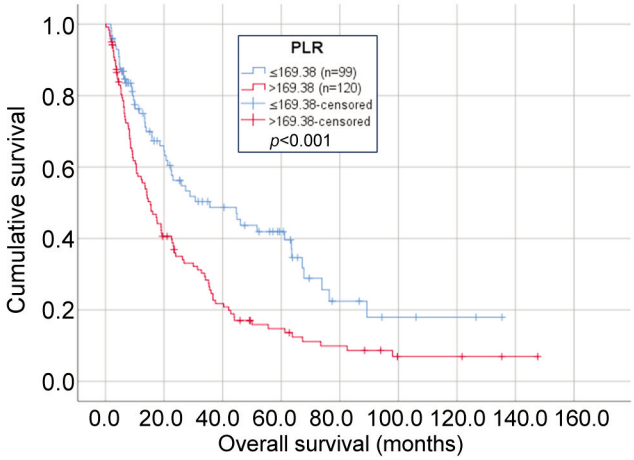
Table I. *Baseline clinicopathologic characteristics of the patients in patients with muscle-invasive bladder cancer stratified based on platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) cut-offs.*

	PLR			NLR			LMR		
	≤169.38 (n=99)	>169.38 (n=120)	*p*-Value	≤3.29 (n=107)	>3.29 (n=112)	*p*-Value	≤2.73 (n=83)	>2.73 (n=131)	*p*-Value
Age, years									
Mean±SD	66.3±10.6	67.2±9.3	0.658	67.1±9.9	66.5±9.9	0.791	68.1±9.2	65.9±10.1	0.130
Sex (%)									
Male	96	88.3	0.072	91.6	92	>0.99	95.2	90.8	0.363
Female	4	11.7		8.4	8		4.8	9.2	
Stage (%)*									
3	57.6	40.8	**0.014**	62.6	34.8	**<0.001**	38.6	55.7	**0.014**
4	42.4	59.2		37.4	65.2		61.4	44.3	
Smoking history (%)									
No	14.1	24.2	0.091	18.7	20.5	0.862	20.5	17.6	0.723
Yes	85.9	75.8		81.3	79.5		79.5	82.4	
Intravesical BCG (%)									
No	81.2	79.8	0.957	80	80.8	>0.99	82.4	78.3	0.608
Yes	18.8	20.2		20	19.2		17.6	21.7	
Bone metastasis (%)									
No	76.8	65.8	0.105	78.5	63.4	0.021	68.7	71.8	0.630
Yes	23.2	34.2		21.5	36.6		31.3	28.2	
Lung metastasis (%)									
No	74.7	72.5	0.708	79.4	67.9	0.074	69.9	75.6	0.359
Yes	25.3	27.5		20.6	32.1		30.1	24.4	
Liver metastasis (%)									
No	91.9	88.3	0.514	95.3	84.8	**0.018**	88	91.6	0.523
Yes	8.1	11.7		4.7	15.2		12	8.4	
Brain metastasis (%)									
No	57.1	100	0.236	71.4	75	>0.99	100	62.5	0.491
Yes	42.9	0		28.6	25		0	37.5	
Cystectomy (%)									
No	44.3	52.1	0.256	38.7	58.2	**0.004**	58.5	41.9	**0.026**
Yes	55.7	47.9		61.3	41.8		41.5	58.1	
CAR									
≤0.33	67.3	32.7	**<0.001**	73.1	25.2	**<0.001**	23.1	64.1	**<0.001**
>0.33	32.7	67.3		26.9	74.8		76.9	35.9	
Hemoglobin (g/dl)									
≤12.3	30.3	76.7	**<0.001**	36.4	74.1	**<0.001**	71.1	45.8	**<0.001**
>12.3	69.7	23.3		63.6	25.9		28.9	54.2	
LDH (U/l)									
≤194	53.1	42.1	0.111	54.4	40.2	**0.040**	39.2	51.6	0.085
>194	46.9	57.9		45.6	59.8		60.8	48.4	

BCG: Bacillus Calmette-Guerin treatment; CAR: C-reactive protein-to-albumin ratio; LDH: lactate dehydrogenase; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio. *Stage 3: locally advanced, stage 4: distant metastatic. Statistically significant *p*-values are shown in bold.

survival (15). Another study by Galsky *et al*. reported results from a revised nomogram which included Eastern Cooperative Oncology Group Performance Status, visceral metastases, site of the primary tumor, presence of lymph node metastasis and total leukocyte count as prognostic factors for patients with metastatic BC on chemotherapy. They found that the total leukocyte count had prognostic weight on the outcomes of these patients (16). The nomogram developed by Necchi *et al*. incorporates several parameters, namely white blood cell count, Eastern Cooperative Oncology Group Performance Status, body mass index, presence of lung, liver, or bone metastases, ethnicity, and the administration of perioperative chemotherapy (17). Another NLR parameter examined in this study was recently evaluated in terms of the effectiveness of immunotherapy in patients with metastatic BC (18-20). Nassar *et al*. stated that among clinical variables, NLR <5 is a parameter that indicates immunotherapy effectiveness but does not indicate taxane effectiveness (18).





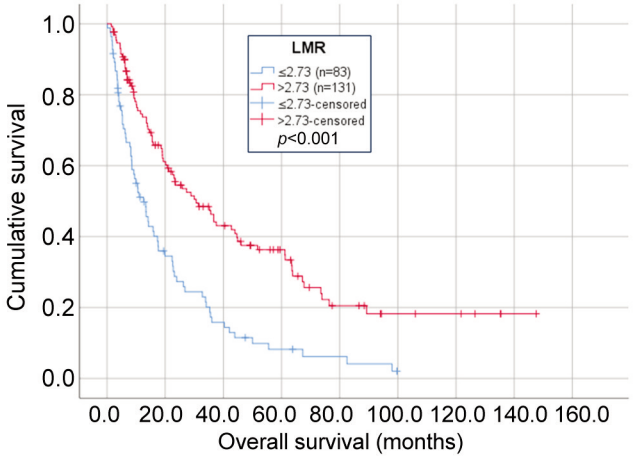


Figure 2. *Demonstration of the Kaplan–Meier curves for overall survival of patients with muscle-invasive bladder cancer stratified according to neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR).*

Sonpavde and Khaki *et al*. also used the LNR parameter to show the effectiveness of immunotherapy (19, 20). Numerous meta-analyses have demonstrated that blood LDH level and CAR are prognostic indicators of poor survival in advanced cancer (21-24). In our case, by multivariate analysis, we were able to show that a PLR >169.38, as well as other established inflammatory markers, such as CAR and serum LDH level, was an independent predictor of OS in stage 3 and 4 BC, while there was no significant association between NLR >3.29 or LMR ≤2.3 and OS.

A closer look at the biology of the immune system and the changes related to the carcinogenic process, development, growth, progression, and metastasis is warranted to identify the importance of these inflammatory biomarkers. Neutrophils and lymphocytes are key players in the inflammatory response (25). Neutrophils often play a pro-inflammatory, pro-tumoral role in the tumor microenvironment (26). Lymphocytes, on the other hand, usually play a defensive role. Neutrophilia occurs as a response to elevated levels of cytokines, such as interleukin-6, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor (27). The microenvironment around precursor and premalignant lesions frequently shows impaired lymphocyte homeostasis and enhanced lymphocyte apoptosis in patients with BC. Under these circumstances, lymphopenia develops (28). However, the exact causes initiating these processes are still not defined. We know that tumor cells can increase expression of transforming growth factor, an important inflammatory mediator, and can express higher lends of pro-apoptotic molecules, such as programmed death-1 ligand-1 and FAS-ligand, causing the destruction of cytotoxic lymphocytes via activation of the extrinsic pathway of apoptosis (29, 30). Increased NLR via either a high level of neutrophils or a low level of lymphocytes, or both, have been shown to result in poor survival outcomes, including of patients with advanced BC receiving systemic therapy in previous studies using cut-off values of NLR ranging from 2.5 to 3 (30-32); in concordance with this, the NLR cut-off in our study for predicting OS was higher at 3.29. In another pooled analysis, high pretreatment NLR was associated with worse survival outcomes (HR=1.63, 95% CI=1.34-1.91) in patients with advanced BC (33). The exact significance of altered PLR and LMR is not yet known. Further investigation is required in BC, especially in subtypes more likely to progress to invasive and metastatic disease. Thrombocytosis is a prognostic factor for worse oncological outcomes in BC. It is usually stimulated by release of growth factors and cytokines from tumor cells, especially interleukin 6, which potently induces platelet production (34). Vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor, thrombospondins, and endostatin can be released from platelets, and they play a major role in

Table II. *Univariate and multivariate Cox regression models analyzing potential parameters for prediction of overall survival in patients with muscle-invasive bladder cancer.*

		Univariate		Multivariate (with backward elimination)	
Variable	Subgroup	HR (95% Cl)	*p*-Value	HR (95% Cl)	*p*-Value
Age		1.021 (1.006-1.037)	**0.008**		
Sex	Female	Reference			
	Male	1.908 (1.057-3.446)	**0.032**		
Pathological stage*	3	Reference			
	4	2.176 (1.582-2.993)	**<0.001**		
Histological differentiation	Pure TCC	Reference			
	Squamous	1.850 (0.864-3.962)	0.114		
	Sarcomatoid	5.820 (1.825-18.566)	**0.003**		
Smoking history	No	Reference			
	Yes	0.956 (0.656-1.392)	0.813		
Intravesical BCG	No	Reference		Reference	
	Yes	1.660 (1.095-2.516)	**0.017**	2.716 (1.708-4.319)	**<0.001**
Bone metastasis	No	Reference		Reference	
	Yes	2.067 (1.492-2.865)	**<0.001**	1.447 (0.979-2.139)	0.064
Lung metastasis	No	Reference		Reference	
	Yes	1.581 (1.134-2.205)	**0.007**	1.579 (1.064-2.345)	**0.023**
Liver metastasis	No	Reference			
	Yes	2.123 (1.351-3.336)	**0.001**		
Brain metastasis	No	Reference			
	Yes	1.055 (0.258-4.307)	0.941		
Progression status	No	Reference			
	Yes	1.253 (0.915-1.715)	0.159		
Cystectomy	No	Reference			
	Yes	1.519 (1.114-2.071)	**0.008**		
LMR	>2.73	Reference			
	≤2.73	2.219 (1.609-3.061)	**<0.001**		
NLR	≤3.29	Reference			
	>3.29	2.208 (1.597-3.052)	**<0.001**		
PLR	≤169.38	Reference		Reference	
	>169.38	1.853 (1.330-2.581)	**<0.001**	1.634 (1.108-2.410)	**0.013**
CAR	≤0.33	Reference	**<0.001**	Reference	
	>0.33	3.031 (2.170-4.233)	**<0.001**	2.337 (1.570-3.478)	**<0.001**
LDH	≤194 U/l	Reference	**<0.001**	Reference	
	>194 U/l	1.841 (1.325-2.557)	**<0.001**	1.587 (1.083-2.325)	**0.018**
Hemoglobin	>12.3 g/dl	Reference	**<0.001**		
	≤12.3 g/dl	2.097 (1.504-2.923)	**<0.001**		

BCG: Bacillus Calmette-Guerin; CAR: C-reactive protein-to albumin ratio; HR: hazard ratio; LDH: lactate dehydrogenase enzyme; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; TCC: transitional cell carcinoma. *Stage 3: locally advanced; stage 4: distant metastatic. Statistically significant *p*-values are shown in bold.

angiogenesis, and the carcinogenic process (35). Monocytes can induce an increase in the number of tumor-associated macrophages in the blood and contribute to tumor infiltration and metastasis. Higher monocytic counts can reflect the activity of tumor-associated macrophages and can be used to predict tumor progression and angiogenesis (36). Altered PLR is associated with poor OS in cancer, such as gastric, lung, and esophageal carcinoma (27, 37-39). Nevertheless, it is unclear whether PLR is a marker predictive of prognosis and therapeutic effect of chemotherapy in patients with advanced BC. Several investigations have been conducted to examine the combined characteristics of NLR and PLR in patients with early-stage BC who have undergone radical cystectomy and transurethral resection of bladder tumor in (40-50). However, there is a scarcity of studies focusing on this patient cohort receiving chemotherapy, and even fewer studies have been conducted in the context of the metastatic stage. A few trials have demonstrated the efficacy of neoadjuvant chemotherapy with complete pathological response, disease-free survival and/or OS in individuals diagnosed with MIBC (10, 51-55). Some studies were not found to be significant for NLR, like our results; Seah *et al*.

indicated no significant association between pretreatment NLR and complete pathological response (HR=0.69, 95% CI: 0.36-1.32, $p=$ 0.26) (51). The study conducted by Ojerholm *et al*. demonstrated that the NLR was not a significant predictor for the response to neoadjuvant chemotherapy (HR=1.01, 95% CI=0.90-1.14; p=0.86) (54). In a study conducted in a metastatic setting, researchers examined the impact of NLR and PLR on OS before the initiation of first-line chemotherapy and found them to be significant (56). Their study included a total of 71 patients. In contrast to their findings, our analysis using a sample size of 226 patients did not yield statistically significant results for the NLR. LMR has been evaluated in several previous reports for its predictive value in patients with different solid tumor types, including hepatocellular carcinoma, colorectal cancer, and lung adenocarcinoma (39, 57, 58). Most studies that focused on the role of LMR as a predictive marker in BC included patients who underwent surgery for early-stage disease. Hai Bi *et al*. found that a higher LMR was an independent predictor of survival in patients after surgery for BC (p<0.001) (59). LMR ≥3 significantly increased OS of patients with BC (HR=0.56, 95% CI=0.35-0.88; p=0.011) in a meta-analysis, but no prognostic value was found in patients with LMR <3 (HR=0.65, 95% CI=0.41-1.04; p=0.075); moreover, the ethnicity, treatment, and analysis method also did not affect the significant predictive value of LMR in patients with BC (60).

Although BC has an immunogenic nature, there is insufficient knowledge in the literature about the functions of inflammatory pathways, immune cells in progression, and immune escape mechanisms in BC.

Limitations of this study are due to its retrospective nature, the fact it was conducted at a single center, with a small sample size, without external validation and using heterogeneous first-line treatments. However, NLR, PLR, and LMR were separately evaluated in predicting OS in most studies mentioned above. We analyzed the impact of these markers on OS in BC patients treated with first-line chemotherapy. Notably, further studies are needed to evaluate the prognostic roles of PLR on BC in larger and more homogeneous populations.

Conclusion

In summary, our results revealed that PLR >169.38 and other markers of inflammation, such as CAR and serum LDH level, the presence of lung metastases and bone metastases, and the absence of intravesical BCG treatment (which means de-novo metastatic disease), were independent prognostic markers for predicting poor OS of patients with BC treated with chemotherapy. PLR can be used as additional prognostic marker for more accurate prognostic prediction and better personalized treatment in patients with BC.

Conflicts of Interest

None declared.

Authors' Contributions

Concept: A.Y. and C.K. Design: A.Y. Supervision: A.Y. Materials: C.K. Data collection &/or processing: C.K. Analysis and interpretation: A.Y., C.K. and A.C. Literature search: C.K. Writing: C.K. Critical review: C.K. and A.Y.

Acknowledgements

This research was made possible by the generosity and support of numerous individuals. The Authors would like to extend their sincere appreciation to everyone indeed and to thank the respondents for this study, who participated and contributed to the success of this investigation.

References

1 Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F: Bladder cancer incidence and mortality: a global overview and recent trends. Eur Urol 71(1): 96-108, 2017. DOI: 10.1016/j.eururo.2016.06.010

2 Jordan B, Meeks JJ: T1 bladder cancer: current considerations for diagnosis and management. Nat Rev Urol 16(1): 23-34, 2019. DOI: 10.1038/s41585-018-0105-y

3 Cathomas R, Lorch A, Bruins HM, Compérat EM, Cowan NC, Efstathiou JA, Fietkau R, Gakis G, Hernández V, Espinós EL, Neuzillet Y, Ribal MJ, Rouanne M, Thalmann GN, van der Heijden AG, Veskimäe E, Alfred Witjes J, Milowsky MI: The 2021 Updated European Association of Urology Guidelines on metastatic urothelial carcinoma. Eur Urol 81(1): 95-103, 2022. DOI: 10.1016/j.eururo.2021.09.026

4 Siegel RL, Miller KD, Wagle NS, Jemal A: Cancer statistics, 2023. CA Cancer J Clin 73(1): 17-48, 2023. DOI: 10.3322/caac.21763

5 Witjes JA, Compérat E, Cowan NC, De Santis M, Gakis G, Lebret T, Ribal MJ, van der Heijden AG, Sherif A: EAU Guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2013 Guidelines. Eur Urol 65(4): 778-792, 2014. DOI: 10.1016/j.eururo.2013.11.046

6 Einstein DJ, Sonpavde G: Treatment approaches for cisplatin-ineligible patients with invasive bladder cancer. Curr Treat Options Oncol 20(2): 12, 2019. DOI: 10.1007/s11864-019-0609-6

7 Galsky MD, Chen GJ, Oh WK, Bellmunt J, Roth BJ, Petrioli R, Dogliotti L, Dreicer R, Sonpavde G: Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. Ann Oncol 23(2): 406-410, 2012. DOI: 10.1093/annonc/mdr156

8 Gakis G: The role of inflammation in bladder cancer. Adv Exp Med Biol 816: 183-196, 2014. DOI: 10.1007/978-3-0348-0837-8_8

9 Bambury RM, Benjamin DJ, Chaim JL, Zabor EC, Sullivan J, Garcia-Grossman IR, Regazzi AM, Ostrovnaya I, Apollo A, Xiao H, Voss MH, Iyer G, Bajorin DF, Rosenberg JE: The safety and efficacy of single-agent pemetrexed in platinum-resistant advanced urothelial carcinoma: a large single-institution

experience. Oncologist 20(5): 508-515, 2015. DOI: 10.1634/theoncologist.2014-0354
10 Kuwada M, Miyake M, Gotoh D, Tatsumi Y, Nakai Y, Anai S, Chihara Y, Hirao Y, Haramoto M, Tanaka N, Fujimoto K: Pretreatment platelet-to-lymphocyte ratio as biomarker for neoadjuvant chemotherapy prior to radical cystectomy in muscle-invasive bladder cancer. J Nara Med Assoc 68(4,5,6): 29-41, 2017.
11 Dalpiaz O, Krieger D, Ehrlich GC, Pohlmann K, Stojakovic T, Pummer K, Zigeuner R, Pichler M, Hutterer GC: Validation of the preoperative platelet-to-lymphocyte ratio as a prognostic factor in a European cohort of patients with upper tract urothelial carcinoma. Urol Int 98(3): 320-327, 2017. DOI: 10.1159/000452109
12 Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP: The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67(2): 93-99, 2017. DOI: 10.3322/caac.21388
13 Flaig TW, Spiess PE, Abern M, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, Chan K, Chang S, Friedlander T, Greenberg RE, Guru KA, Herr HW, Hoffman-Censits J, Kishan A, Kundu S, Lele SM, Mamtani R, Margulis V, Mian OY, Michalski J, Montgomery JS, Nandagopal L, Pagliaro LC, Parikh M, Patterson A, Plimack ER, Pohar KS, Preston MA, Richards K, Sexton WJ, Siefker-Radtke AO, Tollefson M, Tward J, Wright JL, Dwyer MA, Cassara CJ, Gurski LA: NCCN Guidelines® Insights: Bladder Cancer, Version 2.2022. J Natl Compr Canc Netw 20(8): 866-878, 2022. DOI: 10.6004/jnccn.2022.0041
14 Geller NL, Sternberg CN, Penenberg D, Scher H, Yagoda A: Prognostic factors for survival of patients with advanced urothelial tumors treated with methotrexate, vinblastine, doxorubicin, and cisplatin chemotherapy. Cancer 67(6): 1525-1531, 1991. DOI: 10.1002/1097-0142(19910315)67:6<1525::aid-cncr2820670611>3.0.co;2-8
15 Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, Herr H, Higgins G, Boyle MG: Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 17(10): 3173-3181, 1999. DOI: 10.1200/jco.1999.17.10.3173
16 Galsky MD, Moshier E, Krege S, Lin C, Hahn N, Ecke T, Sonpavde G, Godbold J, Oh WK, Bamias A: Nomogram for predicting survival in patients with unresectable and/or metastatic urothelial cancer who are treated with cisplatin-based chemotherapy. Cancer 119(16): 3012-3019, 2013. DOI: 10.1002/cncr.28146
17 Hui G, Khaki AR, Grivas P: Determinants of prognosis in metastatic urothelial carcinoma: a review of the literature. J Cancer Metastasis Treat 8: 34, 2022. DOI: 10.20517/2394-4722.2022.04
18 Nassar AH, Mouw KW, Jegede O, Shinagare AB, Kim J, Liu CJ, Pomerantz M, Harshman LC, Van Allen EM, Wei XX, McGregor B, Choudhury AD, Preston MA, Dong F, Signoretti S, Lindeman NI, Bellmunt J, Choueiri TK, Sonpavde G, Kwiatkowski DJ: A model combining clinical and genomic factors to predict response to PD-1/PD-L1 blockade in advanced urothelial carcinoma. Br J Cancer 122(4): 555-563, 2020. DOI: 10.1038/s41416-019-0686-0
19 Sonpavde G, Manitz J, Gao C, Tayama D, Kaiser C, Hennessy D, Makari D, Gupta A, Abdullah SE, Niegisch G, Rosenberg JE, Bajorin DF, Grivas P, Apolo AB, Dreicer R, Hahn NM, Galsky MD, Necchi A, Srinivas S, Powles T, Choueiri TK, Pond GR: Five-factor prognostic model for survival of post-platinum patients with metastatic urothelial carcinoma receiving PD-L1 inhibitors. J Urol 204(6): 1173-1179, 2020. DOI: 10.1097/JU.0000000000001199
20 Khaki AR, Li A, Diamantopoulos LN, Miller NJ, Carril-Ajuria L, Castellano D, De Kouchkovsky I, Koshkin V, Park J, Alva A, Bilen MA, Stewart T, Santos V, Agarwal N, Jain J, Zakharia Y, Morales-Barrera R, Devitt M, Nelson A, Hoimes CJ, Shreck E, Gartrell BA, Sankin A, Tripathi A, Zakopoulou R, Bamias A, Rodriguez-Vida A, Drakaki A, Liu S, Kumar V, Lythgoe MP, Pinato DJ, Murgic J, Fröbe A, Joshi M, Isaacsson Velho P, Hahn N, Alonso Buznego L, Duran I, Moses M, Barata P, Galsky MD, Sonpavde G, Yu EY, Shankaran V, Lyman GH, Grivas P: A new prognostic model in patients with advanced urothelial carcinoma treated with first-line immune checkpoint inhibitors. Eur Urol Oncol 4(3): 464-472, 2021. DOI: 10.1016/j.euo.2020.12.006
21 Su S, Liu L, Sun C, Yang L, Nie Y, Chen Y, Zhang J, Li S: Prognostic significance of serum lactate dehydrogenase in patients undergoing radical cystectomy for bladder cancer. Urol Oncol 38(11): 852.e1-852.e9, 2020. DOI: 10.1016/j.urolonc.2020.05.031
22 Eggers H, Seidel C, Schrader AJ, Lehmann R, Wegener G, Kuczyk MA, Steffens S: Serum C-reactive protein: a prognostic factor in metastatic urothelial cancer of the bladder. Med Oncol 30(4): 705, 2013. DOI: 10.1007/s12032-013-0705-6
23 Xu HJ, Ma Y, Deng F, Ju WB, Sun XY, Wang H: The prognostic value of C-reactive protein/albumin ratio in human malignancies: an updated meta-analysis. Onco Targets Ther 10: 3059-3070, 2017. DOI: 10.2147/OTT.S137002
24 Takemura K, Fukushima H, Ito M, Kataoka M, Nakanishi Y, Sakamoto K, Suzuki H, Tobisu KI, Koga F: Prognostic significance of serum γ-glutamyltransferase in patients with advanced urothelial carcinoma. Urol Oncol 37(2): 108-115, 2019. DOI: 10.1016/j.urolonc.2018.11.002
25 Galdiero MR, Varricchi G, Loffredo S, Mantovani A, Marone G: Roles of neutrophils in cancer growth and progression. J Leukoc Biol 103(3): 457-464, 2018. DOI: 10.1002/jlb.3mr0717-292r
26 Que H, Fu Q, Lan T, Tian X, Wei X: Tumor-associated neutrophils and neutrophil-targeted cancer therapies. Biochim Biophys Acta Rev Cancer 1877(5): 188762, 2022. DOI: 10.1016/j.bbcan.2022.188762
27 Kastelan Z, Lukac J, Derezić D, Pasini J, Kusić Z, Sosić H, Kastelan M: Lymphocyte subsets, lymphocyte reactivity to mitogens, NK cell activity and neutrophil and monocyte phagocytic functions in patients with bladder carcinoma. Anticancer Res 23(6d): 5185-5189, 2003.
28 Joseph N, Dovedi SJ, Thompson C, Lyons J, Kennedy J, Elliott T, West CM, Choudhury A: Pre-treatment lymphocytopaenia is an adverse prognostic biomarker in muscle-invasive and advanced bladder cancer. Ann Oncol 27(2): 294-299, 2016. DOI: 10.1093/annonc/mdv546
29 Gorelik L, Flavell RA: Transforming growth factor-β in T-cell biology. Nat Rev Immunol 2(1): 46-53, 2002. DOI: 10.1038/nri704
30 Kim R, Emi M, Tanabe K, Uchida Y, Toge T: The role of Fas ligand and transforming growth factor beta in tumor progression: Molecular mechanisms of immune privilege *via* Fas-mediated apoptosis and potential targets for cancer therapy. Cancer 100(11): 2281-2291, 2004. DOI: 10.1002/cncr.20270

31 Taguchi S, Nakagawa T, Matsumoto A, Nagase Y, Kawai T, Tanaka Y, Yoshida K, Yamamoto S, Enomoto Y, Nose Y, Sato T, Ishikawa A, Uemura Y, Fujimura T, Fukuhara H, Kume H, Homma Y: Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of survival in patients with metastatic urothelial carcinoma: A multi-institutional study. Int J Urol 22(7): 638-643, 2015. DOI: 10.1111/iju.12766

32 Rossi L, Santoni M, Crabb SJ, Scarpi E, Burattini L, Chau C, Bianchi E, Savini A, Burgio SL, Conti A, Conteduca V, Cascinu S, De Giorgi U: High neutrophil-to-lymphocyte ratio persistent during first-line chemotherapy predicts poor clinical outcome in patients with advanced urothelial cancer. Ann Surg Oncol 22(4): 1377-1384, 2015. DOI: 10.1245/s10434-014-4097-4

33 Wu S, Zhao X, Wang Y, Zhong Z, Zhang L, Cao J, Ai K, Xu R: Pretreatment neutrophil-lymphocyte ratio as a predictor in bladder cancer and metastatic or unresectable urothelial carcinoma patients: a pooled analysis of comparative studies. Cell Physiol Biochem 46(4): 1352-1364, 2018. DOI: 10.1159/000489152

34 Nakazaki H: Preoperative and postoperative cytokines in patients with cancer. Cancer 70(3): 709-713, 1992. DOI: 10.1002/1097-0142(19920801)70:3<709::aid-cncr2820700328>3.0.co;2-o

35 Nabavizadeh R, Bobrek K, Master VA: Risk stratification for bladder cancer: Biomarkers of inflammation and immune activation. Urol Oncol 38(9): 706-712, 2020. DOI: 10.1016/j.urolonc.2020.04.006

36 Galdiero MR, Bonavita E, Barajon I, Garlanda C, Mantovani A, Jaillon S: Tumor associated macrophages and neutrophils in cancer. Immunobiology 218(11): 1402-1410, 2013. DOI: 10.1016/j.imbio.2013.06.003

37 Cao W, Yao X, Cen D, Zhi Y, Zhu N, Xu L: The prognostic role of platelet-to-lymphocyte ratio on overall survival in gastric cancer: a systematic review and meta-analysis. BMC Gastroenterol 20(1): 16, 2020. DOI: 10.1186/s12876-020-1167-x

38 Liu D, Jin J, Zhang L, Li L, Song J, Li W: The neutrophil to lymphocyte ratio may predict benefit from chemotherapy in lung cancer. Cell Physiol Biochem 46(4): 1595-1605, 2018. DOI: 10.1159/000489207

39 Yang Y, Xu H, Zhou L, Deng T, Ning T, Liu R, Zhang L, Wang X, Ge S, Li H, Ba Y: Platelet to lymphocyte ratio is a predictive marker of prognosis and therapeutic effect of postoperative chemotherapy in non-metastatic esophageal squamous cell carcinoma. Clin Chim Acta 479: 160-165, 2018. DOI: 10.1016/j.cca.2018.01.013

40 D'Andrea D, Moschini M, Gust KM, Abufaraj M, Özsoy M, Mathieu R, Soria F, Briganti A, Rouprêt M, Karakiewicz PI, Shariat SF: Lymphocyte-to-monocyte ratio and neutrophil-to-lymphocyte ratio as biomarkers for predicting lymph node metastasis and survival in patients treated with radical cystectomy. J Surg Oncol 115(4): 455-461, 2017. DOI: 10.1002/jso.24521

41 D'andrea D, Moschini M, Gust K, Abufaraj M, Özsoy M, Mathieu R, Soria F, Briganti A, Rouprêt M, Karakiewicz PI, Shariat SF: Prognostic role of neutrophil-to-lymphocyte ratio in primary non-muscle-invasive bladder cancer. Clin Genitourin Cancer 15(5): e755-e764, 2017. DOI: 10.1016/j.clgc.2017.03.007

42 Guo Y, Cai K, Mao S, Zhang J, Wang L, Zhang Z, Liu M, Zhang W, Wu Y, Yan Y, Yao X: Preoperative C-reactive protein/albumin ratio is a significant predictor of survival in bladder cancer patients after radical cystectomy: a retrospective study. Cancer Manag Res 10: 4789-4804, 2018. DOI: 10.2147/CMAR.S180301

43 Gondo T, Nakashima J, Ohno Y, Choichiro O, Horiguchi Y, Namiki K, Yoshioka K, Ohori M, Hatano T, Tachibana M: Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. Urology 79(5): 1085-1091, 2012. DOI: 10.1016/j.urology.2011.11.070

44 Hermanns T, Bhindi B, Wei Y, Yu J, Noon AP, Richard PO, Bhatt JR, Almatar A, Jewett MA, Fleshner NE, Zlotta AR, Templeton AJ, Kulkarni GS: Pre-treatment neutrophil-to-lymphocyte ratio as predictor of adverse outcomes in patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Br J Cancer 111(3): 444-451, 2014. DOI: 10.1038/bjc.2014.305

45 Krane LS, Richards KA, Kader AK, Davis R, Balaji K, Hemal AK: Preoperative neutrophil/lymphocyte ratio predicts overall survival and extravesical disease in patients undergoing radical cystectomy. J Endourol 27(8): 1046-1050, 2013. DOI: 10.1089/end.2012.0606

46 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 23(1): 335-342, 2016. DOI: 10.1245/s10434-015-4708-8

47 Mano R, Baniel J, Shoshany O, Margel D, Bar-On T, Nativ O, Rubinstein J, Halachmi S: Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non–muscle-invasive bladder cancer. Urol Oncol 33(2): 67.e1-67.e7, 2015. DOI: 10.1016/j.urolonc.2014.06.010

48 Miyake M, Morizawa Y, Hori S, Marugami N, Iida K, Ohnishi K, Gotoh D, Tatsumi Y, Nakai Y, Inoue T, Anai S, Torimoto K, Aoki K, Tanaka N, Shimada K, Konishi N, Fujimoto K: Integrative assessment of pretreatment inflammation-, nutrition, and muscle-based prognostic markers in patients with muscle-invasive bladder cancer undergoing radical cystectomy. Oncology 93(4): 259-269, 2017. DOI: 10.1159/000477405

49 Schulz GB, Grimm T, Buchner A, Jokisch F, Grabbert M, Schneevoigt BS, Kretschmer A, Stief CG, Karl A: Prognostic value of the preoperative platelet-to-leukocyte ratio for oncologic outcomes in patients undergoing radical cystectomy for bladder cancer. Clin Genitourin Cancer 15(6): e915-e921, 2017. DOI: 10.1016/j.clgc.2017.05.009

50 Zhang GM, Zhu Y, Luo L, Wan FN, Zhu YP, Sun LJ, Ye DW: Preoperative lymphocyte-monocyte and platelet-lymphocyte ratios as predictors of overall survival in patients with bladder cancer undergoing radical cystectomy. Tumour Biol 36(11): 8537-8543, 2015. DOI: 10.1007/s13277-015-3613-x

51 Seah JA, Leibowitz-Amit R, Atenafu EG, Alimohamed N, Knox JJ, Joshua AM, Sridhar SS: Neutrophil-lymphocyte ratio and pathological response to neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer. Clin Genitourin Cancer 13(4): e229-e233, 2015. DOI: 10.1016/j.clgc.2015.02.001

52 Buisan O, Orsola A, Areal J, Font A, Oliveira M, Martinez R, Ibarz L: Low pretreatment neutrophil-to-lymphocyte ratio predicts for good outcomes in patients receiving neoadjuvant chemotherapy before radical cystectomy for muscle invasive bladder cancer. Clin Genitourin Cancer 15(1): 145-151.e2, 2017. DOI: 10.1016/j.clgc.2016.05.004

53 Leibowitz-Amit R, Israel A, Gal M, Atenafu E, Symon Z, Portnoy O, Laufer M, Dotan Z, Ramon J, Avni D, Fridman E, Berger R: Association between the absolute baseline lymphocyte count and response to neoadjuvant platinum-based chemotherapy

in muscle-invasive bladder cancer. Clin Oncol (R Coll Radiol) 28(12): 790-796, 2016. DOI: 10.1016/j.clon.2016.07.007

54 Ojerholm E, Smith A, Hwang WT, Baumann BC, Tucker KN, Lerner SP, Mamtani R, Boursi B, Christodouleas JP: Neutrophil-to-lymphocyte ratio as a bladder cancer biomarker: Assessing prognostic and predictive value in SWOG 8710. Cancer 123(5): 794-801, 2017. DOI: 10.1002/cncr.30422

55 Kaiser J, Li H, North SA, Leibowitz-Amit R, Seah JA, Morshed N, Chau C, Lee-Ying R, Heng DYC, Sridhar S, Crabb SJ, Alimohamed NS: The prognostic role of the change in neutrophil-to-lymphocyte ratio during neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer: a retrospective, multi-institutional study. Bladder Cancer 4(2): 185-194, 2018. DOI: 10.3233/BLC-170133

56 Bozkurt O, Doğan E, Fırat ST, Coşar R, İnanç M, Zararsız GE: Role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as prognostic predictors before treatment for metastatic bladder cancer patients receiving first-line chemotherapy. Erciyes Med J 41(3), 2019. DOI: 10.14744/etd.2019.74507

57 Watanabe K, Yasumoto A, Amano Y, Kage H, Goto Y, Yatomi Y, Takai D, Nagase T: Mean platelet volume and lymphocyte-to-monocyte ratio are associated with shorter progression-free survival in EGFR-mutant lung adenocarcinoma treated by EGFR tyrosine kinase inhibitor. PLoS One 13(9): e0203625, 2018. DOI: 10.1371/journal.pone.0203625

58 Shimura T, Shibata M, Gonda K, Hayase S, Sakamoto W, Okayama H, Fujita S, Saito M, Momma T, Ohki S, Kono K: Prognostic impact of preoperative lymphocyte-to-monocyte ratio in patients with colorectal cancer with special reference to myeloid-derived suppressor cells. Fukushima J Med Sci 64(2): 64-72, 2018. DOI: 10.5387/fms.2018-10

59 Bi H, Yan Y, Wang D, Qin Z, Wang G, Ma L, Huang Y, Lu J: Predictive value of preoperative lymphocyte-to-monocyte ratio on survival outcomes in bladder cancer patients after radical cystectomy. J Cancer 12(2): 305-315, 2021. DOI: 10.7150/jca.50603

60 Ma JY, Hu G, Liu Q: Prognostic significance of the lymphocyte-to-monocyte ratio in bladder cancer undergoing radical cystectomy: a meta-analysis of 5638 individuals. Dis Markers 2019: 7593560, 2019. DOI: 10.1155/2019/7593560

Received August 12, 2023
Revised October 1, 2023
Accepted October 5, 2023