Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)
©Scholars Academic and Scientific Publisher
A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Urology

Evaluation of Predictive Value of Pre-treatment Inflammation Based Prognostic Biomarkers for Detection of Invasiveness of Bladder Carcinoma in a Tertiary Care Centre of West Bengal

Souvik Chatterjee[1], Pramod Kumar Sharma[2*], Anshuman Aashu[1], Sudipta Kumar Singh[1], Kanishka Samanta[1], Soumendranath Mandal[3], Dilip Karmakar[4]

[1]Resident, Dept. of Urology, Calcutta National Medical College and Hospital, Kolkata, 32, Gorachand Road, Kolkata-14, West Bengal, India
[2]Assistant Professor, Dept. of Urology, Calcutta National Medical College and Hospital, Kolkata, 32, Gorachand Road, Kolkata-14, West Bengal, India
[3]Professor and HOD, Dept. of Urology, Calcutta National Medical College and Hospital, Kolkata, 32, Gorachand Road, Kolkata-14, West Bengal, India
[4]Professor, Dept. of Urology, Calcutta National Medical College and Hospital, Kolkata, 32, Gorachand Road, Kolkata-14, West Bengal, India

Original Research Article

***Corresponding author**
Pramod Kumar Sharma

Article History
Received: 12.09.2018
Accepted: 24.09.2018
Published: 30.10.2018

DOI:
10.36347/sjams.2018.v06i10.005

Abstract: The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are pretreatment inflammation based prognostic biomarkers used to predict oncologic outcomes in urological and gastrointestinal malignancies. Limited literatures are available in determining their value in prediction of invasiveness of bladder cancer in pretreatment scenario. The current study is conducted to evaluate the predictive value of pre-treatment inflammation based prognostic biomarkers to determine the invasiveness of primary bladder cancer in patients undergoing transurethral resection of bladder tumour (TURBT) surgery. Total 120 primary bladder tumour patients, who underwent TURBT from April, 2016 to March, 2018 in department of Urology, Calcutta National Medical College, Kolkata, were prospectively studied for detection of muscle invasion. The Case Record Proforma (CRP) of Bladder Tumour Registry of our institution was used to document patient demographics, tumour characteristics and prognostic scores of inflammatory biomarkers. Among 120 patients, 76.7% of patients had Nonmuscle invasive bladder cancer and rest had muscle invasive variety. The cut-off values for NLR, LMR and PLR were 3.18, 3.67 and 185.67, respectively. Multivariate logistic regression analysis showed that high grade, larger sized tumor, high NLR and PLR values were independent predictors of muscle invasion. NLR and PLR were identified to be simple, cost-effective and easily measured prognostic biomarker for muscle invasion. These markers will also assist in the preoperative planning and counselling for further treatment and follow-up.

Keywords: Urinary bladder cancer; neutrophil-to-lymphocyte ratio; lymphocyte-to-monocyte ratio; platelet-to-lymphocyte ratio; muscle invasion.

INTRODUCTION

Urinary bladder cancer is most common malignancy of genitourinary tract [1] and it is the sixth most common malignancy in India [2]. Nonmuscle invasive bladder cancer (NMIBC) consists of approximately 75% of total bladder cancer and rest of the tumours are of more invasive variety. NMIBC is adequately treated with TURBT with or without adjuvant intravesical therapy, [3] whereas muscle-invasive bladder cancer (MIBC) is treated with radical cystoprostatectomy, radiotherapy and chemotherapy. The histopathological examination of specimen obtained by TURBT is most accurate method to detect presence of muscle invasion; however, pathological upstaging is common in many patients undergone radical cystoprostatectomy [4].

Cancer associated systemic inflammatory response leads to changes in circulating blood cells, e.g. neutrophilia with relative lymphocytopenia and thrombocytosis. The growth, maturation and differentiation of tumor cells within the tumour microenvironment partly depend on levels of cytokines and chemokines produced by these circulating blood cells [5]. The inflammation-based preoperative biomarkers include preoperative neutrophil-to-

lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). In different studies, their role in prediction of oncologic outcomes has been proved for diverse malignancies, e.g. renal, colorectal, hepatic, breast and lung [6-8]. The association between elevated NLR and muscle invasive bladder cancer have been documented in literature, [9, 10] but relationships between PLR and LMR with muscle invasive bladder cancer are not established. The current study is conducted to evaluate the predictive value of pre-treatment inflammation based prognostic biomarkers to determine the invasiveness of primary bladder cancer in patients undergoing TURBT surgery.

MATERIALS AND METHODS

After matching the inclusion and exclusion criteria, total 120 primary bladder tumour patients, who underwent TURBT from April, 2016 to March, 2018 in department of Urology, Calcutta National Medical College, Kolkata, were prospectively observed. The Case Record Proforma (CRP) of Bladder Tumour Registry of our institution was used to document patient demographics, tumour characteristics (tumour size, grade, and multiplicity), preoperative investigation reports and prognostic scores of inflammatory biomarkers (NLR, PLR, and LMR). The inclusion and exclusion criteria of the patients were as follows:

Inclusion criteria

Patients with primary transitional cell bladder cancer proved by post TURBT biopsy

Exclusion criteria

- Recurrent bladder tumors
- Non-transitional cell bladder carcinoma
- Metastatic disease
- Alternative cancer/hematological disorder diagnosis
- Evidence of active infection (including urinary tract infection)
- Lacking preoperative blood tests

Diagnostic cystoscopy was performed in all patients before surgical resection. The histopathological reports confirmed the stage of the bladder cancer and they were categorised as NMIBC (≤ stage pT1) or MIBC (≥ stage T2) according to the invasion status of detrusor muscle. All necessary preoperative investigations were done for the patients undergoing TURBT. Preoperative complete hemogram reports were obtained within 30 days prior to TURBT and analysed for calculation of prognostic scores.

All statistical analysis was performed by using MedCalc17.9.6. NLR, PLR and LMR were calculated by determining the ratio between absolute neutrophil counts with absolute lymphocyte count, absolute platelet count with absolute lymphocyte count and absolute lymphocyte count with absolute monocyte count, respectively. The cut-off values of prognostic biomarkers were determined by developing the receiver operating characteristics (ROC) curves. Patient and tumor characteristics were stratified into groups based upon the cut-off values and categorical data were compared using a chi-square test. Univariate and multivariate logistic regression analysis were performed to indentify the variables significantly associated with MIBC.

RESULTS

Total 120 patients having primary bladder cancer and fulfilling inclusion and exclusion criteria were studied. Seventy percent of our patients were male. Total 92 patients out of 120 had suffered from NMIBC whereas 23.3% of them had MIBC. High grade cancer was detected in 46.7% patients. Most of our patients (64.2%) had low grade malignancy whereas 70% of them had solitary tumor (Table no. 1).

Table-1: Demographic profile of patients and tumors

Patients characteristics		
Gender	Male	84 (70%)
	Female	36 (30%)
Age group	A (≤ 60 years)	84 (70%)
	B (> 60 years)	36 (30%)
Tumor characteristics		
Tumor stage	NMIBC (Ta,T1)	92 (76.7%)
	MIBC (≥T2)	28 (23.3%)
Tumor grade	Low (LG)	64 (53.3%)
	High (HG)	56 (46.7%)
Tumor size	Small (≤3cm)	77 (64.2%)
	Large (>3cm)	43 (35.8%)
Tumor number	Solitary	84 (70%)
	Multiple	36 (30%)

Preoperative complete hemogram reports were obtained within 30 days prior to TURBT and used for calculation of prognostic scores. NLR, PLR, and LMR for each patient were calculated. MIBC was used as a

classification variable for development of ROC curves for each prognostic score (Fig. 1). On analysis of each prognostic score, all of the scores were significantly important for detection of muscle invasion. Among them, NLR covered highest area under curve (AUC) in ROC curve, followed by PLR and LMR respectively (Table no. 2). Threshold values for NLR, LMR and PLR were 3.18, 3.67 and 185.67, respectively.

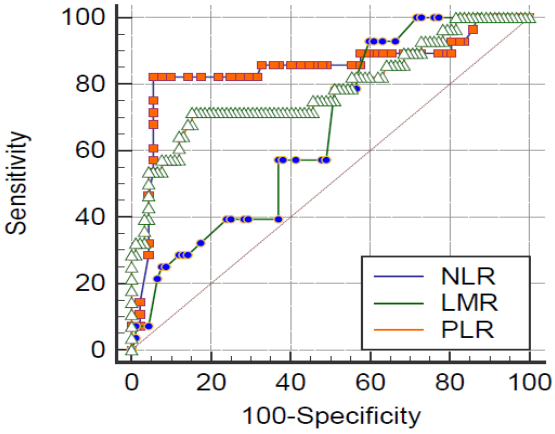

Fig-1: ROC for NLR, LMR, and PLR

Table-2: Values of ROC of each inflammatory biomarker

Inflammatory biomarker	AUC	Association criterion	Sensitivity	Specificity	p Value
NLR	0.845	>3.18	82.14%	94.57%	<0.0001
LMR	0.66	≤3.67	92.86%	40.22%	0.0029
PLR	0.785	>185.67	71.43%	84.78%	<0.0001

Based on the ROC threshold values, patients were stratified into two groups for each prognostic marker. Both the groups were compared for patients' baseline and tumor characteristics (Table no. 3). Chi-square analysis was used to compare the categorical data and p-values <0.05 was considered to be significant. Adverse tumor characteristics (invasion, grade, size and number of the lesions) were significantly associated with higher NLR and PLR values and lower LMR values.

Table-3: Baseline characteristics of patients and tumors according to the NLR, LMR and PLR values

		NLR		p Value	LMR		p Value	PLR		p Value
		≤3.18	>3.18		≤3.67	>3.67		≤185.67	>185.67	
Gender	Male	61	23	0.109	54	30	0.251	59	25	0.596
	Female	31	5		27	9		27	9	
Age group	≤60yr	64	20	0.851	57	27	0.898	61	23	0.724
	>60yr	28	8		24	12		25	11	
Tumor invasion	NMIBC	87	5	<0.0001	55	37	0.001	78	14	<0.0001
	MIBC	5	23		26	2		8	20	
Tumor grade	HG	33	23	<0.0001	46	10	0.001	31	25	<0.0001
	LG	59	5		35	29		55	9	
Tumor size	≤3cm	68	9	<0.0001	46	31	0.015	63	14	0.001
	>3cm	24	19		35	8		23	20	
Number of tumors	Single	72	12	<0.0001	51	33	0.015	68	16	0.001
	Multiple	20	16		30	6		18	18	

Univariate analysis showed that tumor grade, size, multiplicity, NLR, LMR and PLR were significant predictor of muscle invasion (Table no. 4). The multivariate logistic regression model identified that high grade, larger sized tumor, high NLR and PLR values were independent predictors of muscle invasion.

Table-4: Univariate and Multivariate logistic regression analysis of risk factors

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	p Value	OR	95%CI	p Value
Age (>60 yrs)	1.75	1.07-3.85	0.14	2.27	0.93-4.82	0.73
Gender (Male)	0.64	0.32-1.3	0.42	0.52	0.28-1.73	0.35
Tumor grade (HG)	28.37	9.87-56.29	0.001	29.01	10.13-71.09	<0.0001
Tumor size (>3cm, large)	6.38	3.27-14.92	0.0001	4.53	1.74-8.43	0.006
Tumor number (Multiple)	1.54	0.47- 3.78	0.045	1.08	0.72-4.36	0.08
NLR (>3.18)	6.73	2.78-12.69	<0.0001	7.42	2.46- 25.31	0.001
LMR (≤3.67)	3.29	1.94-8.45	0.001	2.16	0.57-5.83	0.735
PLR (>185.67)	4.38	2.08-7.91	<0.0001	1.97	0.89-6.05	0.03

DISCUSSION

Accurate staging by histopathological analysis of TURBT specimen is required optimum management of urinary bladder cancer. Restaging TURBT has proved its efficacy in decreasing the chance of staging error. Several reports have demonstrated upstaging of 50% of radical cystoprostatectomy specimens. [11,12] Among the imaging modalities, magnetic resonance imaging and computed tomography have proved their efficacy in predicting locoregional staging in conjunction with histology pathological reports. Recently, few nomograms have been developed to predict preoperative invasion status of bladder cancer with or without utilising molecular markers [13, 14].

Inflammatory cells and innate immune system play an important role in carcinogenesis and tumor progression. [5] Carcinogenesis pathway leads to systemic inflammatory response which in turn causes in change in relative levels of circulating leukocytes with neutrophilia, relative lymphocytopenia and thrombocytosis [6, 7]. Preoperative inflammatory biomarkers, e.g. NLR, PLR, and LMR, are potential prognostic factors for preoperative determination of muscle invasion in urinary bladder cancer.

In our study, NLR and PLR were found to have predictive efficacy for detection of muscle invasion in bladder cancer. In lieu with literatures, we have found that tumor grade and size were independent predictors in bladder cancer [15]. The present study did not identify any role of LMR as preoperative prognostic marker in spite of its promising result in univariate analysis. Kaynar *et al*. [10] did not demonstrate significant association between PLR and muscle invasion, though the present study had identified the relation. NLR and PLR are representative of degree of systemic inflammatory response [16]. Higher values of NLR and PLR reflect an increased neutrophil and platelet dependent inflammatory response and lower value of LMR represents a decreased lymphocyte mediated immune response. [17] They can easily be calculated from preoperative routine full blood count using limited expenditure. Their usage in bladder cancer is limited due to lack of available data.

Histopathological examination of TURBT specimen is the gold standard for diagnosis of status of muscle invasion in bladder cancer. In literatures, there is a chance of false negative diagnosis of MIBC in TURBT specimen [12]. There is around 40 – 50% chance of getting the evidence of muscle invasion in radical cystectomy specimen done for clinical T1 disease diagnosed by TURBT [18]. On the hand, inflammatory biomarkers are surrogate maker for identifying the patients having significant risk for muscle-invasive disease. Different studies show that patients of bladder cancer with high NLR and low LMR are at higher risk of muscle-invasive disease. Thus, patients with significant prognostic biomarkers should undergo more stringent follow up with cystoscopy or repeat resection to identify any residual muscle-invasive disease, which was missed during initial TURBT. Limited data regarding the significance of inflammatory markers demands further evaluation.

In present study, after multivariate logistic regression, we found that higher NLR and PLR values were associated with MIBC as compared to NMIBC. Most of the literatures showed relationship between NLR and PLR with muscle invasion in univariate analysis; [9, 10] one study however demonstrated same association by multivariate analysis. [19] It is identified in different literatures that elevated NLR is associated with extra-vesical disease in post radical cystectomy specimen [20-22]. There is no consensus regarding cutoff values of biomarkers as wide range of ROC curve cutoff values is available for them in detecting muscle invasion in preoperative scenario. Non specific nature of the inflammatory markers may explain the wide variation in cutoff values of the biomarkers.

Inflammatory biomarkers, particularly NLR, are associated with inverse relationship with disease recurrence and progression in bladder cancer. Modern studies indentified elevated NLR as an independent predictor 1recurrence-free, disease-specific and overall survival [20, 22]. In a study conducted by Mano *et al*. [23], it became evident that patients of NMIBC with elevated NLR had significant disease recurrence and progression. This finding was further confirmed by Ozyalvacli *et al*. [24] in patients of stage pT1 bladder tumours. The association between elevated

inflammatory biomarkers with invasive disease, disease recurrence and survival were well established. This serves as surrogate marker of high risk disease with aggressive tumour biology.

Luo *et al*. [25] in their study determined association between pretreatment NLR and PLR with advanced tumor stages, grade and size in patients with bladder cancer. In our study, we have found the significance of NLR and PLR in detection of muscle invasion. NLR is an independent prognostic factor to determine the response to neoadjuvant chemotherapy (NACT) in patients with MIBC [26]. A high preoperative NLR is associated with poor response to NACT, particularly in patients with sustained high NLR during mid-NACT cycle. Thus, NLR also serves as a prognostic biomarker for MIBC patients treated with NACT.

Coexisting inflammatory conditions (e.g., infection, hematological disorder) may act as confounding factor which may cause erroneous interpretation. In present study, we have obtained preoperative complete hemogram reports within 30 days prior to TURBT and analysed for calculation of prognostic scores. Any report prior to that was excluded and fresh blood reports were obtained. However, Viers *et al*. [22] demonstrated that NLR remained more or less stable over a period as long as 90 days. No such data is available on LMR and PLR.

In our study, we indentified a particular cutoff values for both NLR and PLR for detection of muscle invasion for our study population. Thus NLR and PLR are appeared to be promising marker for invasive bladder cancer and may be used as important variable in future for development of predictive nomograms. The MIBC may further be sub-classified into T2, T3 and T4 disease. The role of prognostic biomarkers in differentiating each stage of MIBC was not elucidated in present study. Further studies may be required to identify the patients who will be most appropriately managed by radical surgery. Despite the utility of inflammatory biomarkers in genitourinary malignancies, larger, prospective studies are required to fully define their role in clinical setting.

CONCLUSIONS

Accurate histopathological staging of bladder tumor following TURBT is vital as it determines the further management. In present study on pretreatment inflammation-based prognostic scores indicates that high NLR and PLR values are independent, simple, and cost-effective and easily measured markers of muscle invasion. Preoperative measurement of inflammatory biomarkers at the time of diagnostic cystoscopy helps to make a plan of further treatment, counseling of patients and future follow-up.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: a cancer journal for clinicians. 2014 Jan;64(1):9-29.
2. Ray D, Mondal R, Acharya S, De S, Mondal S. A retrospective study of bladder cancer and the impact of age, sex and smoking habits related clinicopathological correlations in tribal population of Bankura, WB, India. IOSR J Dent Med Sci. 2013;10(4):29-32.
3. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Compérat E, Sylvester RJ, Kaasinen E, Böhle A, Redorta JP, Rouprêt M. EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder: update 2013. European urology. 2013 Oct 1;64(4):639-53.
4. Dutta SC, SMITH Jr JA, Shappell SB, Coffey CS, Chang SS, Cookson MS. Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. The Journal of urology. 2001 Aug 1;166(2):490-3.
5. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420:860-7.
6. Kumar R, Geuna E, Michalarea V, Guardascione M, Naumann U, Lorente D, Kaye SB, De Bono JS. The neutrophil–lymphocyte ratio and its utilisation for the management of cancer patients in early clinical trials. British journal of cancer. 2015 Mar;112(7):1157.
7. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6:149-63.
8. Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wang J, Wang T, Zhu W, Liu P. Prognostic value of PLR in various cancers: a meta-analysis. PloS one. 2014 Jun 26;9(6):e101119.
9. Ceylan C, Doluoğlu ÖG, Keleş I, Gazel E, Temuçin T, Odabaş Ö, Karalar M. Importance of the neutrophil-to-lymphocyte ratio in muscle-invasive and non-muscle invasive bladder tumors. Urologia Journal. 2014 Apr;81(2):120-4.
10. Kaynar M, Yıldırım ME, Badem H, Çaviş M, Tekinarslan E, İstanbulluoğlu MO, Karataş ÖF, Çimentepe E. Bladder cancer invasion predictability based on preoperative neutrophil–lymphocyte ratio. Tumor Biology. 2014 Jul 1;35(7):6601-5.
11. Shariat SF, Palapattu GS, Karakiewicz PI, Rogers CG, Vazina A, Bastian PJ, Schoenberg MP, Lerner SP, Sagalowsky AI, Lotan Y. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. European urology. 2007 Jan 1;51(1):137-51.
12. Ark JT, Keegan KA, Barocas DA, Morgan TM, Resnick MJ, You C, Cookson MS, Penson DF, Davis R, Clark PE, Smith Jr JA. Incidence and predictors of understaging in patients with clinical T 1 urothelial carcinoma undergoing radical

cystectomy. BJU international. 2014 Jun;113(6):894-9.
13. Karakiewicz PI, Shariat SF, Palapattu GS, Gilad AE, Lotan Y, Rogers CG, Vazina A, Gupta A, Bastian PJ, Perrotte P, Sagalowsky AI. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. The Journal of urology. 2006 Oct 1;176(4):1354-62.
14. Margel D, Harel A, Yossepowitch O, Baniel J. A novel algorithm to improve pathologic stage prediction of clinically organ-confined muscle-invasive bladder cancer. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2009 Apr 1;115(7):1459-64.
15. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, Newling DW, Kurth K. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. European urology. 2006 Mar 1;49(3):466-77.
16. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratislavske lekarske listy. 2001;102(1):5-14.
17. Paramanathan A, Saxena A, Morris DL. A systematic review and meta-analysis on the impact of pre-operative neutrophil lymphocyte ratio on long term outcomes after curative intent resection of solid tumours. Surg Oncol 2014;23:31-9.
18. Mariappan P, Finney SM, Head E, Somani BK, Zachou A, Smith G, Mishriki SF, N'Dow J, Grigor KM, members of the Edinburgh Urological Cancer Group. Good quality white-light transurethral resection of bladder tumours (GQ-WLTURBT) with experienced surgeons performing complete resections and obtaining detrusor muscle reduces early recurrence in new non-muscle-invasive bladder cancer: validation across time and place and recommendation for benchmarking. BJU international. 2012 Jun;109(11):1666-73.
19. Lee SM, Russell A, Hellawell G. Predictive value of pretreatment inflammation-based prognostic scores (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio) for invasive bladder carcinoma. Korean journal of urology. 2015 Nov 1;56(11):749-55.
20. Krane LS, Richards KA, Kader AK, Davis R, Balaji KC, Hemal AK. Preoperative neutrophil/lymphocyte ratio predicts overall survival and extravesical disease in patients undergoing radical cystectomy. Journal of endourology. 2013 Aug 1;27(8):1046-50.
21. Potretzke A, Hillman L, Wong K, Shi F, Brower R, Mai S, Cetnar JP, Abel EJ, Downs TM. NLR is predictive of upstaging at the time of radical cystectomy for patients with urothelial carcinoma of the bladder. InUrologic Oncology: Seminars and Original Investigations 2014 Jul 1 (Vol. 32, No. 5, pp. 631-636). Elsevier.
22. Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, Thompson RH, Tollefson MK. Pretreatment neutrophil-to-lymphocyte ratio is associated with advanced pathologic tumor stage and increased cancer-specific mortality among patients with urothelial carcinoma of the bladder undergoing radical cystectomy. European urology. 2014 Dec 1;66(6):1157-64.
23. 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. InUrologic Oncology: Seminars and Original Investigations 2015 Feb 1 (Vol. 33, No. 2, pp. 67-e1). Elsevier.
24. Ozyalvacli ME, Ozyalvacli G, Kocaaslan R, Cecen K, Uyeturk U, Kemahlı E, Gucuk A. Neutrophil-lymphocyte ratio as a predictor of recurrence and progression in patients with high-grade pT1 bladder cancer. Canadian Urological Association Journal. 2015 Mar;9(3-4):E126.
25. Luo Y, Shi X, Li W, Mo L, Yang Z, Li X, Qin L, Mo W. Evaluation of the clinical value of hematological parameters in patients with urothelial carcinoma of the bladder. Medicine. 2018 Apr;97(14).
26. Kaiser J, Li H, North SA, Leibowitz-Amit R, Seah JA, Morshed N, Chau C, Lee-Ying R, Heng DY, Sridhar S, Crabb SJ. 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. 2018 Jan 1;4(2):185-94.