

Original Article

## Age Limit of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Correlation of Bladder Cancer Tumor Stage and Grade

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### HIGHLIGHTS

- This was the first study conducted in Iran to evaluate the predictive value of NLR and PLR with the staging and grading of bladder tumors to attain defined cut-offs.
- The predictive accuracy of these ratios improves when the data is divided into specific groups. Opium usage and non-O blood type were positively correlated with an elevated NLR.

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### ABSTRACT

#### Introduction

This study was conducted to investigate the predictive value of NLR and PLR with staging and grading of bladder tumors in Iran for the first time; as well as producing comprehensive data to attain defined cut-offs.

#### Methods

The medical records of 454 patients between 2016 and 2022 have been collected, and diagnosed with bladder cancer by cystoscopy and transurethral resection of bladder tumor (TURBT). Clinical and demographic parameters including age, weight, diabetes, smoking, opium usage, and hematuria were registered. The stage of BC was defined based on the results of physical exams, biopsies, and imaging tests.

#### Results

The study comprised 393 males and 61 females ranging from 28 to 97 years old. The cut-off of NLR as a predictor of grade was 3.09 and 3.78 for the stage, which was 100.8 and 109.6 for PLR respectively. Taller people had lower PLR. There was a relationship between PLR and smoking with non-smokers having significantly higher levels of PLR (P-values=0.039 and 0.025 for grade and stage respectively). Overall NLR (AUC=71.4 and 72.4% for grade and stage respectively) and PLR (70.6 and 73.8% for grade and stage respectively) have shown predictive value for stage and grade of BC in patients younger than 65.

#### Conclusions

Our findings suggest that PLR and NLR can be reliable predictors of the stage and grade of BC in patients under 65 years old, however, their predictor values increase when data are stratified. Higher NLR was associated with opium usage and non-O

blood type.

**Keywords:** Bladder Cancer; Stage; Grade; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio

## Introduction

Bladder cancer is the most common malignancy of the urinary system and the 10th most common cancer worldwide. Overall, in 2020, it caused 3% of new cancer cases and 2.1% of all new cancer deaths (1). Based on staging, bladder cancer can be divided into non-muscle invasive bladder cancer (NMIBC, 01, 0is, 1) and muscle-invasive bladder cancer (MIBC, II, IIIA, IIIB, IVA, IVB). NMIBC is further subdivided into low, intermediate, and high-risk diseases. This type represents almost 70% of organ-confined bladder cancer, while the muscle-invasive class counts for 30% of bladder cancers (2, 3).

Diagnosis of bladder cancer is made by workup of hematuria. The method depends on the type of hematuria, but it always involves cystoscopy. Other imaging modalities such as sonography, CT, or MRI may be needed if the patient is not a low-risk patient. Afterward, the mass is resected via transurethral resection of bladder tumor (TURBT) to perform staging (2, 4).

Treatment for bladder cancer varies based on the staging and classification of the disease. It includes intravesical therapy, TURBT, neoadjuvant therapy, radical cystectomy, pelvic lymph node dissection, and urinary diversion. Despite the many treatments available, the long-term prognosis remains poor due to recurrence with local or distant metastasis (2, 5, 6). Unfortunately, the current prognostic and predictive factors are insufficient; also, some are not readily available before procedures (7). Moreover, upstaging the bladder mass is quite common (8). Routine blood examination, readily available, can reflect a patient's inflammatory status. Studies have shown that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be independent prognostic and predictive factors for various cancers such as colorectal, gastric, lung, and ovarian cancer (7, 9, 10). Some studies in the literature investigate the predictive value of inflammatory markers, including NLR and PLR, for bladder cancer. Gondo et al., first used the prognostic value of NLR for bladder cancer (11).

Even though many papers have been published about the prognostic and predictive value of NLR and PLR in bladder cancer, an established cut-off has not been obtained.

The cut-offs range from 2-5 for NLR and 123-218 for PLR (7, 12, 13). Other than NLR and PLR other serum biomarkers such as systemic immune-inflammation index (SII), De Ritis ratio, and albumin to globulin ratio have been suggested to have prognostic value in NMIBC (14-16). These markers can be very helpful since they do not cause any financial burden and are readily available in routine blood tests.

The purpose of this study is to investigate the diagnostic value of NLR and PLR with staging and grading of bladder cancer.

## Methods

After receiving the ethical code (IR.TUMS.MEDICINE.REC.1401.535) under the ethical committee of Sina hospital (Tehran university of medical sciences, Tehran, Iran), we gathered the medical record of patients admitted to our center, Sina hospital, with bladder cancer between April 2016 and May 2022. We retrospectively reviewed the medical records of these patients, and the ones with missing data, loss of follow up, having simultaneous immunological or hematological disorders were excluded. Variables such as sex, age, BMI, weight, height, diabetes, hematuria, smoking, and opium usage were gathered and included in this study. These were gathered using a questionnaire filled out by the patients at the time of admittance. We evaluated hematuria by referring to the patients themselves and using urine analysis. Microscopic hematuria was defined as having more than 3 RBCs per power field. The diagnosis of bladder cancer was made by cystoscopy and TURBT. The number of neutrophils, lymphocytes, platelet cells, and blood type was gathered from the routine blood work before TURBT. Staging and grading of the tumor were determined after taking a biopsy by TURBT. We used the AJCC classification for tumor stage (NMIBC; 0a, 0is, I and MIBC; IIA, IIB, IIIA, IIIB, IVA, IVB). For grading, we classified the patients into high-grade and low-grade. Recurrence was defined by cystoscopy during the follow-up of the patients.

## Statistical Analysis

For statistical analysis, we used the statistical software STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). NLR was defined as the absolute neutrophil count divided by the absolute count of lymphocytes. PLR was defined as the absolute platelet count divided by the absolute number of lymphocytes. To obtain cut-offs for NLR and PLR, the logistic regression models were fitted, taking stage and grade as the response variables. Accordingly, the cut-offs, areas under the receiver operating characteristic curves (AUCs), sensitivities, and specificities were reported. Besides, the cut-offs were applied on NLR and PLR, and the proportions were higher than those reported. We stratified the data on age, BMI, blood type, and smoking. Lastly, we adjusted the data for smoking and BMI. We considered the cutoffs with an AUC higher than 70% to be valuable (17). A P-value lower than 0.05

**Table 1.** The descriptive statistics

Variable		N (%)
Sex	Male	393 (86.6%)
	Female	61 (13.4%)
Age	Mean	68.5 ± 13.6
	<65	172 (37.9%)
	≥65	282 (62.1%)
BMI	Mean	23.9 ± 2.9
	<25	332 (74.6%)
	≥25	113 (25.4%)
Weight		68.1 ± 10.0
Height		168.7 ± 7.3
Grade	Low	195 (42.9%)
	High	259 (57.1%)
TNM stage	Non-muscle	293 (64.5%)
	Muscle	161 (35.5%)
Hematuria	Macro	400 (88.1%)
	Micro	36 (7.9%)
	Non	18 (4.0%)
Somker		245 (54.0%)
Opium user		130 (28.6%)
Blood type	O	182 (40.1%)
	A	137 (30.2%)
	B	110 (24.2%)
	AB	25 (5.5%)
Diabetes		57 (12.6%)
Recurrence		36 (7.9%)
Death		107 (23.6%)
NLR (IQR)		3.3 (2.1-5.5)
PLR (IQR)		135.6 (89.6-211.1)
Treatment plan	TURBT	348 (76.7%)
	Radical cystectomy	Ileal loop 90 (19.8%) Orthotopic 16 (3.5%)
	Chemotherapy	Mitomycin 31 (6.8%) BCG vaccine 136 (30.0%) Mitomycine and BCG vaccine 5 (1.1%)

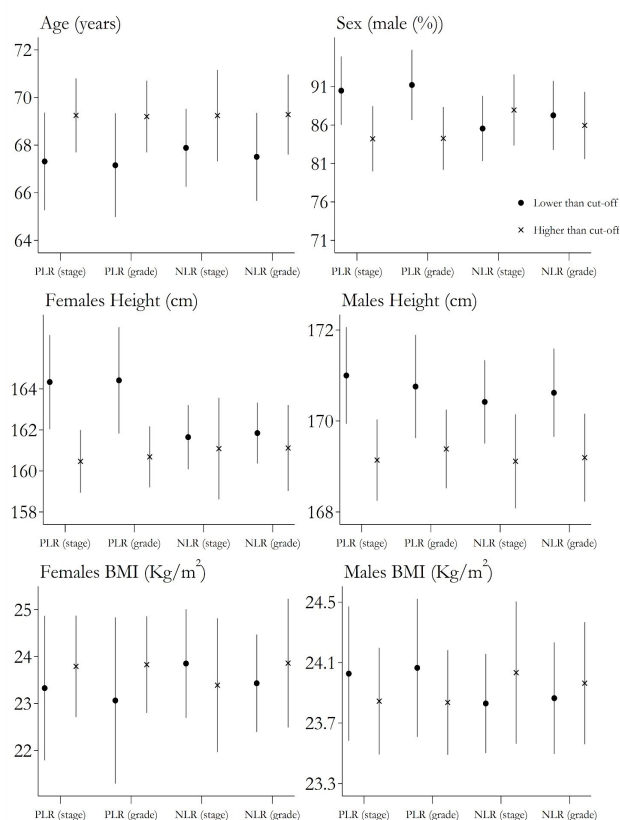
SD: standard deviation; IQR: interquartile range

was considered significant.

## Results

In total, we gathered the medical records of 590 patients. After gathering, the data 454 patients entered the study, and the rest were omitted because of missing data, loss of follow-up, or having hematological or immunological diseases.

As seen in Table 1, out of 454 patients, ranging from 28 to 97 years, 393 were males (86.6%) and 61 were females. 6.4% (29 patients) had a previous cancer history. 37.9% (172 patients) of patients were under 65 years old.



**Figure 1.** Comparing sex, age, BMI, and height distributions between the levels (arrows represent 95% CIs)

42.9% were low grades and 57.1% were high grades (195 and 259 patients respectively). 64.5% of patients were non-muscle invasive (293 patients) and 35.5% were muscle invasive (161 patients). 88.1% of patients had macro hematuria while 7.9% had micro and 4% had no hematuria (400, 36 and 18 patients respectively). 54% or 254 patients were smokers and 28.6% were opium users (130 patients). 36 patients experienced recurrence (7.9%) and 107 patients died (23.6%). The median for NLR and PLR was 3.3 (interquartile range 2.1-5.5) and 135.6 (IQR 89.6-211.1), respectively. 76.7% of our patients underwent TURBT while the rest underwent radical cystectomy. Chemotherapy with mitomycin, or BCG vaccine was used in 172 of patients as seen in Table 1.

Fitting the logistic regression model, the appropriate cut-off for NLR as a predictor of the grade was 3.09 and the cutoff for NLR as a predictor of the stage was 3.78 (AUC 59.0 and 58.1%, respectively). The cut-off for PLR as a predictor of the grade was 100.8 (AUC 58.9%), and the cut-off for the stage was 109.6 (AUC 59.8%) as seen in table 2. Later we analyzed our data to see if the cutoffs for PLR and NLR have any relationship with other factors such as age, gender, height, and BMI (height and BMI were analyzed for each gender separately). The only

**Table 2.** Cut-offs for NLR and PLR, as predictors of stage and grade

	Cut-off	AUC	Sensitivity	Specificity	Proportion higher than the cut-off
<b>NLR as a predictor of grade</b>	3.09	59.0 %	60.6 %	56.4 %	242 (53.3 %)
<b>NLR as a predictor of stage</b>	3.78	58.1 %	52.2 %	62.8 %	191 (42.1 %)
<b>PLR as a predictor of grade</b>	100.8	58.9 %	74.4 %	42.1 %	305 (67.3 %)
<b>PLR as a predictor of stage</b>	109.6	59.8 %	73.9 %	42.8 %	285 (62.5 %)

**Table 3.** The association of categorized forms of NLR and PLR with the covariates, reported as number of cases higher than the cutoff(percent)

		<b>NLR = 3.09 (grade)</b>	<b>NLR = 3.78 (stage)</b>	<b>PLR = 100.8 (grade)</b>	<b>PLR = 109.6 (stage)</b>
<b>Smoking</b>	No	109 (52.2 %)	89 (42.6 %)	151 (72.3 %)	143 (68.4 %)
	Yes	133 (54.3 %)	102 (41.6 %)	154 (63.1 %)	142 (58.2 %)
<b>P-value</b>		0.650	0.833	0.039	0.025
<b>Opium</b>	No	163 (50.3 %)	129 (39.8 %)	224 (69.3 %)	209 (64.7 %)
	Yes	79 (60.8 %)	62 (47.7 %)	81 (62.3 %)	76 (58.5 %)
<b>P-value</b>		0.043	0.124	0.148	0.213
<b>Blood type</b>	O	90 (49.5 %)	69 (37.9 %)	123 (67.6 %)	113 (62.1 %)
	non-O	149 (55.4 %)	119 (44.2 %)	179 (66.8 %)	169 (63.1 %)
<b>P-value</b>		0.123	0.046	0.473	0.402
<b>Recurrence</b>	No	219 (52.4 %)	172 (41.2 %)	277 (66.4 %)	259 (62.1 %)
	Yes	23 (63.9 %)	19 (52.8 %)	28 (77.8 %)	26 (72.2 %)
<b>P-value</b>		0.185	0.175	0.164	0.228
<b>Death</b>	No	176 (50.7 %)	139 (40.1 %)	227 (65.6 %)	212 (61.3 %)
	Yes	66 (61.7 %)	52 (48.6 %)	78 (72.9 %)	73 (68.2 %)
<b>P-value</b>		0.051	0.118	0.160	0.193

P-values from the Chi-squared test

significant relationship was seen between PLR (cutoff of 109.6, for stage) and height (in both genders, both P-values <0.01), as seen in Figure 1.

The association between the mentioned cutoffs for NLR and PLR with other variables including smoking, opium blood type recurrence, and death is shown (Table 3). Opium usage, blood type recurrence, and death had no relationship with PLR. On the other hand, smoking, recurrence, and death had no significant relationship with NLR. Significant relationships were seen between NLR with opium and blood type. In patients who used opium, NLR as the predictor of the grade was significantly higher than 3.09 (60.8% of opium users were above the mentioned cut-off compared to 50.3% of non-opium users who had a higher NLR than 3.09, P-value 0.035). Patients with non-O blood type with NLR higher than 3.78 (cutoff set for stage) were significantly higher than O blood type patients (44.2% of non-O blood type patients had NLR higher than 3.78 vs 37.9% of O blood

type patients, P-value=0.043). We also saw a significant relationship between smoking and PLR. Non-smokers had a significantly higher PLR than smokers (PLR cutoff 100.8; 72.3% of nonsmokers vs. 63.1% of smokers had higher PLR, P-value=0.039, PLR cutoff 109.6; 68.4% of nonsmokers had a PLR higher than 109.6 vs. 58.2% of smokers, P-value=0.025).

After stratifying the data for age, BMI, smoker, and blood type the analysis gave us, cut-offs for each specific stratification. As seen in Table 4, We saw that in patients younger than 65, NLR and PLR, both as predictors of grade have an area under the curve above 70% and could have predictive value (NLR cutoff=3.16; AUC=70.3%, PLR cutoff=70.5; AUC=70.5%). Also, in patients younger than 65, a PLR value of 109.57, as a predictor of the stage had an AUC of 67.6%. The rest of the stratified defined cutoffs all had an AUC lower than 65%.

Later the NLR and PLR stratified for age and blood type were adjusted for smoking and BMI, as seen in Table

**Table 4.** Cut-offs for NLR and PLR, as predictors of stage and grade, stratified for age, BMI, blood type, and smoking

			Cut-off	AUC	Sensitivity	Specificity
NLR as a predictor of grade	Age	<65	3.16	<b>70.3 %</b>	63.8 %	70.5 %
		≥65	3.09	51.7 %	58.8 %	47.9 %
	BMI	<25	3.13	56.7 %	59.5 %	56.1 %
		≥25	2.50	64.6 %	79.2 %	48.3 %
	Smoker	No	2.91	61.7 %	69.4 %	55.1 %
		Yes	3.11	57.1 %	59.5 %	55.7 %
	Blood type	O	1.62	52.6 %	88.9 %	24.3 %
		non-O	3.78	63.5 %	55.7 %	68.3 %
PLR as a predictor of grade	Age	<65	109.57	70.5 %	78.5 %	60.3 %
		≥65	71.96	48.2 %	13.9 %	88.9 %
	BMI	<25	111.22	57.6 %	69.8 %	47.0 %
		≥25	136.68	61.7 %	56.6 %	65.0 %
	Smoker	No	129.52	60.0 %	70.3 %	49.0 %
		Yes	102.98	58.6 %	68.7 %	49.5 %
	Blood type	O	109.84	52.8 %	66.7 %	44.6 %
		non-O	116.67	62.4 %	68.9 %	52.5 %
NLR as a predictor of stage	Age	<65	3.42	64.4 %	62.7 %	64.6 %
		≥65	6.23	54.3 %	26.5 %	82.8 %
	BMI	<25	4.89	57.0 %	38.9 %	75.2 %
		≥25	3.09	61.9 %	71.9 %	53.1 %
	Smoker	No	2.95	61.1 %	68.3 %	50.7 %
		Yes	3.42	56.5 %	56.1 %	57.8 %
	Blood type	O	3.35	50.4 %	53.2 %	59.2 %
		non-O	5.21	63.3 %	43.9 %	79.5 %
PLR as a predictor of stage	Age	<65	109.57	67.6 %	81.4 %	50.0 %
		≥65	136.49	55.1 %	57.8 %	52.2 %
	BMI	<25	109.57	59.9 %	75.4 %	42.0 %
		≥25	103.24	59.7 %	78.1 %	43.2 %
	Smoker	No	124.74	61.0 %	74.6 %	43.2 %
		Yes	113.83	60.2 %	68.4 %	52.1 %
	Blood type	O	111.63	52.1 %	69.4 %	43.3 %
		non-O	208.33	64.8 %	41.8 %	82.4 %

5. In patients younger than 65, NLR as a predictor of grade with a cutoff of 3.89 had an AUC of 71.4. In addition, in the same category of patients PLR as a predictor of grade with a cutoff of 180.50 had an AUC of 70.6%. In patients younger than 65, an NLR value of 4.00 and PLR value of 248.99 as predictors of the stage had AUCs of 72.4% and 73.8% respectively. Adjusting the stratified data for non-O blood type raised the AUC to higher than 65%. For example, a PLR cutoff of 123.16 in these patients' groups had an AUC of 69.5%.

### Discussion

In this study, we wanted to find out in NLR, and PLR can predict stage and grade in patients with bladder cancer. We also used these cutoffs to see if they have any relationship with the clinical features of our patients. Lastly stratified and later adjusted our data to see if we could reach a better cutoff for stage and grade.

Even though smoking is a major risk factor for bladder cancer, we did not find any relationship between NLR. On the other hand, PLR was significantly higher among

**Table 5.** Cut-offs for NLR and PLR, as predictors of stage and grade, stratified for age and blood type, adjusted for smoking and BMI

Variables			Cut-off	AUC	Sensitivity	Specificity
NLR as a predictor of grade	Age	<65	3.89	71.4 %	72.0 %	63.6 %
	Blood type	non-O	4.46	66.8 %	78.5 %	49.2 %
PLR as a predictor of grade	Age	<65	180.50	70.6 %	54.3 %	84.4 %
NLR as a predictor of stage	Age	<65	4.00	72.4 %	79.7 %	57.7 %
	Blood type	non-O	3.58	68.8 %	74.7 %	55.7 %
PLR as a predictor of stage	Age	<65	248.99	73.8 %	59.3 %	82.7 %
	Blood type	non-O	123.16	69.5 %	72.6 %	58.4 %

nonsmokers (P-value=0.039 and 0.025). This finding was also observed by Mano et al., who said that PLR was significantly lower in smokers compared to nonsmokers (P-value=0.043) (18). This relationship between PLR and smoking was also seen in non-cancer patients (19). NLR did not have any relationship with smoking in other studies by Mano et al., Tang et al., and Pujani et al., (18-21).

In our study, the NLR level of patients who used opium was significantly higher than 3.09 compared to those who did not use opium. However, when the cutoff was set at 3.78 the relationship lost its significance. Opium usage may be able to decrease the level of PLR; however, the relationship was insignificant. According to earlier studies, opium usage does not affect NLR, however, it can significantly decrease PLR (22). Up to now, we analyzed the relationship of blood type with NLR and PLR. Even though it has been said that O blood type is associated with worse tumor grade and mortality rate (23), and based on other findings one can speculate that it may have higher NLR and PLR, we saw that patients with non-O blood type have an NLR significantly higher than those with O blood type patients.

According to our data, NLR and PLR do not have a relationship with gender. The same finding was found in other studies (7, 8, 12, 20, 24-26). On the other hand, Mano et al., observed that NLR was significantly higher among males (18). We did not find any relationship between NLR, PLR, and age. This finding was also seen in other researches (18, 20, 24, 25). However, according to Luo et al., NLR is significantly associated with age (26). According to a meta-analysis by Wang et al., PLR is associated with age (12).

We also saw that in both females and males, patients with a PLR lower than 109.6 were significantly taller than those with a higher PLR were. This finding was more noticeable in females as the difference between the two groups was close to 4cm (160 vs 164). This means that people with shorter stature and under the age of 65 may have a better disease characteristic; however, more research needs to be carried out to confirm this finding.

We did not see any relationship between NLR, PLR, and BMI, like previous findings by Chung et al., and Li et al., (18, 24).

Even though it seems like patients who died or experienced recurrence have higher NLR and PLR, no significant relationship was seen. According to a meta-analysis, in patients with NMIBC treated with BCG and TURBT, NLR was independently associated with disease recurrence and could predict a worse progression-free survival (PFS) (13). In a more recent study by Chung et al., NLR higher than 2.29 was associated with lower risk-free survival (RFS) and PFS and was an independent risk factor for recurrence (24). In another study by Yildiz et al., in NMIBC patients, NLR with a cutoff of 2.54 was significantly associated with recurrence. However, NLR lost its significance in the multivariate study (including factors like age, gender, size grade, carcinoma in situ (CIS), and size (27). Albayrak et al., stated that NLR was positively correlated with recurrence risk score; however, NLR lost its significance after adjustment for age (28). According to a meta-analysis by Wang X et al., PLR was significantly associated with worse overall survival (OS), however, it was not associated with recurrence-free survival (RFS) (12). The current data on patients receiving neoadjuvant chemotherapy is inconclusive, a higher PLR was associated with a worse pathological response, however; NLR lacked this association (29).

After stratifying the data, the value of NLR and PLR as predictors of grade increased for patients under 65. Later we adjusted the data the predictability value of NLR and PLR for patients under 65 increased further. To predict the grade 3.89 was the optimum cutoff for NLR, and 180.5 was set as the cutoff for PLR. To predict stage 4 was the optimum cutoff for NLR while 248.99 was the cutoff for PLR. According to a study by Tang et al., NLR and PLR both had predictive value for the pathological grade (high vs. low) and muscle invasiveness of bladder cancer. For grading the cutoff for NLR was 4.24 (AUC=0.643, P-value<0.001), and the cutoff for PLR was set as 190.44 (AUC=0.579, P-value<0.001). For the invasiveness of the disease, the cutoff for NLR was 6.58

(AUC=0.766, P-value<0.001) and for PLR it was 248.86 (AUC=0.672, P-value<0.001) (20). In one meta-analysis, NLR was associated with pathological grading but not with its staging (P-values<0.001 and 0.311, respectively), also it was said that NLR had no association with the invasiveness of the disease (30). In another recent study, where they analyzed the diagnostic and predictive value of NLR and PLR in patients undergoing radical cystectomy, they concluded that NLR and PLR had no diagnostic value for grade, tumor stage, and systematic metastasis. For grading, they used 2.71 and 181.37 for NLR and PLR respectively (AUC=0.523 and 0.703, P-value=0.8 and 0.2 respectively). For staging, the NLR cutoff was 1.8 (AUC=0.567, P-value=0.5) and PLR cutoff was 172.82 (AUC=0.667, P-value=0.2) (31). In another study by Lee et al., they concluded that NLR with a cutoff of 3.89 (AUC=0.710) can help differentiate MIBC vs NMIBC (8).

This was a single center study, carried out in Sina hospital, which is a tertiary surgical center. As a result, some of the patients are complicated cases referred to our center, moreover, the number of cases may not be large enough, and larger multi center prospective studies are needed. In addition, this was a retrospective study, meaning it is prone to selection and recall bias. Lastly, inflammatory markers evaluated in this study are susceptible to many factors and it is not possible to omit all of them, also they were assessed preoperatively at a single time meaning variability overtime and response to treatment was not assessed.

### Conclusions

Based on our findings NLR and PLR are promising as predictors of stage and grade for patients under 65 and show to have promising value in predicting stage and grade in non-O blood group patients. Opium can significantly increase the level of NLR. We also found that patients with shorter stature significantly have a higher PLR than 109.6.

### Authors' contributions

NA and SFH wrote the manuscript, RMF, RAB and MN collected data, AKH analyzed the data, and MKH, LOR and VAY edited the manuscript.

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### Conflict of interest

All authors declare that there is no conflict of interest.

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### Ethics statement

All patients signed the written informed consent, and the study was approved by the Tehran University of Medical Sciences' ethical committee (IR.TUMS.MEDICINE.REC.1401.535).

### Data availability

Data will be provided on request.

### Abbreviations

NLR	Neutrophil-to-Lymphocyte Ratio
PLR	Platelet-to-Lymphocyte Ratio
RFS	Recurrence-free survival
SII	Systemic immune-inflammation index
TURBT	Transurethral resection of bladder tumor

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