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# Prognostic Significance of Neutrophil-to-Lymphocyte Ratio in Patients with Nonmuscle-Invasive Bladder Cancer who Underwent Intravesical Bacillus Calmette-Guérin Treatment

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## Abstract

**Background:** The ninth most prevalent cancer worldwide and the 13th major reason of cancer-related fatalities is urinary bladder cancer (BC).

**Aim and objectives:** To evaluate the effect of pretreatment neutrophil-to-lymphocyte ratio (NLR) as a clinical outcome predictor in patients with intravesical Bacillus Calmette-Guérin-treated nonmuscle-invasive bladder cancer (NMIBC).

**Patients and methods:** From the El-Hussein Hospital and Kobry-Alkobba Military Hospital, 126 patients with NMIBC participated in this retrospective cohort research.

**Result:** No significant differences were found between cancer-free patients and patients with recurrence at first follow-up cystoscopy regarding tumor size ( $P > 0.05$ ). Tumor multiplicity showed a significant difference between the two groups, as it was substantially greater in cases with recurrence ( $P < 0.001$ ). There was a significant relation between results of first follow-up cystoscopy and further follow-up cystoscopy ( $P < 0.001$ ). By using receiver operating characteristic curve analysis, NLR can predict recurrence at first follow-up cystoscopy at a cutoff of 2.2 with sensitivity, specificity, positive predictive value, and negative predictive value of 93.55, 78.26, 65.9, and 96.4%, respectively, and area under the curve was 0.850.

**Conclusion:** Along with the well-established prognostic variables, a higher value of NLR measured preoperatively may be beneficial to predict the Bacillus Calmette-Guérin effect and therefore give crucial information for the clinical treatment of high-risk NMIBC cases.

**Keywords:** Bladder cancer, Lymphocyte, Neutrophil, Nonmuscle, Prognostic

## 1. Introduction

The ninth most prevalent cancer worldwide and the thirteenth major reason for cancer-related mortality is urinary bladder cancer (BC).<sup>1</sup>

Transurethral resection of the bladder tumor (TURBT) combined with intravesical chemotherapy or intravesical Bacillus Calmette-Guérin (BCG) immunotherapy is the usual therapy for nonmuscle-invasive bladder cancer (NMIBC). However, the rates of NMIBC development and recurrence

during a 5-year period vary from 1 to 45% and 31–78%, respectively.<sup>2</sup>

The numbers of neutrophils divided by the numbers of lymphocytes is known as the neutrophil-to-lymphocyte ratio (NLR). Physiologic stress results in a rise in neutrophils and a decrease in lymphocytes. Both of these changes are combined using the NLR, making it more sensitive than each would be by itself.

In individuals with NMIBC, a higher NLR score is related with T1 tumors, high grades, multiple

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tumors, more than 3-cm tumors, and the high-risk group of the European Organization for Research and Treatment of Cancer. Additionally, there was a favorable connection between NLR and European Organization for Research and Treatment of Cancer progress and recurrent scores.

## 2. Patients and methods

Consent was taken from cases for the study. This retrospective cohort research was based on the hospital registry (El-Hussein Hospital and Kobry-Alkobba Military Hospital). This study included cases that underwent TURBT in both El-Hussein Hospital and Kobry-Alkobba Military Hospital during the period from January 2015 till January 2021.

**Inclusion criteria:** all patients with NMIBC who received six sessions of intravesical BCG 2–6 weeks after TURBT with no reported complication from BCG and underwent follow-up cystoscopy at least after 3 months from TURBT were included.

### 2.1. Exclusion criteria

Patients with any of the followings were excluded: missing preoperative differential blood cell count, concurrent cancer, hematological problems, radiation history, concurrent infection, or chronic inflammatory illnesses.

**Operational design:** data were collected from files of patients who underwent TURBT from January 2015 till January 2021. The following data were collected.

**Initial assessment:** completely history taking, mentioning personal history (name, age, and occupation), present history, past history of any disease (diabetes mellitus and hypertension), and family history of BC.

**Clinical examination** focusing on general evaluation such as vital signs (blood pressure, temperature, pulses, and respiratory rate), and disease signs (jaundice, cyanosis, pallor, and enlarged lymph nodes).

Investigations included preoperative differential blood cell count, preoperative imaging studies, and tumor characteristic during initial cystoscopy.

**TUR procedure:** bimanual examination was done before and after TURBT in every patient to check resectability of the tumor.

**Histopathological characteristic:** specimens were examined for identification of the type of the tumor.

**Intravesical BCG administration:** 2 weeks after uncomplicated resection, we started to administrate BCG intravesically once weekly for 6 weeks. Overall,

40 mg of BCG diluted with 50 ml of saline 0.9% was used for intravesical injection after emptying of the bladder by urethral catheter.

**Follow-up cystoscopy:** the studied cases underwent follow-up cystoscopy according to EAU guidelines schedule at least after 3 months from TURBT.

**Designing for administration and ethics:** Al-Azhar University's Faculty of Medicine granted official clearance to the study (Cairo). A formal approval was obtained from the administrators of the hospital registry (El-Hussein Hospital and Kobry-Alkobba Military Hospital). Approval was obtained from the medical school's ethics committee (Institutional Research Board IRB).

**Management of data and statistical analysis:** statistical Package for the Social Sciences (SPSS), version 22 was employed to gather, tabulate, and statistically analyze all data (SPSS Inc. Chicago, Illinois, USA).

## 3. Results

This retrospective cohort research included 126 patients with NMIBC who received six sessions of intravesical BCG and were referred to El-Hussein Hospital and Kobry-Alkobba Military Hospital (Table 1).

The age of studied patients ranged between 40 and 70 years with a mean age of  $59.44 \pm 6.46$  years. More than half of patients (53.2%) were more than 60 years. It was noticed that there was a higher prevalence of males than females (88.1 vs. 11.9%).

All patient underwent successful complete transurethral removal of bladder tumor and received six sessions of intravesical BCG 2–6 weeks after TURBT with no reported complication from BCG, as shown in Table 2.

The studied patients underwent follow-up cystoscopy after 3 and 6 months from TURBT. The first follow-up cystoscopy revealed that recurrence of tumor occurred in 43 (34.1%) patients, and after 6

Table 1. Demographic data of the studied patients (N = 126).

	Studied patients [n (%)]
Sex	
Males	111 (88.1)
Females	15 (11.9)
Age (years)	
Mean $\pm$ SD	59.44 $\pm$ 6.46
Median	60.0
Range	40.0–70.0
Age categories	
<60 years	59 (46.8)
$\geq$ 60 years	67 (53.2)

Table 2. Distribution of the studied patients as per transurethral resection procedure and Bacillus Calmette-Guérin (N = 126).

	Studied patients [n (%)]
Outcome of TURBT	
Complete resection	126 (100.0)
Incomplete resection	0
Number of BCG instillation	
6 sessions	126 (100.0)

BCG, Bacillus Calmette-Guérin; TURBT, transurethral resection of the bladder tumor.

months, the recurrence increased to 37.3% of patients, as shown in Table 3.

We adopted a cut-off of 2.2 for the NLR based on the receiver operating characteristic (ROC) curve, which had an area under the curve of 0.804 and a 95% confidence interval (CI) of 0.724–0.869 ( $P < 0.001$ ), providing the optimal balance between sensitivity (90.7%) and specificity (62.7%), as shown in Table 4 and Fig. 1.

NLR more than 2.2 was related to poorer disease recurrence in the multivariate Cox regression analysis [hazard ratio (HR) = 6.887, 95.0% CI: 2.286–20.748;  $P = 0.01$ ]. Additionally, tumor sizes more than or equal to 3 cm were independently related with a greater risk of the illness returning (HR = 2.339, 95.0% CI: 1.065–5.140;  $P = 0.034$ ). Using the multivariate Cox regression analysis, there was no relation between disease progression and age,

Table 3. Distribution of the study patients as per follow-up (N = 126).

Description	Studied patients [n (%)]
First follow up cystoscopy	
Recurrence	
Absent	83 (65.9)
Present	43 (34.1)
Type	
TCC	126 (100.0)
Stage	
Ta	56 (44.4)
T1	70 (55.6)
Grade	
Low	85 (67.5)
High	41 (32.5)
Further follow-up cystoscopy	
Recurrence	
Absent	79 (62.7)
Present	47 (37.3)
Type	
TCC	126 (100.0)
Stage	
Ta	32 (25.4)
T1	94 (74.6)
Grade	
Low	75 (59.5)
High	51 (40.5)

sex, tumor grade, tumor stage, or tumor multiplicity (Table 5).

The period between the date of diagnosis and the date of recurrent was used to calculate recurrence-free survival. The mean recurrence-free survival for all patients under study was 5.565 months for those with NLR less than or equal to 2.2 and 3.623 months for those with NLR more than 2.2. NLR less than or equal to 2.2 patients had a greater median recurrence-free survival than NLR more than 2.2 patients ( $P < 0.001$ ) (Table 6, Fig. 2).

#### 4. Discussion

It is now understood that altered acute-phase reactive chemical and hematologic components are caused by enhanced systemic inflammatory reactions brought on by tumor microenvironments.<sup>3</sup> Neutrophil and lymphocyte numbers, which might show comparable neutrophilia and lymphocytopenia, are among these blood indicators. A larger proportion of neutrophils than lymphocytes is linked to worse overall and cancer-free survival in a variety of patients with tumor.<sup>4–6</sup>

In terms of demographic information for the group under research, the current study revealed that the age range of the patients was between 40 and 70 years old, with a mean age of  $59.44 \pm 6.46$  years. More than half of patients (53.2%) were more than 60 years. It was noticed that there was a higher prevalence of males than females (88.1 vs. 11.9%).

The present study was supported by Kim and Patel,<sup>7</sup> who analyzed the predictability of preoperative NLR in patients with BC that is not invasive to the muscles (NMIBC). A total of 281 individuals who had intravesical BCG treatment after transurethral excision of a BC were included in the research. In the study groups, women made up 12.8% (36/281) of the patients. The mean age was  $67.38 \pm 10.58$  years.

In the current study, we found that all patients underwent successful complete transurethral removal of bladder tumor and received six sessions of intravesical BCG 2–6 weeks after TURBT with no reported complication from BCG. The first follow-up cystoscopy revealed that recurrence of tumor occurred in 43 (34.1%) patients, and after 6 months, the recurrence increased to 37.3% of patients.

We chose a cut-off of 2.2 for the NLR based on the ROC curve because it had the greatest balance of sensitivity (90.7%) and specificity (62.7%), an area under the curve of 0.804, and a 95% CI of 0.724–0.869 ( $P < 0.001$ ). The patients in the study were split into two groups based on this cutoff: NLR less than or equal to 2.2, in which 56 (44.4%) were

Table 4. The best cutoff value for neutrophil-to-lymphocyte ratio based on receiver operating characteristic curve.

Parameters	Cutoff value	Sensitivity	Specificity	AUC	95% CI	P value
NLR	>2.2	90.7%	62.7%	0.804	0.724–0.869	<0.001

AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio.

included, and NLR more than 2.2, in which 70 (55.6%) patients were included.

The current study was supported by Kim and Patel,<sup>7</sup> who reported that the cut-off NLR value was set at 2.29 based on a ROC curve. A total of 173 patients had an NLR of 2.29 (61.6%), and 108 (38.4%) had an NLR more than 2.29. Overall, 84 (29.9%) patients had recurrence and 14 (5.0%) showed progression after TUR and BCG therapy.

Moreover, the study by Getzler et al.<sup>3</sup> reported that the mean follow-up period for patients without recurrent was 18 months, whereas 64 (56.6%) patients had recurrences throughout the course of the trial, with recurrences occurring at a mean time of 9 months [interquartile range (IQR) 6, 13] (IQR 14, 30). A total of 69 (58%) patients had a mean NLR of 2.69 (IQR 1.9, 4.35) and an NLR more than 2.5.

However, D'Andrea et al.<sup>8</sup> reported that overall, 95 (8.5%) patients had two or more past recurrences, 89 (7.9%) had one prior recurrence, and 933 (83.5%) had primary identified NIMBC. NLR was  $2.56 \times 10^9$  per liter on average (IQR 2.1–3.7). A total of 361 (32.3%) patients had an NLR more than or equal to 3, and the average age of patients was 67 years (IQR 58–74) in this group. The illness recurred in 469 (42%) individuals, progressed in 103 (9.2%), and killed 50 (4.5%) people during the course of a mean follow-up of 62.6 months (IQR 25–110). In all, 274 (29.8%) patients had early recurrent, and 27 (2.9%) experienced early progression.

In terms of the patients' demographics according to the NLR, our findings revealed that when compared with those with NLR more than or equal to 2.2, patients with NLR more than 2.2 exhibited

significant differences of upper system state ( $P = 0.029$ ), number of multifocal lesions (38.6 vs. 10.7%;  $P < 0.001$ ), and CIS (50.0 vs. 16.94%;  $P < 0.05$ ).

During the follow-up study, four (7.1%) and 39 (55.7%) patients with NLR less than or equal to 2.2 and more than 2.2, respectively, experienced recurrence with significant increase of recurrence rate in patients with NLR more than 2.2 ( $P < 0.001$ ). The two groups did not substantially vary in terms of age, sex, and tumor grade, stage, or size ( $P > 0.05$ ).

In line with our findings, Kim and Patel<sup>7</sup> showed that the two groups did not vary substantially regarding sex, age, BMI, tumor grade, tumor stage, or tumor size; nevertheless, there were statistically significant differences in terms of recurrence and progression.

Table 5. Multivariate Cox regression analysis for tumor recurrence predictions.

	HR	95.0% CI		P value
		Lower	Upper	
Age	0.910	0.446	1.858	0.796
Sex (males vs. females)	1.400	0.466	4.209	0.549
Tumor grade (low vs. high)	1.400	0.466	4.209	0.057
Tumor stage (Ta vs. T1)	0.968	0.456	2.055	0.933
Tumor multiplicity	0.754	0.332	1.713	0.500
Tumor size ( $\geq 3$ cm vs. $< 3$ cm)	2.339	1.065	5.140	0.034
NLR ( $> 2.2$ vs. $\leq 2.2$ )	6.887	2.286	20.748	0.001

CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 6. Recurrence-free survival analysis in the studied patients with patients with neutrophil-to-lymphocyte ratio less than or equal to 2.2 and neutrophil-to-lymphocyte ratio more than 2.2

Recurrence-free survival median survival		
	Mean survival (months)	95% CI
NLR $\leq 2.2$	5.565	5.171–5.958
NLR $> 2.2$	3.623	3.160–4.085
Overall	4.361	3.985–4.737
Comparison of survival curves (Log rank test)		
$\chi^2$	28.154	
DF	1	
Significance	$P < 0.001$	
Hazard ratio with 95% CI		
Hazard ratio	8.333	
95% CI	2.95–23.26	

CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio.

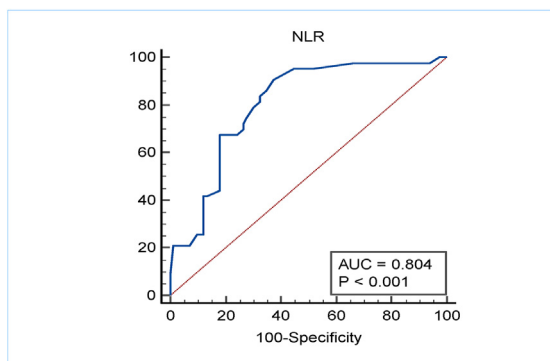


Fig. 1. The ROC curve's recommended cutoff for the NLR value. NLR, neutrophil-to-lymphocyte ratio; ROC, receiver operating characteristic.

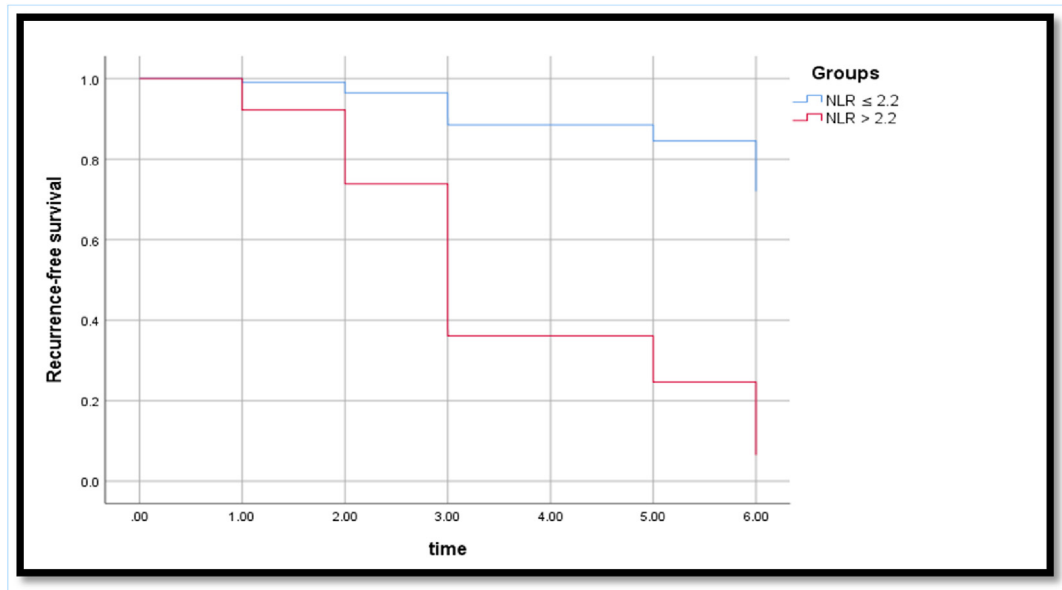


Fig. 2. Kaplan–Meier curve analysis of recurrence-free survival stratified by NLR. NLR, neutrophil-to-lymphocyte ratio.

Moreover, the study by Getzler et al.<sup>3</sup> reported that regarding recurrence, stage, and CIS, there were statistically significant differences between the examined groups (with a criterion of NLR = 2.5). The tested groups did not vary statistically significantly in terms of age, sex, grade, number of tumors, or tumor diameter.

From our results and literature, we can see that the value of NLR was very sensitive, as at different cutoff values, it not only correlated with recurrence and progression risks but can differentiate tumor grade, stage, and size.

NLR more than 2.2 was related to poorer disease recurrence in the multivariate Cox regression analysis (HR = 6.887, 95.0% CI: 2.286–20.748;  $P = 0.01$ ). Moreover, tumor size more than or equal to 3 cm was an independent predictor of disease recurrence (HR = 2.339, 95.0% CI: 1.065–5.140;  $P = 0.034$ ). No association was found between disease progression and age, sex, tumor grade, tumor stage, as well as tumor multiplicity at the multivariate Cox regression analysis.

However, the study by Kim and Patel<sup>7</sup> reported that in a multivariate Cox proportional risks regression model for predicting recurrent, female sex, contemporaneous CIS, multiplicity (>3), prior relapse status, and an NLR more than 2.29 were independent indicators of tumor relapse (HR = 2.565, 95% CI = 1.485–4.431,  $P = 0.001$ ; HR = 2.007, 95% CI = 1.059–3.802,  $P = 0.033$ ; HR = 1.874, 95% CI = 1.165–3.012,  $P = 0.010$ ; HR = 2.320, 95% CI = 1.280–4.207,  $P = 0.006$ ; and HR = 2.451; 95% CI = 1.567–3.834,  $P < 0.001$ , respectively).

Moreover, the study by D'Andrea et al.<sup>8</sup> reported that the discrimination for recurrence prediction rose from 67.2 to 67.8% and recurrence from 67 to 69.3%, respectively, with the inclusion of NLR to a basic model that included pathological T stage, grade, concurrent CIS, diameter, and focality of tumor. They also discovered that patients with NLR 3 had greater rates of early recurrent (35.1 vs. 27.4%;  $P = 0.02$ ) and early progress (5.1 vs. 1.9%;  $P = 0.007$ ). They also reported that age but not sex was a predictor of recurrence.

In the present study, we found that the recurrence-free survival of all studied patients was measured and had a median of 5.565 months for patients with NLR less than or equal to 2.2 and 3.623 months for patients with NLR more than 2.2.

Patients with NLR less than or equal to 2.2 showed higher median recurrence-free survival than those with NLR more than 2.2 ( $P < 0.001$ ).

In agreement with the current study, Kim and Patel<sup>7</sup> reported that according to Kaplan–Meier curve analysis, a higher NLR was linked to shorter recurrence-free survival and progression-free survival ( $P < 0.001$ ) and progression-free survival ( $P = 0.002$ , respectively). An NLR more than 2.29 were discovered as a relevant predictor for predicting tumor recurrence and progression in patients with NMIBC, according to the study's findings.

#### 4.1. Conclusion

An NLR more than 2.2 was shown to be a substantial predictor of tumor recurrent, tumor

multiplicity, and upper system status in patients with NMIBC. The NLR ( $>2.2$  vs.  $\leq 2.2$ ) and tumor size were shown to be independent risk factors for tumor recurrence. NLR more than 2.2 patients had a greater recurrence-free survival rate. NLR may be done in conjunction with a diagnostic flexible cystoscopy, making it a simple, affordable, and straightforward marker for NMIBC that can help with the planning of follow-up care. The function of NLR as a risk factor in NMIBC has to be further validated in large prospective studies with extended follow-up periods.

#### Conflict of interest

None declared.

#### References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2013;63:11–30.
2. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. 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. *Eur Urol.* 2006;49:466–500.
3. Getzler I, Bahouth Z, Nativ O, Rubinstein J, Halachmi S. Preoperative neutrophil to lymphocyte ratio improves recurrence prediction of non-muscle invasive bladder cancer. *BMC Urol.* 2018;18:1–10.
4. Ceylan C, Doluoğlu ÖG, Keleş I, et al. Importance of the neutrophil-to-lymphocyte ratio in muscle-invasive and non-muscle invasive bladder tumors. *Urol J.* 2014;81:120–124.
5. Viers BR, Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Tollefson MK. Preoperative neutrophil-lymphocyte ratio predicts death among patients with localized clear cell renal carcinoma undergoing nephrectomy. *Urol Oncol.* 2014;32:1277–1284.
6. Lee BS, Lee SH, Son JH, et al. Neutrophil–lymphocyte ratio predicts survival in patients with advanced cholangiocarcinoma on chemotherapy. *Cancer Immunol Immunother.* 2016;65:141–150.
7. Kim LH, Patel MI. Transurethral resection of bladder tumour (TURBT). *Transl Androl Urol.* 2020;9:3056.
8. D'Andrea D, Moschini M, Gust K, et al. Prognostic role of neutrophil-to-lymphocyte ratio in primary non–muscle-invasive bladder cancer. *Clin Genitourin Cancer.* 2017;15:e755–e764.