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Prognostic Significance of Neutrophil to Lymphocyte Ratio in Patient with Non-Muscle Invasive Bladder Cancer Who Underwent Intravesical BCG Treatment

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ABSTRACT

Urinary bladder cancer (BC) is the ninth most common cancer in the world and the 13th cause of cancer deaths.

Aim of work: The aim of our study was to assess the role of pretreatment neutrophil-to- lymphocyte ratio (NLR) as a predictor of clinical outcomes in patients with non-muscle invasive bladder cancer (NMIBC) who underwent intravesical Bacillus Calmette-Guérin (BCG) treatment.

Methods: This retrospective study was conducted at Ain-shams university hospital and included 100 patients having NMIBC.

Results: NLR can predict recurrence at further follow up cystoscopy at cutoff 3.3 with sensitivity of 89.7%, specificity of 85.2%, PPV of 79.5%, NPV of 92.9% and AUC was 0.90.

Conclusions: Our data showed that a high value of NLR (add cutoff) evaluated preoperatively might be helpful to predict the BCG response and therefore provide critical information for the clinical management of high-risk NMIBC patients together with the prognostic factors already known.

Keywords: *Neutrophil to lymphocyte ratio, non-muscle invasive bladder cancer intravesical BCG*
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INTRODUCTION

Urinary bladder cancer (BC) is the ninth most common cancer in the world and the 13th cause of cancer deaths (1). 2.7 million people is the estimated number of patients who have a history of BC worldwide (2), and nearly 75% of newly diagnosed patients present with non-muscle invasive bladder cancer (3).

The standard treatment for NMIBC is transurethral resection of bladder tumor (TURBT) with intravesical chemotherapy or intravesical Bacillus Calmette-Guérin (BCG) immunotherapy. However, the recurrence and progression rates of NMIBC for 5 years range from 31% to 78% and from 1% to 45%, respectively (4).

The identification of patients with higher risk of recurrence and progression is mandatory in order to predict oncological outcomes and for optimal tailored therapeutic decision-making (5).

Since Virchow first described a possible connection between inflammation and cancer in 1876 after observing the presence of leukocytes within neoplastic tissues (6), clear evidence now supports the crucial role played by SIR in the development, progression, metastasis, and survival of malignant cells in most cancers (7).

The prognostic value of SIR has been vigorously assessed in urologic cancers, including prostate cancer, kidney cancer, and urothelial carcinoma (UC) (cancers of the bladder (8) and upper urinary tract (UUT) (9).

The neutrophil to lymphocyte ratio (NLR) is a marker of systemic inflammatory response, which has been associated with the tumor recurrence and progression (10).

Neutrophils act as short-lived effector cells of the innate immune system and play a primary role in resistance against extracellular pathogens and inflammation (11)

METHODS

This retrospective study was conducted Ain-shams university hospital. This study was conducted on 100 patients having NMIBC.

Inclusion criteria

Male gender, age 40:80 years and all patients with NMIBC.

Exclusion criteria

Patients have any of the followings: Concomitant malignancy, hematological disorders, history of radiation, concomitant infection, or chronic inflammatory diseases, missing preoperative differential blood cell count and patients who show hemodynamic instability.

Operational design

From each patient the following data had been collected upon admission

Initial assessment

Complete history taking, including personal, present, past medical and surgical history and family history of cancers

Full Clinical examination focusing on

General examination: Vital signs (Blood pressure, Temperature, Heart rate, Respiratory rate), Signs of (Pallor, Cyanosis, Jaundice, and Lymph node enlargement) including digital rectal examination (DRE).

Search strategy for identification of studies

The following electronic databases were searched, the MEDLINE via the free PubMed provider and google scholar search engine, using the key words "prognostic role, NLR, NMIBC, intravesical BCG treatment ". No restrictions on the language of publications were employed.

METHODS OF THE REVIEW

Locating and selecting studies

The selected studies were eligible if they contained the target keywords in title or abstract, after reviewing the abstract, the full text was retrieved and a further selection was carried out. Afterwards, the full texts of the articles were reviewed to exclude full texts not fulfilling the criteria or deviating from the initial impression taken from the title/abstract reviewing.

Data extraction

Studies that fit the inclusion criteria was manually reviewed and data was analyzed. All the primary research studies that come out from the search were screened regarding the title to remove any duplicate. Included studies were categorized according to level of evidence and evaluated for quality.

Types of outcome measures

The primary outcomes measures to evaluate prognostic role of NLR in patients with NMIBC who underwent trans urethral resection and received intravesical installation BCG immunotherapy within 2 to 6 weeks post TURBT as regards:

No recurrence on follow up cystoscopy and pelvi-abdominal ultrasound.

Administrative and Ethical Design

An Official permission was obtained from Faculty of Medicine, Ain-shams University. An official permission was obtained from Ain-shams university hospital, Approval from ethical committee in the faculty of medicine (Institutional Research Board IRB).

Data management and Statistical Analysis

All data were collected, tabulated and statistically analyzed using statistical package of special science SPSS version 22 (SPSS Inc. Chicago, IL, U.S.A) Independent t-test and Mann Whitney test were used to calculate difference between quantitative variables in two groups. Paired t-test was used to compare between two dependent groups of normally distributed variables. Chi square test ($\chi 2$) and fisher exact was used to calculated difference between qualitative variables. Regression analysis using the stepwise method was used to determine the potential risk factor of hypomagnesemia.

RESULTS

This retrospective cohort study was conducted on 100 patients with NMIBC who at Ain shams university hospital.

Patient's age at diagnosis showed a mean of 59.30 ± 5.06 years with range from 45 years to 75 years. Assessing of NLR showed median level of 3.2 with range from 1.5 to 5.5. CTUT was the most frequent preoperative imaging study done for 62% of cases while PAUS was done for 38% cases. Table (1) Assessing of tumor size showed median level of 1*1 cm. Tumor multiplicity was observed in 27% of cases. All cases underwent complete TURBT. Concerning first? follow up cystoscopy, recurrence was reported in 31% cases meanwhile further follow up cystoscopy showed that recurrence occurred in 39% cases. Table (2)

TABLE 1: Clinicodemographic characteristics of the studied cases

		No.= 100
Age (years)	**Mean±SD**	59.30 ± 5.06
	Range	45 – 75
NLR	**Median (IQR)**	3.2 (2 – 4.85)
	Range	1.5 – 5.5
Preoperative imaging study	**CTUT**	62 (62.0%)
	PAUS	38 (38.0%)
Tumor site	**Posterior**	25 (25.0%)
	Lt poster lateral	20 (20.0%)
	Rt poster lateral	28 (28.0%)
	Dome& posterior	27 (27.0%)
Tumor Grade	**1**	53 (53.0%)
	2	36 (36.0%)
	3	11 (11.0%)

TABLE 2: Tumor characteristics of the studied cases

Tumor stage		**No.= 100**
Tumor size 1	Median (IQR)	1 (0.5 – 2)
	Range	0.25 – 9
Tumor size 2	Median (IQR)	1 (0.5 – 2)
	Range	0.5 – 4
Tumor multiplicity	No	73 (73.0%)
	Yes	27 (27.0%)
First follow up cystoscopy	Free	69 (69.0%)
	Recurrence	31 (31.0%)
Further follow up cystoscopy	Free	61 (61.0%)
	Recurrence	39 (39.0%)

NLR showed significant elevation in patients with recurrence compared to cancer free patients (p<0.001). Preoperative imaging study showed significant difference between the two groups as CTUT was significantly higher in cases with recurrence (p=0.033). Left posterolateral site had significant higher prevalence in cancer free cases (p=0.023) while Dome& posterior had significant higher prevalence in cases with recurrence (p<0.001). there was significant difference between the two groups regarding grade (p<0.001). Table (3)

TABLE 3: Relation between results of First follow up cystoscopy and clinicodemographic characteristics

		First follow up cystoscopy		**Test value**	**P-value**	**Sig.**
		Free	**Recurrence**			
		No.= 69	**No.= 31**			
Age	Mean±SD	59.55 ± 4.57	58.74 ± 6.07	0.737•	0.463	NS
	Range	48 – 66	45 – 75			
NLR	Median (IQR)	2.2 (2 – 3.3)	4.9 (4.3 – 5.2)	-5.595≠	<0.001	HS
	Range	1.5 – 5.3	2.3 – 5.5			
Tumor site	Posterior	20 (29.0%)	5 (16.1%)	1.886*	0.170	NS
	Lt poster lateral	18 (26.1%)	2 (6.5%)	5.154*	0.023	S
	Rt poster lateral	20 (29.0%)	8 (25.8%)	0.107*	0.744	NS
	Dome& posterior	11 (15.9%)	16 (51.6%)	13.809*	<0.001	HS
Tumor Grade	1	50 (72.5%)	3 (9.7%)	44.823*	<0.001	HS
	2	19 (27.5%)	17 (54.8%)			
	3	0 (0.0%)	11 (35.5%)			

P-value > 0.05: Nonsignificant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

No significant differences were found between cancer free patients and patients with recurrence at further follow up cystoscopy regarding tumor size (p>0.05). Tumor multiplicity showed significant difference between the two groups as it was significantly higher in patients with recurrence (p=0.001). There was significant relation between results of first follow up cystoscopy and further follow up cystoscopy (p<0.001). Table (4)

TABLE 4: Relation between results of further follow up cystoscopy and tumor characteristics

Tumor stage		**Further follow up cystoscopy**		**Test value**	**P- value**	**Sig.**
		Free	**Recurrence**			
		No.= 61	**No.= 39**			
Tumor size 1	Median (IQR)	1 (0.5 – 2)	1 (0.5 – 4)	-0.590≠	0.555	NS
	Range	0.25 – 6	0.25 – 9			
Tumor size 2	Median (IQR)	1 (0.5 – 1)	1 (1 – 2)	-1.659≠	0.097	NS
	Range	0.5 – 1	0.5 – 4			
Tumor multiplicity	No	52 (85.2%)	21 (53.8%)	11.900*	0.001	HS
	Yes	9 (14.8%)	18 (46.2%)			
First follow up cystoscopy	Free	61 (100.0%)	8 (20.5%)	70.271*	0.000	HS
	Recurrence	0 (0.0%)	31 (79.5%)			

P-value > 0.05: Nonsignificant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test; ≠: Mann-Whitney test

By using ROC-curve analysis, NLR can predict recurrence at first follow up cystoscopy at cutoff 3.3 with sensitivity, specificity, PPV and NPV was 93.55%, 78.26%, 65.9% and 96.4% respectively and AUC was 0.850.

By using ROC-curve analysis, NLR can predict recurrence at further follow up cystoscopy at cutoff 3.3 with sensitivity, specificity, PPV and NPV was 89.74%, 85.25%, 79.5% and 92.9% respectively and AUC was 0.905.

NLR >3.3 (OR = 52.2, p <0.001), Preoperative imaging study (CTUT) (OR = 2.797, p = 0.037), Lt posterolateral (OR = 0.195, p = 0.037), Dome & posterior site (OR = 5.624, p<0.001), histological grade (OR = 20.373, p<0.001) and Tumor multiplicity (OR = 5.624, p<0.001) were significant factors associated with recurrence at first follow up cystoscopy. The above significant factors were put into multivariate logistic regression analysis to further evaluate significant clinical variables with recurrence. Factors significant in the univariate analysis were adjusted in the multivariate model. Recurrence at first follow up cystoscopy was significantly associated with NLR >3.3 (vs. ≤3.3, OR = 942.35, <0.001) Dome & posterior (OR = 0.032, p = 0.023) and histological grades (OR = 57.871, p = 0.001). Table (7)

TABLE 5: Univariate and multivariate logistic regression analysis for factors associated with recurrence at first follow up cystoscopy.

	Univariate				**Multivariate**			
	P-value	**Odds ratio (OR)**	**95% C.I. for OR**		**P-value**	**Odds ratio (OR)**	**95% C.I. for OR**	
			Lower	**Upper**			**Lower**	**Upper**
NLR >3.3	**0.000**	52.200	11.159	244.190	**0.000**	942.350	26.371	33674.731
Preoperative imaging study (CTUT)	**0.037**	2.797	1.064	7.351	0.486	0.463	0.053	4.046
Lt poster lateral	**0.037**	0.195	0.042	0.903	0.215	0.107	0.003	3.648
Dome & posterior	**0.000**	5.624	2.165	14.613	**0.023**	0.032	0.002	0.628
Tumor Grade	**0.000**	20.373	5.986	69.332	**0.001**	57.871	5.887	568.862
Tumor multiplicity	**0.000**	5.624	2.165	14.613	–	–	–	–

DISCUSSION

It is now recognized that increased systemic inflammatory responses induced by tumor microenvironments trigger alteration of acute-phase reactive substance and hematologic ingredient. Among these serum markers are neutrophil and lymphocyte counts, which can indicate relative neutrophilia and lymphocytopenia. In various tumor patients, a higher percentage of neutrophils than lymphocyte is associated with reduced cancer-free and overall survival (12).

This retrospective cohort study was carried upon 100 patients having NMIBC and will be done in Ain shams university hospital. The duration of the study ranged from 6-12 months.

The mean age of the studied group was 59.30 ± 5.06 years. The median NLR was 3.2 (2 – 4.85). As regard Preoperative imaging study, 62% of them were CTUT. As regard tumor site, 28% were in Rt poster lateral and 27% were in Dome& posterior. As regard grade, 53% were grades 1 and 36% were grade 2.

In First follow up cystoscopy, there was statistically significant association between free and recurrence as regard NLR, Preoperative imaging study, tumor site (Lt poster lateral and Dome& posterior) and grade. In Further follow up cystoscopy, there was statistically significant association between free and recurrence as regard NLR, Preoperative imaging study, tumor site (Posterior and Dome& posterior) and grade.

Our results were supported by study of Yuk et al., (13) as they reported that the median age of patients was 67.5 ± 10.7 years. The mean value of NLR in all patients was 3.17 ± 1.12. The mean NLR value was 2.61 ± 0.77 in BCG - responder group and of 3.65 ± 1.16 in BCG - non responder group (p value: 0.01), and 2.32 ± 0.41 in NLR<3 group and 3.90 ± 0.88 in NLR ≥3 (p value: 0.01).

Whereas in the study of Favilla et al., (14) their study included 148 (83.1%) male and 30 (16.9%) female patients. The median age of all 178 patients enrolled in the study was 69.27 (IQR: 63.78-79.44), with a median follow-up of 53 months (IQR: 33.0-76.25). Patients with NLR≥3 were older (74.45 versus 67.94; p=0.02) and exhibited significant differences in term of pathological stage (26.6% versus 20.33%; p<0.05) if compared with those with NLR<3.

The present study showed that the median of tumor size 1 was 1 (0.5 – 2). The median of tumor size 2 was 1 (0.5 – 2). 27% of the studied group has Tumor multiplicity. As regard Outcome of TURBT, all of them underwent complete resection. In First follow up cystoscopy, 69% were free and 31% were recurrent. In Further follow up cystoscopy, 61% were free and 39% were recurrent.

In the study of Yuk et al., (13) nearly half (48.3%) of these patients experienced recurrence and 11.4% of patients had disease progression. Radical cystectomy was performed for 13.2% of patients. The overall mortality rate was 18.2%. Cancer-specific mortality rate was 4.7%. The mean time to recurrence was 43 months while the mean time to progression was 31 months.

According to Favilla et al., (14) during the follow-up study, 14 (23.3%) and 44 (37.9%) (p=0.04) patients respectively with NLR<3 and ≥3 experienced recurrence and 2 (3.3%) and 14 (11.9%) experienced progression (p=0.06), respectively.

Our results showed that using ROC curve for NLR to predict recurrence at first follow up cystoscopy; Cut off point was >3.3, AUC was 0.85, sensitivity was 93.55% & specificity was 78.26%. Using ROC curve for NLR to predict recurrence at further follow up cystoscopy; Cut off point was >3.3, AUC was 0.905, sensitivity was 89.74% & specificity was 85.25%.

Univariate and multivariate logistic regression analysis for factors associated with recurrence at first follow up cystoscopy showed that NLR >3.3, Dome & posterior and Grade were factors associated with recurrence at first follow up cystoscopy. Univariate and multivariate logistic regression analysis for factors associated with recurrence at further follow up cystoscopy showed that tumor site (posterior) and grade were factors associated with recurrence at further follow up cystoscopy. By Univariate logistic regression analysis for factors associated with recurrence, all factors including NLR >3.3 were associated with recurrence.

Furthermore, Kim et al., (15) stated that shows a multivariate Cox proportional hazards regression model for predicting recurrence. Female gender, concomitant CIS, multiplicity (> 3), prior recurrence status and an NLR > 2.29 were independent prognostic factors for tumor recurrence (hazard ratio [HR], 2.565; 95% confidence internal [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; Page 9/20 P = 0.010 / HR, 2.320; 95% CI, 1.280–4.207; P = 0.006 / HR, 2.451; 95% CI, 1.567–3.834; P < 0.001, respectively). Kaplan–Meier curve analyses with a log-rank test are shown. A high NLR (> 2.29) were associated with significantly low RFS and PFS (P < 0.001, P = 0.002).

Yuk et al., (13) showed that patients were divided into two groups according to pretreatment NLR (<1.5 vs. ≥1.5), dNLR (<1.2 vs. ≥1.2). Patients with NLR ≥ 1.5 and dNLR ≥ 1.2 were associated with poor prognosis in terms of overall survival and cause-specific survival. Cox multivariate analysis revealed that age, NLR, dNLR, hemoglobin, and pathologic T stage were significant factors predicting overall survival. Age, NLR, and pathologic T stage were significant factors predicting cancer-specific survival, NLR and tumor number were the most important predictors of bladder preserving survival. NLR before treatment was correlated with both oncological outcomes and survival outcomes in NMIBC patients undergoing initial intravesical BCG treatment after TURBT. Increased NLR reflects a poor prognosis of these outcomes.

Curiously, most of the studies investigating the role of NLR in patients with NMIBC specifically have been retrospective – including two previously published articles (16). Albayrak et al., (17) argued that correction for age might alter the results, so a logistic regression analysis (backwards, conditional) of the NLR 2.5 and Age as a covariate, was performed. This regression resulted in only NLR 2.5 as a significant variable (p = 0.005) with Odds ratio of 3.045 (CI 1.392–6.661), meaning that there is an average of at least 3-fold higher probability of recurrence for a person with NLR > 2.5 compared with NLR < 2.5. Age was removed from the model because of insignificance (p = 0.988).

CONCLUSION

Our data showed that a high value of NLR cutoff …. evaluated preoperatively might be helpful to predict the BCG response and therefore provide critical information for the clinical management of high-risk NMIBC patients together with the prognostic factors already known.

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