SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 9.
Issue: 10
Page N. 186-196
Year: 2025

Original Article

www.wjahr.com

SIGNIFICANCE OF TUMOR-ASSOCIATED NEUTROPHILS, LYMPHOCYTES, AND NEUTROPHIL-TO-LYMPHOCYTE RATIO IN NON-INVASIVE AND INVASIVE BLADDER UROTHELIAL CARCINOMA

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Article Received date: 05 August 2025 **Article Revised date:** 26 August 2025 **Article Accepted date:** 15 September 2025

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DOI: https://doi.org/10.5281/zenodo.17224140

ABSTRACT

Background: Bladder cancer accounts for 3% of global cancer diagnoses and is estimated to be the 7th most common cancer worldwide. Urothelial carcinoma is the most common type of bladder cancer, constituting up to 95% of bladder malignancies. Tumor-infiltrating neutrophils and lymphocytes play essential roles in promoting or combating various neoplasms. **Aim of the study:** This study aimed to investigate the association between tumor-Infiltrating neutrophils and lymphocytes and the neutrophil-to-lymphocyte ratio in the progression of urothelial carcinoma. **Material and Method:** This study included 100 patients pathologically diagnosed with urothelial bladder neoplasm by TURBT from November 2023 to November 2024. Clinical and pathological data of age, sex, pathological grade, and pTNM stage were recorded. The tumors were classified and graded according to the 2022 World Health Organization/ International Society of Urological Pathology classification. **Results:** Regarding the presented study, the percentage of total cases (100%) was diagnosed with urothelial cancer. The presence of neutrophils and the neutrophil-to-lymphocyte ratio correlated with high-grade urothelial neoplasms. In both low- and high-grade tumors, the lymphocytes increased during progression from a non-invasive neoplasm to an early-invasive neoplasm. Lymphocytes increased in low-grade non–muscle-invasive tumors compared to invasive tumors. There was a significant decrease in lymphocytes during progression to muscle-invasive tumors. **Conclusion**: Our results suggest that tumor-infiltrating neutrophils, lymphocytes and N: L ratio has a significant effect on tumor grade and invasion.

KEYWORDS: Urothelial cancer, tumor-infiltrating neutrophils, Iraqi patients. Bladder.

INTRODUCTION

Bladder cancer accounts for 3% of global cancer diagnoses and is estimated to be the 10th most common cancer worldwide[1] and 6th most common cancer in Iraq according to 2023 cancer registry . Urothelial carcinoma is the most common type of bladder cancer.[2] Most patients with urothelial carcinoma presented with non-invasive papillary neoplasms or superficially invasive tumors limited to the mucosa and submucosa.[3] These neoplasms do not reach the muscle layer (i.e., they constitute non–muscle-invasive urothelial carcinoma [NMIUC; pTa or pT1]). For such neoplasms, transurethral resection of the bladder tumor (TURBT) is followed by adjuvant intravesical instillation therapy.[4] However, approximately 30% of patients presented with muscle invasion (i.e., muscle-invasive urothelial carcinoma [MIUC]; pT2).[5] The five year survival rate of NMIUC ranges from 50% to 70%, whereas that with MIUC, despite radical cystectomy and chemotherapy, is 30%–40%.[4][5]

Moreover, NMIUC progresses to MIUC in about 43% of patients.[6] despite advancements in the management of bladder carcinomas, the outcomes have remained largely unchanged over several decades[7], highlighting the need to identify additional pathological parameters and biomarkers that could affect carcinogenesis and help improve management procedures.[8] The link between tumor microenvironment inflammation and tumor progression has been reported in several malignancies.[9]

Neutrophils and lymphocytes are the main inflammatory cells observed in the tumor microenvironment.[10] Several study have highlighted the significance of elevated neutrophil-to-lymphocyte ratio (NLR) in patients with urothelial carcinoma and its association with a higher risk of recurrence and progression in NMIUC, as well as increased mortality and decreased overall survival in patients with MIUC.[11] Tumor-associated lymphocytes (TALs) exhibit diverse functions in various subsets. CD8 T lymphocytes are primarily responsible for attacking tumor cells.[10] CD4 T lymphocytes are considered a double-edged immunologic sword: they can initiate and maintain CD8 lymphocyte anti-cancer immune responses.[10] but can also convert anti-tumor activity to pro-tumor activity.[10]

METHOD

Study place and time

This study has been conducted at Al-Kufa Training Center – Iraqi Board of Medical Specialization, at Al-Sadder Teaching Medical City hospital in Al Najaf during the period 1st November 2023 to 1st December 2024. The data was collected from patient for the last 3 years during the period from January 2022 to Jun 2024.

Study design and setting

An analytic cross sectional design has been selected for this study.

Research Population

The population involved was Iraqi patient in Middle Euphrates area with the clinical diagnosis of bladder urothelial carcinoma.

Inclusion Criteria

All bladder urothelial carcinoma patients within any age group, with essential clinical data were included in the study.

Exclusion Criteria

Cases that not satisfy the selection criteria with missing data regarding age, final diagnosis and insufficient tissue was excluded from the study.

Selection of the research population

Hundred cases have been collected from the histopathology laboratory in ALSadder Teaching Medical City hospital in Al-Najaf and private laboratories in the Governorates.

The cases were included in this study that diagnosed previously with bladder urothelial carcinoma by histopathological examination. The diagnosis was reviewed by examining the H&E stained slide. Clinical and pathological data of age, sex, pathological grade, and pTNM stage were recorded. The tumors were classified and graded according to the 2016 World Health organization/International Society of Urological Pathology classification. The specimens were formalin fixed paraffin embedded (FFPE) tissue block.

Approval and official permission

An official letter of approval has been obtained from the scientific committee of the scientific council of Histopathology Iraqi Board for Health Specialization.

Histopathological evaluation

The samples were already embedded in paraffin. From each block, histological sections of 4 μm thicknesses were submitted, mounted to a glass slide, stained by hematoxylin and eosin, and reviewed to confirm the diagnosis of urothelial bladder neoplasm and to identify tumor grade, invasion depth, and presence of lympho-vascular invasion. TANs and TALs were identified.

Tumor associated neutrophils (TANs) or TALs were defined as any neutrophils or lymphocytes that were in close proximity to the tumor base in non-invasive neoplasms or between tumor nests in invasive neoplasms. Ten fields from the tumor were selected under low magnification (×100), and the neutrophils and lymphocytes were counted at high magnification (× 400). Care was taken not to count such inflammatory cells in areas of ulceration or erosion. Then, the average number was calculated and scored. TANs and TALs were identified in the lamina propria just beneath the lower margin of the noninvasive urothelial neoplasm or infiltrated in the cancer nests or stroma.

Data entry and analysis

Data entry was done using Microsoft Excel 2019. Data was recorded into different quantitative and qualitative variables for the purpose of analysis. Using the statistical package SPSS v26 (Statistical package for Social Sciences). The statistical significance of association between two categorical variables was assessed by Chi-Square test. P value less than the 0.0001 level of significance was considered.

RESULTS

A total of 100 urothelial bladder cancer cases during January 2022 to Jun 2024 were studied.

The age of studied cases ranged between (17 –77 years), with a mean age of (64 years ± 10.76 SD). The age group distribution was recorded highest frequency in the age group (61-70) was 38 cases (38%). (Table1)

Table 1: Age distribution frequency.

		Frequency	Valid Percent	Cumulative Percent
Age group	20-30	1	1.0	1.0
	31-40	2	2.0	3.0
	41-50	10	10.0	13.0
	51-60	24	24.0	37.0
	61-70	38	38.0	75.0
	71-80	20	20.0	95.0
	81-90	5	5.0	100.0
	Total	100	100.0	

There were 84 males (84%) and 16 females (16%) in the study as shown in table 2.

Table 2: Gender frequency.

	Frequency	Valid Percent	Cumulative Percent
female	16	16.0	16.0
male	84	84.0	100.0
Total	100	100.0	

Grading was made for 100 cases with, however, majority, 52 (52%), of these cases had high grade and 48 (48%) had low grade. As shown in Table 3.

Table 3: Histological grading.

		Frequency	Valid Percent	Cumulative Percent
grade	high grade	52	52.0	52.0
	low grade	48	48.0	100.0
	Total	100	100.0	

The study included 100 cases, were 58 cases (58%) diagnosed with (T1) urothelial carcinoma, 20 cases (20%) diagnosed with T2 urothelial carcinoma, 10 cases (10%) diagnosed with (Ta) urothelial carcinoma, and 2 cases (2%) diagnosed with(Tis), 10% of cases in which the stage not mentioned in the report, as shown in table 4.

Table 4: Histological staging.

		Frequency	Valid Percent	Cumulative Percent
stage		10	10.0	10.0
	T1	58	58.0	68.0
	T2	20	20.0	88.0
	Ta	10	10.0	98.0
	Tis	2	2.0	100.0
	Total	100	100.0	

The presence of neutrophils correlated with high-grade urothelial neoplasms. Specifically, there was a significant increase in neutrophil number in high-grade UC cases with mean of (327.1 ± 82.7 SD) compared to low-grade cases with mean of (155 ± 58.3 SD). A statistically significant association was found between neutrophils count and tumor grade (p value 0.0001) (Table 5).

There was a decrease in total lymphocyte count in high-grade neoplasms with mean of (138.07 ± 58.9 SD) compared to low-grade neoplasms with mean of (316.02± 105.9 SD). A statistically significant association was found between lymphocyte count and tumor grade (p value = 0.0001). (Table 5)

The NLR correlated with tumor grade specifically, there was a significant increase in the ratio in high-grade urothelial neoplasms with mean of (2.69 ± 1.39 SD) compared to low-grade neoplasms with mean of (0.45± 0.105 SD).

A statistically significant association was found between neutrophils to lymphocyte ratio and tumor grade (p value = 0.0001) (Table 5)

Table 5: Relationship between TAN, TAL and N/L ratio to tumor grade.

	Std. Error Difference	95% Confidence Interval of the Difference		P Value
TANin10HPF	14.43	200.77	200.77	0.001
	14.23	14.23	200.40	0.001
TALin10HP	16.97	16.97	144.26	0.001
	17.33	17.33	143.38	0.001
N/L ratio	0.20	0.20	2.63	0.001
	0.19	0.19	2.62	0.001

We found a significant increase in the number of neutrophils in the progression from NIUC to MIUC in both low grade and high grade tumor.

Our study included 100 cases TAN/ 10HPF in 10 of them Ta with mean of (146.20 ± 40.31 SD), 2 cases Tis with mean of (197.50 ± 53.03 SD), 58 cases T1 with mean of (225.82 ± 95.80 SD) and 20 cases T2 with mean of (360.75 ± 105.54 SD).

A statistically significant association was found between neutrophils and tumor stage (p value = 0.0001) (Table 6).

The presence of lymphocytes correlated with progressive invasion of urothelial neoplasms than with neoplasm grade. TAL/10 HPF in 10 cases diagnosed with Ta with mean of (270.30 ± 75.96 SD), 2 cases Tis with mean of (117.50 ± 41.71 SD), 58 cases T1 with mean of (239.55 ± 129.9 SD) and 20 cases T2 with mean of (171.55 ±119.05 SD). A statistically association between lymphocyte and tumor stage it was marginally significant (p value =0.063) (Table 6)

Significant increase in N/L ratio during progression of invasion, N/L ratio in 10 cases diagnosed with Ta with mean of (0.641 ± 0.519SD), 2 cases Tis with mean of (1.708± 0.155SD), 58 cases T1 with mean of (1.436 ± 1.680 SD) and 20 cases T2 with mean of (2.636± 0.927 SD).

A statistically significant association was found between N/L ratio and tumor stage (p= 0.0003) (Table 6).

Table 6: Relationship between TAN, TAL and N/L ratio to tumor stage.

		Sum of Squares	df	Mean Square	F	P Value
TANin10HPF	Between Groups	391247.87	3	130415.95	14.910	0<001
	Within Groups	752234.12	86	8746.90		
	Total	1143482	89			
TALin10HPF	Between Groups	113051.22	3	37683.74	2.522	0.063
	Within Groups	1284869.89	86	14940.34		
	Total	1397921.122	89			
N/L ratio	Between Groups	32.216	3	10.739	5.138	0.003
	Within Groups	179.745	86	2.090		
	Total	211.961	89			

Table 7: Receiver operator curve (ROC) showing cut off value of TAN in relation to tumor grade and stage.

Variables			ROC characteristics				
	Area Under The Curve	95% Confidence interval for area under the curve	Significance level P (Area=0.5)	cutoff value	95% Confidence interval	sensitivity%	Specificity %
TAN and grade	0.8 3	0.749 to 0.903	<0.0001	>210	>186 to >210	76.19	91.89
TAN and stage	0.8 4	0.755 to 0.914	<0.0001	>311	>235 to >372	80.00	78.57

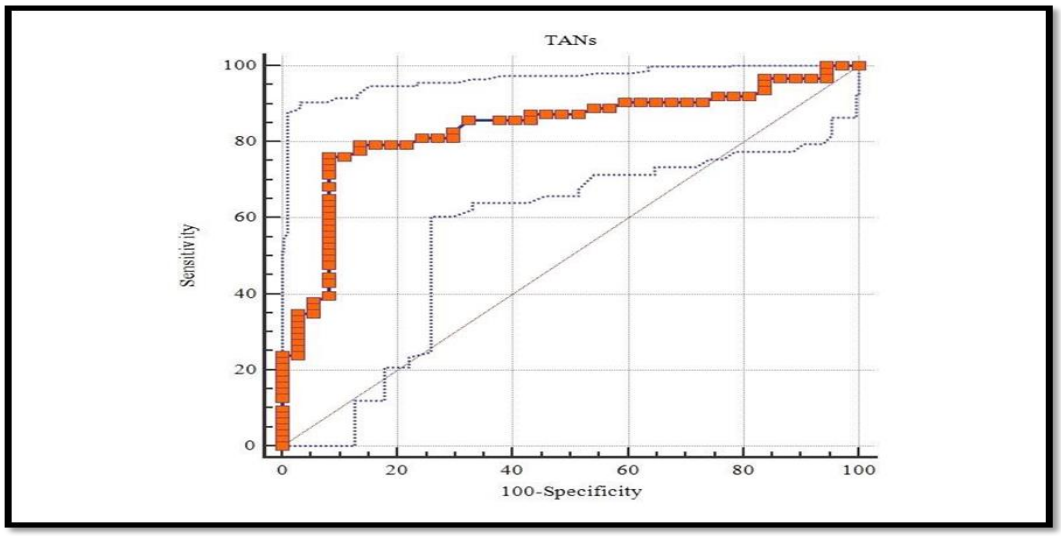

Figure 1: Receiver operator curve (ROC) showing cut off value of TAN in relation to tumor grade.

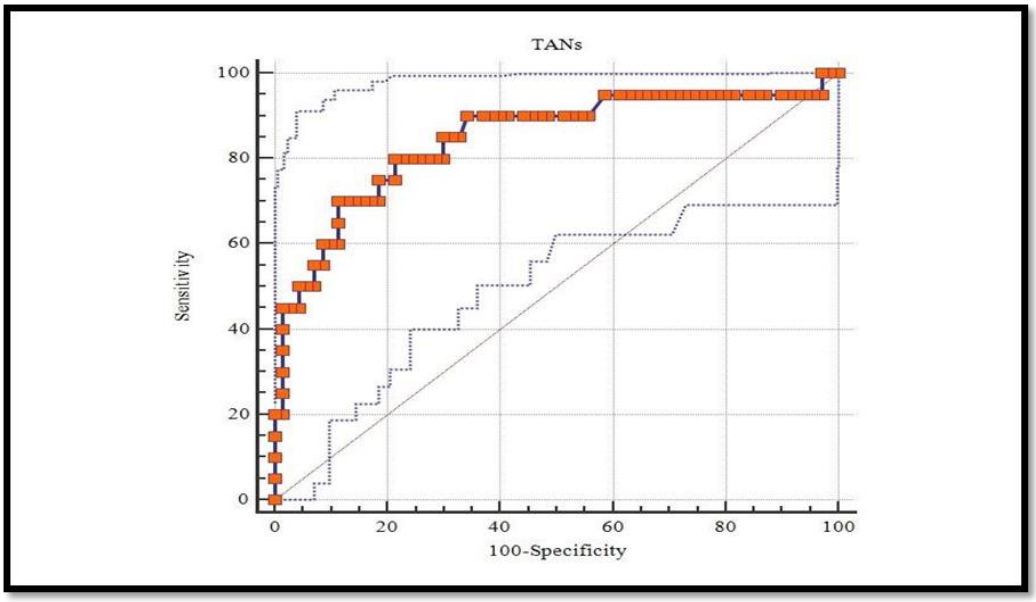

Figure 2: Receiver operator curve (ROC) showing cut off value of TAN in relation to tumor stage.

Table 8: Receiver operator curve (ROC) showing cut off value of TAL in relation to tumor grade and stage.

Variable			ROC characteristics				
	Area Under The Curve	95% Confidence interval for area under the curve	Significance level P (Area=0 .5)	cutoff value	95% Confidence interval	Sensitivity %	Specificity %
TAL and grade	0.845	0.759 to 0.910	<0.0001	≤192	0.5361 to0.8142	79.37	89.19
TAL and stage	0.656	0.548 to 0.753	0.0201	≤157	0.3109 to0.6643	90.00	61.43

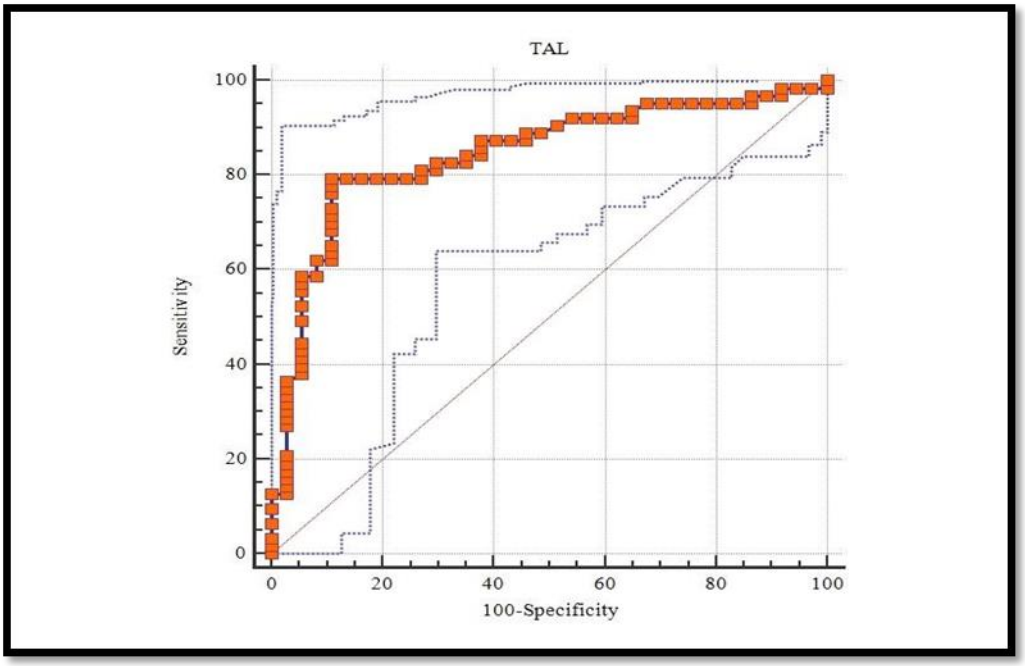

Figure 3: Receiver operator curve (ROC) showing cut off value of TAL in relation to tumor grade.

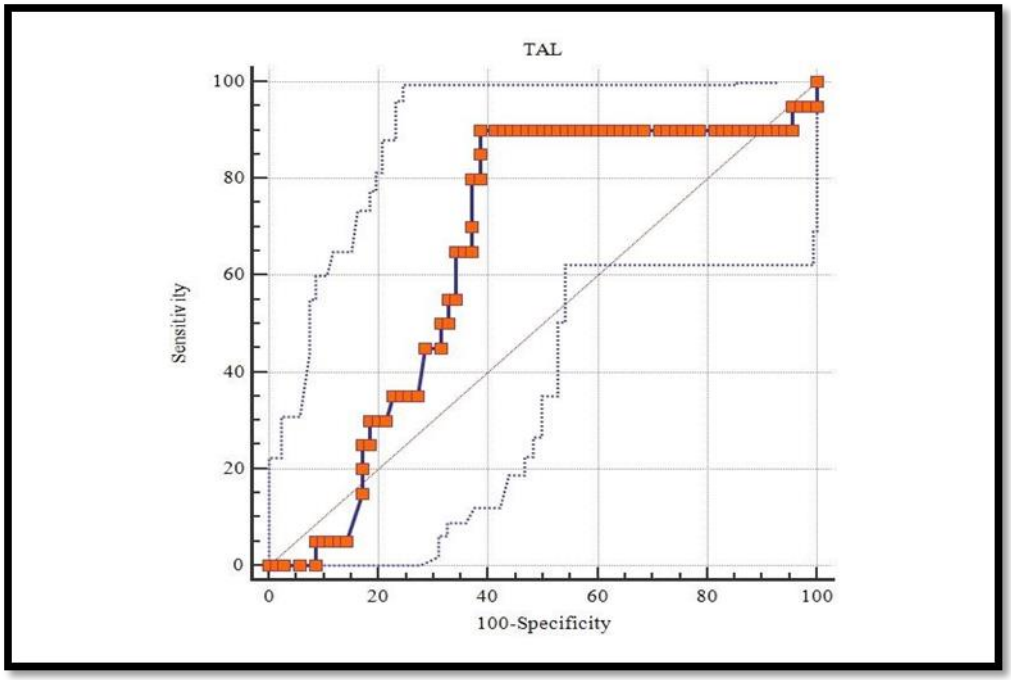

Figure 4: Receiver operator curve (ROC) showing cut off value of TAL in relation to tumor stage.

Table 9: Receiver operator curve (ROC) showing cut off value of N/L ratio in relation to tumor grade and stage.

Variables			ROC characteristics				
	Area Under The Cue	95% Confidence interval for area under the curve	Significance level P (Area=0.5)	cutoff value	95% Confidence interval	Sensitivity %	Specificity %
N/L ratio and grade	0.896	0.819 to 0.948	<0.0001	>0.72	0.6508 to 0.8571	77.78	100.00
N/L ratio and stage	0.816	0.720 to 0.890	<0.0001	>2.39	0.3249 to 0.7214	80.00	80.00

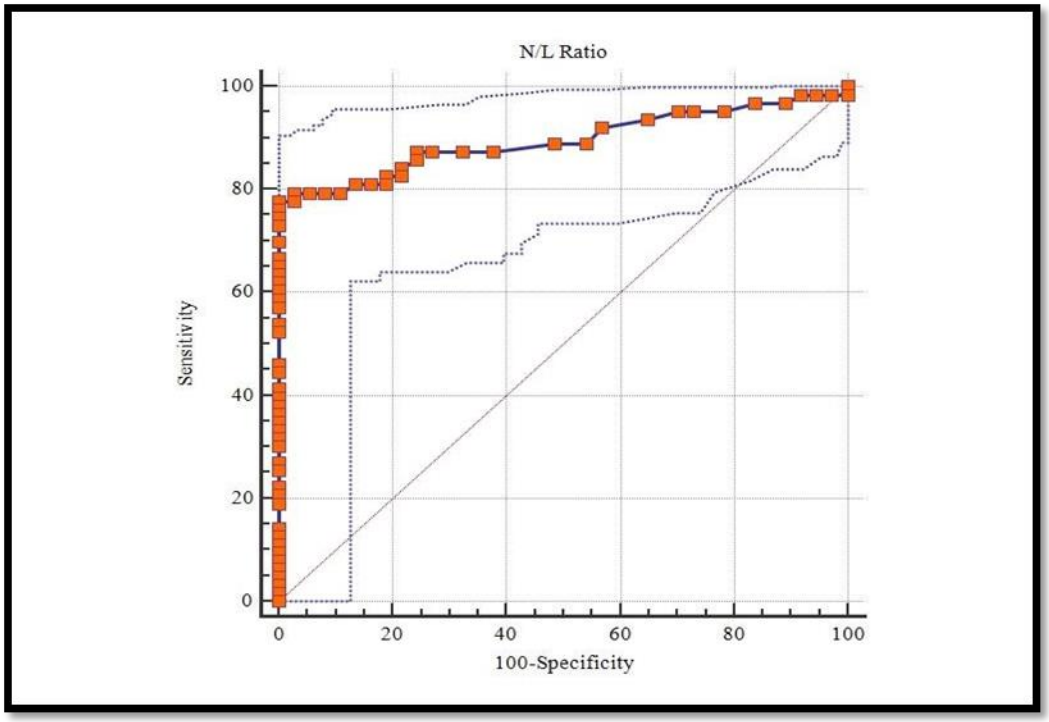

Figure 5: Receiver operator curve (ROC) showing cut off value of N/L ratio in relation to tumor grade.

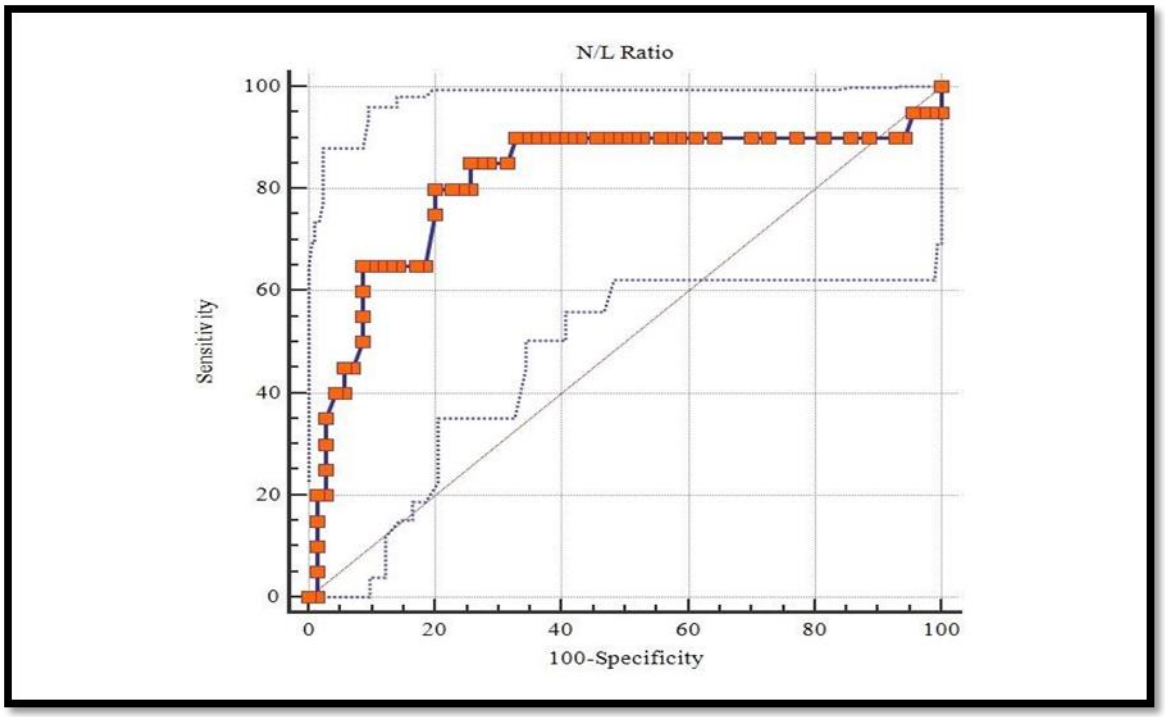

Figure 6: Receiver operator curve (ROC) showing cut off value of N/L ratio in relation to tumor stage.

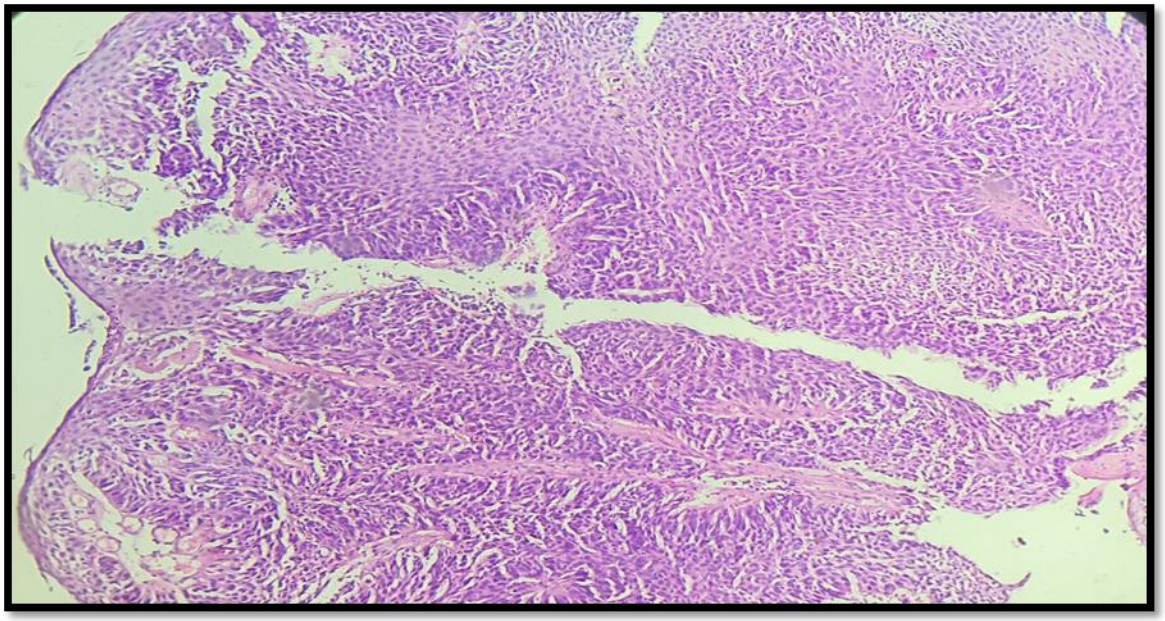

Figure 7: section reveals Low grade papillary urothelial carcinoma with invasion to lamina properia. At (10x, H&E).

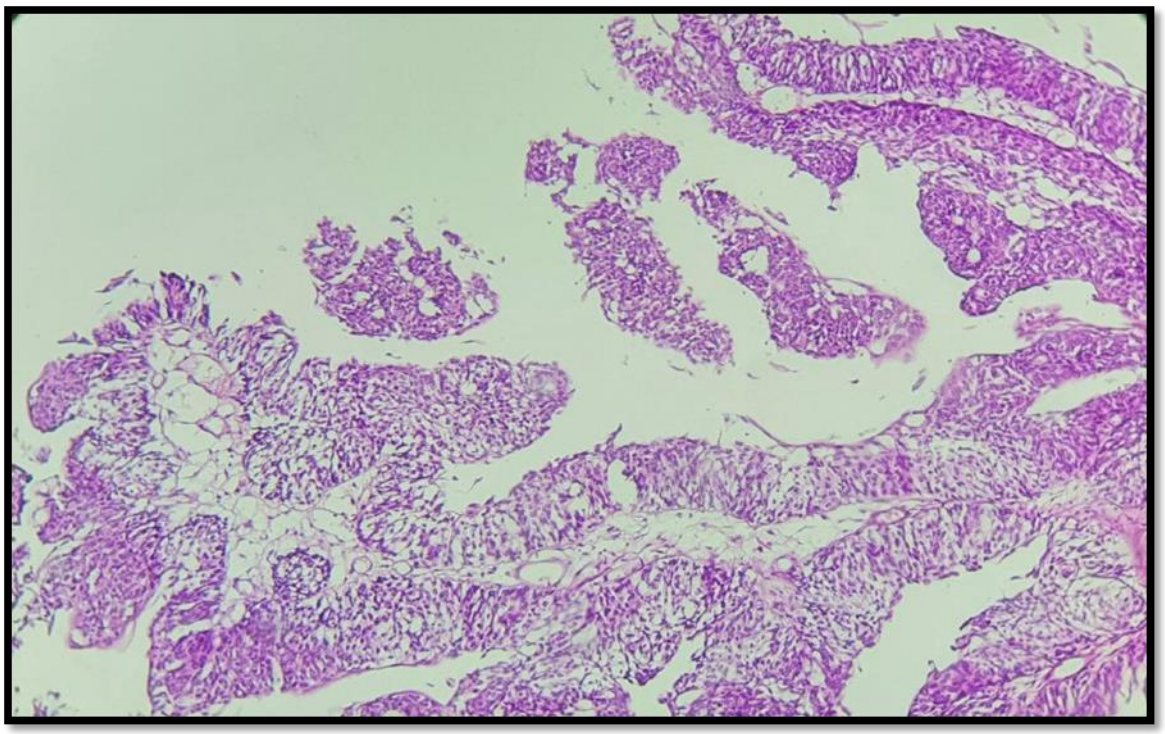

Figure 8: Low grade papillary urothelial carcinoma. neoplastic cells arranged in papillary structure of fused and branching pattern. At (10x).

DISCUSSION

Inflammation in tumor microenvironment plays an essential role in tumor progression, There is a lot of inflammation in the area around the tumor, and this inflammation is very important for tumor growth, also the inflammation works at different stages of tumor development, initiation, promotion, invasion, and metastasis.[12]

In recent years, the host inflammatory response has gained increasing attention in oncology research. In fact, increasing evidence showed the association of inflammation and cancer. Initially thought to represent an antitumor response, immune cells, particularly those of the innate immune system, also exhibit effects that promote carcinogenesis and cancer progression. Proposed mechanisms may include more growth factors, survival factors, proangiogenic factors, extracellular

matrix-modifying enzymes, and inductive signals that can cause the epithelial-to-mesenchymal transition.[13]

An important inflammation component Neutrophils, which exhibit distinct functions and considered to have dual roles in tumor biology. It can polarize into either an anti-tumoral or a pro-tumoral phenotype and show different functions.[14]

Early studies suggested that TANs, which are short-lived, have no role in cancer progression, recently become evident that TANs play a significant role in tumor progression.[15]

Neutrophils within tumor nests can induce anti-tumoral immune memory. also, they may have a pro-tumoral phenotype that induce angiogenesis, invasion, metastasis, and immunosuppression.[14]

Neutrophils are key effectors and regulators of the immune system. They can activate endothelial and parenchymal cells, facilitating the transfer of tumor cells in circulation. Additionally, neutrophils are very important for the creation of neutrophil extracellular traps (NETs). NETs form when neutrophils release their decondensed chromatin along with granule contents.[16]

Studies have found that central granulocytes can promote tumor angiogenesis, invasion, and metastasis of tumor cells by releasing proangiogenic factors, proteases, and cytokines, neutrophils can also affect tumor immune escape and drug resistance by controlling the levels cytokines and chemical factors in the tumor microenvironment.[17][18] Furthermore, studies have revealed a strong correlation between the prognosis of tumors and the number and activity of central granulocytes, and the high density of central granulocyte infiltration is related to the malignant degree and poor prognosis of tumors.[19]

This study revealed that the presence of neutrophils correlate with high grade urothelial neoplasms, with significant increase in neutrophil count in high-grade UC cases compared to low-grade cases (p=0.001).

High neutrophil counts in high-grade and deeply invasive tumors may indicate a negative prognosis for TANs. In their study on localized bladder cancer, Liu et al.[12] found a similar correlation between an increased count of TANs and deeper tumor invasion and higher grade. This finding agreed with many studies on various tumor types in different organs, such as renal cell carcinoma, head and neck squamous cell carcinoma, and pancreatic adenocarcinoma.[20]

Neutrophils' pro-tumor activity could be due to the release of metalloproteinase 9, which releases vascular endothelial growth factor from the extracellular matrix to enhance angiogenesis, and secretes arginase 1, which suppresses CD8 T lymphocytes. Also, TANs generate reactive oxygen species, which induce tumor progression.[20][21]

Zhou's study found that patients with high level of TINs had significantly poor overall survivals, and was an independent prognostic factor for overall survival in bladder cancer patients.[22]

In our study, TINs was significantly associated with pathological stages and grades of tumors. Regarding the prognosis, high level of TINs significantly associated with the shorter OS.[14] We conclude that tumor infiltrating neutrophils associated with deeper invasion and high grades. Tumor infiltrating immune cells not only play essential roles in tumor microenvironment, but also are important predictors of bladder cancer survivals.[12]

Correspondingly, TALs play a dual regulatory role by inducing an antitumor immune response, inhibiting tumor growth and progression, and creating a microenvironment that stimulates tumor outgrowth. The role of lymphocytes in the tumor microenvironment mainly includes anti-tumor immune response and regulation of the tumor microenvironment. Lymphocytes play an antitumor role by recognizing and eliminating tumor cells. Besides to direct antitumor effects, lymphocytes can also regulate the tumor microenvironment and inhibit tumor growth and spread by releasing cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor (TNF).[23] However, some studies have found that tumor cells can inhibit the activity of lymphocytes by releasing immunosuppressive factors such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10) in the tumor microenvironment, which stops the immune system from getting rid of the tumor.[23]

Some studies have shown that lymphocytes can affect the expression of extracellular matrix components and proteases in the tumor microenvironment, thereby promoting tumor cell invasion and metastasis. In addition, lymphocytes can also affect tumor angiogenesis, epithelial-mesenchymal transition of tumor cells, and other processes, and further affect tumor metastasis and invasion.[24]

We found a significant increase in lymphocytes during progression of invasion in both low- and high-grade neoplasms (in deeply invasive tumor). This finding coincides with a previous study that reported an association between the adaptive immune response and tumor progression.[25][26]

Regarding the lymphocyte population, we found that the number of lymphocytes in low-grade neoplasms was significantly increased in the NMIUC group compared to the NIUC group. Similarly, Pichler et al.[27], and Masson-Lecomte et al.,[28] reported an increased number of lymphocytes in T1 bladder cancer compared to Ta

bladder cancer. On the other hand, Faraj et al.,[29] found no significant relation between T lymphocytes and any clinicopathological parameters; however, they did report a significant correlation with overall survival and disease-specific survival.

Unlike our results, Hulsen et al.,[30] found significantly higher values for T-cell infiltration in grade 3 tumors. They also found that increased expression was related to decreased survival and increased recurrence and was associated with poor prognosis. They only included specimens were of patients diagnosed with T1 urothelial carcinoma, preventing comparison between tumor stages or relation of their findings to tumor progression.[30]

The relation between neutrophil counts in blood and lymphocytes has been correlated to clinicopathological parameters and has been suggested as a prognostic factor for urothelial carcinoma in many studies.[31][32][33]

In the present study, we studied the NLR at the tissue level. We found that the ratio correlated with tumor grade, with significant increase in the ratio in high-grade urothelial neoplasms compared to low-grade neoplasms. We found a significant increase in this ratio in the MIUC cases compared to the NMIUC cases in high-grade neoplasms, confirming the tumor-promoting effect of neutrophils. It has been suggested that TANs are different from circulating neutrophils. To increase clarity, replace with: Cytokines within the tumor microenvironment induce a population of neutrophils with a pro-tumor phenotype that inhibits CD8+ T cells, and its tumor promotion increases with tumor progression.[14] On the other hand, Mandelli et al.[34], discovered that there was no significant link between the tissue NLR and any of the clinicopathological variables they looked at, such as the stage and grade of the tumor. Such a disagreement in the results highlights the complication of the inflammatory response in urothelial carcinogenesis, and that other factors can potentiate or attenuate the role of inflammatory cells as anti- or pro-tumor cells.

It could be also postulated that NLR alterations in NIMBC patients mainly depends of tumor inflammatory microenvironment and cancer biology raising new opportunities for therapeutic interventions.[35] Future applications of NLR could also focus on interpreting the immune response to BCG therapy. However, it is important to remember that NLR is an expression of the immune system, a marker that can be also associated with immunotherapy and considered as a potential predictive factor of BCG response.[31]

Further prospective, well-controlled clinical studies of diverse patients in multiple institutions are required to validate the role of NLR as a prognostic marker, which may improve current risk stratification tools and treatment outcome. Therefore, NLR has the potential to serve as a prognostic marker for predicting disease recurrence in NMIBC, and it could enhance patient risk stratification in both pre- and postoperative settings, thereby guiding treatment strategies.[31]

In summary, this study highlighted the significance of inflammatory cells within the tumor environment of bladder urothelial carcinoma. TANs correlated with tumor grade and stage, whereas TALs, more likely to be associated with progression of tumor invasion rather than tumor grade. Further prospective multicenter studies with prolonged follow-up are recommended to confirm our results and to reveal the prognostic role of inflammatory cells in the progression of urothelial carcinoma.

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