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Association of preoperative hematological indices with high-grade pathology in non-muscle-invasive bladder cancer: A retrospective cross-sectional study

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Abstract

This study evaluated the associations and standalone discriminatory performance of preoperative hemoglobin-adjusted lymphocyte-to-neutrophil ratio (HLNR), lymphocyte-to-neutrophil ratio (LNR), hemoglobin-adjusted lymphocyte-to-platelet ratio (HLPR) for high-grade pathology in patients undergoing transurethral resection of bladder tumor (TURBT) for primary non-muscle-invasive bladder cancer. We further assessed whether LNR or HLNR provided incremental information beyond demographic and endoscopic variables available before histopathological assessment. We retrospectively analyzed 176 patients with primary non-muscle-invasive bladder cancer (NMIBC) (Ta–T1) who underwent TURBT between February 2016 and February 2025. The primary endpoint was high-grade tumor on the initial TURBT histopathological examination. Model A included age, sex, endoscopic tumor size, and tumor multiplicity; Model B added LNR and Model C added HLNR. Model fit, discrimination, internal validation, and calibration were assessed. Of 176 patients, 57 (32.4%) had high-grade tumors. LNR was associated with high-grade pathology in univariable analysis (Odds Ratio (OR) = 1.013, 95% confidence interval (CI) 1.002 – 1.025; $p = 0.024$). Model A had an Area Under Curve (AUC) of 0.762. After adjustment, LNR (Model B: OR = 1.012, $p = 0.089$) and HLNR (Model C: OR = 1.07, $p = 0.140$) were not independently associated with high-grade pathology, and neither significantly improved model fit or AUC. The hemoglobin $\times$ LNR interaction was nonsignificant ($p = 0.389$). After exclusion of 43 T1 low-grade tumors, LNR ($p = 0.366$) and HLNR ($p = 0.521$) remained nonsignificant. LNR was associated with high-grade pathology in univariable analysis, but this association was attenuated after adjustment for demographic and endoscopic tumor characteristics. Neither LNR nor HLNR significantly improved model fit or discrimination beyond the pre-pathology clinical model. These findings are exploratory and require validation in larger cohorts.

Keywords: Hematologic tests; prognosis; carcinoma, transitional cell; urinary bladder neoplasms

Introduction

Bladder cancer is one of the most common malignancies of the urinary tract and represents a clinically heterogeneous disease with varying risks of recurrence and progression. Approximately 75% of newly diagnosed bladder tumors are classified as non-muscle-invasive bladder cancer (NMIBC), including Ta tumors, carcinoma in situ (CIS), and tumors invading the lamina propria (T1) [1,2]. Although low-grade Ta tumors generally have a favorable prognosis, they may recur repeatedly and require long-term cystoscopic surveillance. In contrast, high-grade and T1 tumors are associated with an increased risk of progression to muscle-invasive disease and cancer-related mortality. Tumor

grade therefore plays a central role in risk stratification and influences decisions regarding repeat transurethral resection of bladder tumor (TURBT), intravesical treatment, surveillance intensity, and, in selected patients, early radical cystectomy [1,2]. However, definitive tumor grade is generally established only after histopathological examination of the TURBT specimen. Readily available parameters associated with aggressive pathological features could therefore provide additional information during the initial evaluation of patients with suspected bladder cancer.

Systemic inflammation is increasingly recognized as an important component of cancer development and progression. Interactions among tumor cells, inflammatory cells, and the

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host immune response may promote tumor-cell proliferation, angiogenesis, invasion, and metastatic spread [3]. Neutrophils can contribute to a tumor-promoting microenvironment through the release of inflammatory cytokines, reactive oxygen species, proteolytic enzymes, and proangiogenic mediators. Conversely, lymphocytes are essential components of antitumor immunity and contribute to immune surveillance and tumor-cell destruction. An imbalance between neutrophil-mediated inflammation and lymphocyte-mediated immune activity may therefore reflect the biological behavior of a tumor. Studies examining circulating and tumor-associated inflammatory cells have demonstrated associations between neutrophil-lymphocyte balance and adverse pathological or oncological characteristics in urothelial carcinoma [4-6]. Nevertheless, systemic inflammatory parameters can also be influenced by age, infection, comorbidities, medication use, and nutritional status and should therefore be regarded as indirect indicators of the interaction between the tumor and the host response rather than tumor-specific biomarkers.

Routine preoperative complete blood count parameters provide a simple, inexpensive, and widely available means of assessing systemic inflammatory and immune status. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), hemoglobin level, and several derived indices have been investigated in bladder cancer, primarily in relation to recurrence, progression, and survival [4,7-13]. Composite indices may provide a broader representation of the interaction between systemic inflammation, immune competence, anemia, and the patient's general condition. The hemoglobin-adjusted lymphocyte-to-neutrophil ratio (HLNR), calculated as hemoglobin multiplied by the lymphocyte-to-neutrophil ratio (LNR), combines hemoglobin with the balance between lymphocyte-mediated immunity and neutrophil-related inflammation. In comparison, the hemoglobin-adjusted lymphocyte-to-platelet ratio (HLPR) incorporates platelet count and may reflect a different inflammatory pathway, as platelets may contribute to tumor growth, angiogenesis, and metastatic dissemination. The HLNR approach was originally proposed by our group in a renal cell carcinoma study [14]. Its evaluation in NMIBC is based on the broader hypothesis that systemic inflammation and host immune status may be associated with tumor pathology, rather than on an assumption that renal cell carcinoma and urothelial carcinoma have similar biological behavior. Evidence regarding HLNR and HLPR in NMIBC remains limited [8,10,14]. Evaluating both indices may help determine whether neutrophil- or platelet-related pathways provide more relevant information regarding tumor grade.

Accordingly, this study aimed to evaluate the associations and standalone discriminatory performance of preoperative HLNR, LNR, and HLPR for high-grade pathology in patients undergoing TURBT for primary NMIBC. We further assessed whether LNR or HLNR added information to a model restricted to demographic and endoscopic variables available before histopathological assessment.

Material and Methods

Ethical Consideration

This study was approved by the Clinical Research Ethics Committee of Alanya Alaaddin Keykubat University (approval number:10354421-2025/03-17; approval date:12.02.2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. Because of the retrospective design, the requirement for specific informed consent for participation in this study was waived by the ethics committee. All patients had provided routine informed consent for TURBT and related clinical procedures.

Study Design and Patient Population

This retrospective cross-sectional study evaluated patients who underwent TURBT for primary NMIBC at our institution between February 2016 and February 2025. The available analytical database contained 180 patients after preliminary application of the stage, tumor-history, and hematological-data criteria. Three patients with missing grade and one additional patient with non-urothelial histology were excluded, leaving 176 patients in the final analysis (Figure 1). Because the original screening log could not be reconstructed reliably, the total number of TURBT procedures initially screened and the category-specific early exclusions were unavailable. None of the included patients had received intravesical *Bacillus Calmette-Guérin* (BCG) or intravesical chemotherapy before blood sampling.

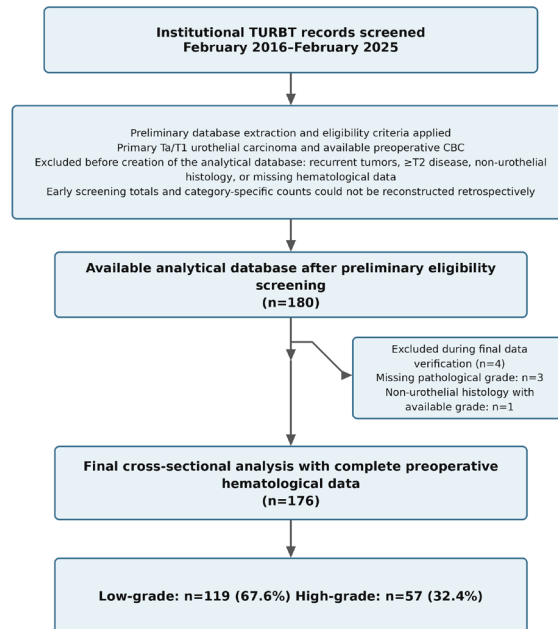


Figure 1. Patient selection and study flow diagram. The available analytical database contained 180 patients after preliminary eligibility screening. Three patients with missing pathological grade and one patient with non-urothelial histology were excluded, leaving 176 patients in the final cross-sectional analysis (119 low-grade and 57 high-grade tumors). The original number of TURBT records screened and category-specific early exclusion counts could not be reconstructed reliably from the retrospective database. CBC, complete blood count; TURBT, transurethral resection of bladder tumor.

Data Collection and Clinicopathological Assessment

Demographic, clinical, hematological, operative, and pathological data were retrospectively obtained from institutional medical records. Age, sex, endoscopic tumor size, and endoscopic tumor multiplicity were treated as demographic and pre-pathology variables. Pathological T stage, tumor grade, concomitant CIS, and lymphovascular invasion (LVI) were obtained from TURBT pathology reports.

Tumor size was defined as the largest endoscopically estimated diameter of the dominant lesion and was recorded in millimeters. Tumors were classified as solitary or multiple according to the number of lesions identified endoscopically at TURBT. These variables were available before the histopathological determination of grade. Pathological T stage was determined according to the seventh edition of the tumor–node–metastasis classification system, retained for consistency with institutional records. Tumor grade was classified according to the 2004 World Health Organization/International Society of Urological Pathology system.

The original TURBT specimens were evaluated as part of routine clinical practice by institutional pathologists; no dedicated central uropathology review or study-specific pathological re-review was performed. The primary grade and T-stage classifications were based on the initial TURBT pathology reports. Repeat TURBT (re-TURBT) findings, when available, were not incorporated into the primary endpoint classification. The presence of concomitant CIS and LVI was determined by histopathological examination of the initial TURBT specimens. Specimens were also evaluated for the presence of detrusor muscle. The absence of detrusor muscle was not considered an exclusion criterion in patients with pathologically confirmed Ta disease. Patients whose specimens were insufficient for reliable determination of tumor stage or grade were excluded.

Hematological Measurements and Calculation of Indices

Hematological measurements were obtained from the most recent complete blood count performed within 14 days before TURBT and before any tumor-directed treatment. Hemoglobin concentration and absolute neutrophil, lymphocyte, and platelet counts were recorded. The hematological indices were calculated using the following formulas:

$HLNR = \text{Hemoglobin (g/dL)} \times [\text{Lymphocyte count} / \text{Neutrophil count}]$

$LNR = \text{Lymphocyte count} / \text{Neutrophil count} \times 100$

$HLPR = \text{Hemoglobin (g/dL)} [\text{Lymphocyte count} / \text{Platelet count}] \times 1000$

$NLR = \text{Neutrophil count} / \text{Lymphocyte count}$

$PLR = \text{Platelet count} / \text{Lymphocyte count}$

Neutrophil, lymphocyte, and platelet counts were obtained from the units reported in the complete blood count. All indices were calculated before the statistical analyses. LNR and NLR were exact mathematical reciprocals, with $LNR = 100/NLR$. Therefore, they were regarded as alternative parameterizations of the same neutrophil–lymphocyte balance rather than independent hematological markers and were not entered simultaneously into any multivariable model.

Study Outcome

The primary outcome was high-grade tumor on histopathological examination of the TURBT specimen. The multivariable analyses assessed whether LNR or HLNR added information beyond age, sex, endoscopic tumor size, and tumor multiplicity, all of which were available before histopathological assessment. Pathological T stage and concomitant CIS were not included in the multivariable models because they were obtained from the same TURBT specimen as tumor grade.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median with interquartile range, as appropriate. Age and tumor size were compared using the independent-samples t test, and hematological indices were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test when expected cell counts were small.

Receiver operating characteristic (ROC) analysis was used to describe discrimination between low- and high-grade tumors. Area Under Curve (AUCs) were reported with 95% confidence intervals obtained using 1,000 bootstrap resamples. Because all individual indices showed poor discrimination, Youden-derived cut-offs and associated sensitivity, specificity, positive predictive value, and negative predictive value were not reported to avoid implying clinically actionable thresholds.

Associations between the candidate variables and high-grade pathology were initially examined using univariable binary logistic regression. The univariable analyses used the untransformed LNR and NLR values. Because reciprocal transformation is nonlinear, logistic regression models containing untransformed LNR and NLR represent different functional forms and are not expected to produce identical coefficients or p values. As a sensitivity analysis, the logistic regression analyses were repeated using natural-log-transformed LNR and NLR. On the logarithmic scale, $\log(LNR) = \log(100) - \log(NLR)$; therefore, the two models are mathematically equivalent and yield identical model fit and p values, with coefficients in opposite directions.

Age, sex, endoscopic tumor size, and tumor multiplicity were included in the pre-pathology Model A. LNR was added to construct Model B, and HLNR was added separately to construct

Model C. Pathological T stage and concomitant CIS were not included because they were determined from the same TURBT specimen as the outcome. Because HLNR is mathematically derived from hemoglobin and LNR, HLNR and LNR were not entered together.

Model discrimination was evaluated using the AUC with 95% bootstrap confidence intervals. Incremental model fit was assessed with likelihood-ratio tests, and correlated AUCs were compared using the DeLong method. Internal validation using 1,000 bootstrap resamples was performed for Models A–C. To assess whether HLNR added information beyond its components, hemoglobin and LNR were entered separately after mean-centering, followed by their interaction term. A sensitivity analysis excluded the 43 tumors reported as T1 low grade and repeated Models A–C. Potential nonlinearity was assessed using restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles. Three knots were selected to limit model complexity given 57 high-grade events. Spline models were compared with the corresponding linear models by likelihood-ratio tests.

Results

Patient Selection and Clinicopathological Characteristics

The available analytical database contained 180 patients after preliminary eligibility screening. Three patients with missing grade information and one additional patient with non-urothelial histology were excluded. The final analysis included 176 patients with complete hematological data: 119 (67.6%) had low-grade and 57 (32.4%) had high-grade tumors (Figure 1).

The mean age of the study population was 65.7 ± 11.2 years, and 160 patients (90.9%) were male. Compared with patients with low-grade tumors, those with high-grade tumors were older (68.9 ± 12.3 vs. 64.2 ± 10.4 years, $p = 0.003$), had larger tumors (34.1 ± 13.4 vs. 24.3 ± 12.0 mm, $p < 0.001$), and more frequently presented with multiple tumors (56.1% vs. 38.7%, $p = 0.043$) and pathological T1 disease (77.2% vs. 36.1%, $p < 0.001$). Among the 87 tumors classified as T1 in the original TURBT reports, 43 were low grade and 44 were high grade. Sex, smoking status, concomitant CIS, and LVI did not differ significantly between grade groups (Table 1).

Table 1. Demographic and clinicopathological characteristics

Variable	Total (n = 176)	Low-grade (n = 119)	High-grade (n = 57)	p-value
Age (years), mean±SD	65.7 ± 11.2	64.2 ± 10.4	68.9 ± 12.3	0.003
Male sex, n (%)	160 (90.9%)	111 (93.3%)	49 (86.0%)	0.114
Smoker, n (%)	112 (63.6%)	81 (68.1%)	31 (54.4%)	0.110
Multiple tumor, n (%)	78 (44.3%)	46 (38.7%)	32 (56.1%)	0.043
Tumor size (mm), mean±SD	27.5 ± 13.3	24.3 ± 12.0	34.1 ± 13.4	< 0.001
T1 stage, n (%)	87 (49.4%)	43 (36.1%)	44 (77.2%)	< 0.001
Concomitant CIS, n (%)	29 (16.5%)	17 (14.3%)	12 (21.1%)	0.360
LVI, n (%)	5 (2.8%)	2 (1.7%)	3 (5.3%)	0.393
High-grade tumor (primary outcome)	57 (32.4%)	—	—	—

Age and tumor size were compared using the independent-samples t test. Categorical variables were compared using the chi-square test or Fisher’s exact test when expected cell counts were small; Fisher’s exact test was used for LVI. Abbreviations: CIS, carcinoma in situ; LVI, lymphovascular invasion. SD, standard deviation.

Preoperative Hematological Parameters

The distributions of the preoperative hematological parameters according to tumor grade are presented in Table 2. Median HLNR was numerically higher in patients with high-grade tumors than in those with low-grade tumors, although the difference was not statistically significant (6.37 (IQR, 4.79 – 9.32) vs. 5.80 (IQR, 4.33 – 8.66), $p = 0.207$). Median LNR was higher in patients with high-grade tumors than in those with low-grade tumors (46.88 (IQR, 33.9 – 67.7) vs. 41.79 (IQR, 32.5 – 58.6)), whereas median NLR was correspondingly lower

(2.13 (IQR, 1.48 – 2.95) vs. 2.39 (IQR, 1.71 – 3.08)). Because LNR and NLR are reciprocal transformations of the same values, their two-sided Mann–Whitney U tests yielded the same result ($p = 0.098$). Neither comparison reached statistical significance.

Hemoglobin was lower in the high-grade group, with a borderline difference between the groups (13.80 (IQR, 12.50 – 14.73) vs. 14.30 (IQR, 12.95 – 15.33) g/dL, $p = 0.061$). No statistically significant differences were observed for WBC, neutrophil, lymphocyte, platelet, PLR, or HLPR values (all $p > 0.05$).

Table 2. Preoperative hematological parameters by tumor grade

Parameter	Low-grade (n = 119) Median (IQR)	High-grade (n = 57) Median (IQR)	p-value
Hb (g/dL)	14.30 (12.95 – 15.33)	13.80 (12.50 – 14.73)	0.061
WBC (×10 ³ /μL)	7.27 (6.30 – 8.96)	7.63 (6.43 – 8.86)	0.531
Neutrophil (×10 ³ /μL)	4.40 (3.53 – 5.67)	4.40 (3.30 – 5.50)	0.446
Lymphocyte (×10 ³ /μL)	1.95 (1.45 – 2.31)	2.10 (1.67 – 2.77)	0.059
Platelet (×10 ³ /μL)	237 (206 – 278)	234 (205 – 306)	0.804
NLR	2.39 (1.71 – 3.08)	2.13 (1.48 – 2.95)	0.098
PLR	122.86 (93.4 – 163.3)	116.67 (88.1 – 154.3)	0.404
LNR	41.79 (32.5 – 58.6)	46.88 (33.9 – 67.7)	0.098
HLPR	117.64 (82.0 – 161.5)	123.53 (77.2 – 154.6)	0.726
HLNR	5.80 (4.33 – 8.66)	6.37 (4.79 – 9.32)	0.207
HLNR formula	Hb × Lymphocyte / Neutrophil		

Mann-Whitney U test. Abbreviations: Hb, hemoglobin; HLNR, hemoglobin-adjusted lymphocyte-to-neutrophil ratio; HLPR, hemoglobin-adjusted lymphocyte-to-platelet ratio; IQR, interquartile range; LNR, lymphocyte-to-neutrophil ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; WBC, white blood cells.

ROC Curve Analysis

The discriminatory performance of the individual hematological indices was poor (Table 3 and Figure 2A). HLNR had an AUC of 0.557 (95% CI, 0.462 – 0.653), LNR 0.576 (95% CI, 0.483 – 0.664), NLR 0.575 (95% CI, 0.486 – 0.667), HLPR 0.513, PLR 0.536, and hemoglobin 0.589 (95% CI, 0.505 – 0.665). None achieved an AUC greater than 0.60, and several confidence intervals included 0.50. Cut-offs and associated diagnostic performance measures were therefore not reported because they should not be interpreted as clinically actionable thresholds.

Table 3. Discriminatory performance of individual hematological indices and the pre-pathology reference model

Marker	AUC (95% CI)
HLNR	0.557 (0.462 – 0.653)
LNR	0.576 (0.483 – 0.664)
HLPR	0.513 (0.417 – 0.600)
NLR	0.575 (0.486 – 0.667)
PLR	0.536 (0.435 – 0.633)
Hemoglobin	0.589 (0.505 – 0.665)
Primary Model A	0.762 (0.679 – 0.844)

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; HLNR, hemoglobin-adjusted lymphocyte-to-neutrophil ratio; LNR, lymphocyte-to-neutrophil ratio; HLPR, hemoglobin-adjusted lymphocyte-to-platelet ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Logistic Regression Analysis

In the univariable logistic regression analysis, age (OR = 1.04 per year; 95% CI, 1.01 – 1.07; p = 0.012), tumor multiplicity (OR = 2.10; 95% CI, 1.11 – 4.00; p = 0.023), tumor size (OR = 1.06 per mm; 95% CI, 1.03 – 1.09; p < 0.001), pathological T1 stage (OR = 5.98; 95% CI, 2.90 – 12.33; p < 0.001), and LNR (OR = 1.013 per one-unit increase; 95% CI, 1.002 – 1.025; p = 0.024) were significantly associated with high-grade pathology. HLNR showed a borderline association (OR = 1.07; 95% CI, 1.00 – 1.16; p = 0.063), whereas NLR was not significantly associated with high-grade pathology (OR = 0.868; 95% CI, 0.715 – 1.053; p = 0.151). The difference between the LNR and NLR results reflects the different functional forms imposed by entering these reciprocal variables on their original scales and does not indicate that they contain different biological information (Table 4).

In the sensitivity analysis using natural-log-transformed values, log-transformed LNR and NLR produced identical model fit and p values, with coefficients in opposite directions. Both log-transformed LNR and NLR were significantly associated with high-grade pathology in the univariable analysis (p = 0.045).

In the pre-pathology analysis, Model A included age, sex, endoscopic tumor size, and tumor multiplicity (Table 5). Age (OR = 1.05 per year, 95% CI 1.02 – 1.09; p = 0.004), tumor size (OR = 1.07 per mm, 95% CI 1.04 – 1.10; p < 0.001), and multiplicity (OR = 2.30, 95% CI 1.12 – 4.71; p = 0.023) were independently associated with high-grade pathology. Model A had an apparent AUC of 0.762 (95% CI, 0.679 – 0.844) (Figure 2B).

Adding LNR to Model A produced Model B. LNR was not independently associated with high-grade pathology (OR = 1.012, 95% CI 0.998 – 1.026; p = 0.089), and the AUC increased to 0.774 (95% CI, 0.692 – 0.845). The likelihood-ratio test ($\chi^2 = 3.37$; p = 0.066) and DeLong comparison (p = 0.313) were not significant. Adding HLNR produced Model C; HLNR was also not significant (OR = 1.07, 95% CI 0.98 – 1.17; p = 0.140). Model C had an AUC of 0.768 (95% CI, 0.693 – 0.847), with nonsignificant likelihood-ratio ($\chi^2 = 2.38$; p = 0.123) and DeLong (p = 0.535) comparisons (Table 5).

Table 4. Univariable logistic regression analysis for high-grade pathology

Variable	OR (95% CI)	p
Age (per year)	1.04 (1.01 – 1.07)	0.012
Male sex	0.44 (0.16 – 1.24)	0.122
Smoking	0.58 (0.30 – 1.11)	0.100
Multiple tumor	2.10 (1.11 – 4.00)	0.023
Tumor size (per mm)	1.06 (1.03 – 1.09)	< 0.001
T1 stage (vs. Ta)	5.98 (2.90 – 12.33)	< 0.001
Concomitant CIS	1.60 (0.71 – 3.63)	0.260
LVI	3.25 (0.53 – 20.02)	0.204
HLNR	1.07 (1.00 – 1.16)	0.063
LNR	1.01 (1.00 – 1.03)	0.024
HLPR	1.00 (1.00 – 1.01)	0.092
NLR	0.87 (0.71 – 1.05)	0.151
Hemoglobin	0.85 (0.72 – 1.00)	0.050

LNR and NLR are mathematical reciprocals ($LNR = 100/NLR$) and represent alternative parameterizations of the same underlying cell-count ratio. Differences between their untransformed logistic regression results reflect differences in functional form and should not be interpreted as independent biological effects. The outcome was high-grade pathology; low-grade pathology was the reference category. Abbreviations: CI, confidence interval; CIS, carcinoma in situ; HLNR, hemoglobin-adjusted lymphocyte-to-neutrophil ratio; HLPR, hemoglobin-adjusted lymphocyte-to-platelet ratio; LNR, lymphocyte-to-neutrophil ratio; LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio.

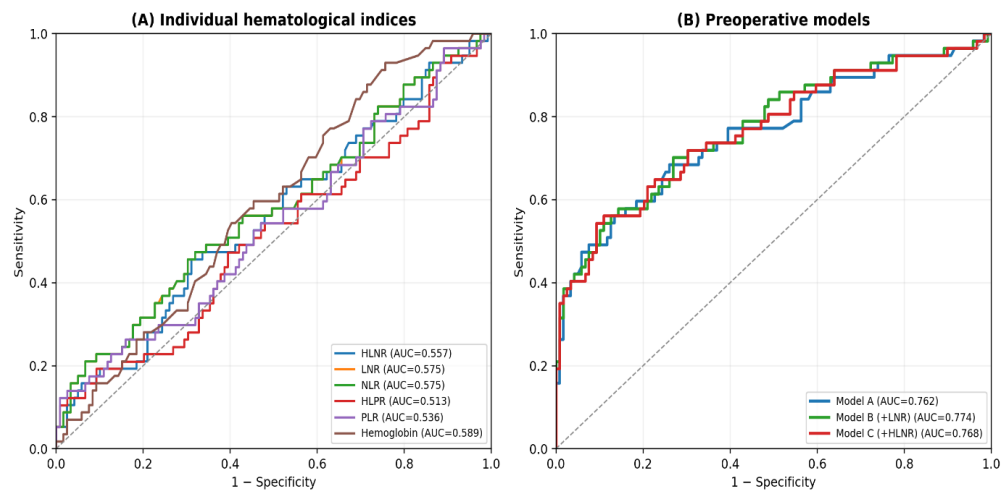


Figure 2. ROC curves for high-grade pathology. (A) Standalone discrimination of individual preoperative hematological indices. (B) Pre-pathology multivariable models: Model A included age, sex, endoscopic tumor size, and tumor multiplicity; Model B added LNR; and Model C added HLNR. Pathological T stage and concomitant CIS were not included because they were obtained from the same TURBT specimen as tumor grade. The increases in AUC for Models B and C versus Model A were small and were not statistically significant by DeLong testing. Abbreviations: AUC, area under the curve; HLNR, hemoglobin-adjusted lymphocyte-to-neutrophil ratio; HLPR, hemoglobin-adjusted lymphocyte-to-platelet ratio; LNR, lymphocyte-to-neutrophil ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic.

Table 5. Multivariable logistic regression models for high-grade pathology. Model A included age, sex, endoscopic tumor size, and tumor multiplicity; Model B added LNR; Model C added HLNR

Variable	Model A		Model B (+LNR)		Model C (+HLNR)	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (per year)	1.05 (1.02 – 1.09)	0.004	1.05 (1.02 – 1.09)	0.003	1.06 (1.02 – 1.10)	0.003
Male sex	0.483 (0.145 – 1.613)	0.237	0.601 (0.179 – 2.022)	0.411	0.558 (0.167 – 1.864)	0.343
Tumor size (per mm)	1.07 (1.04 – 1.10)	< 0.001	1.07 (1.03 – 1.10)	< 0.001	1.07 (1.03 – 1.10)	< 0.001
Multiple tumor	2.30 (1.12 – 4.71)	0.023	2.40 (1.15 – 5.00)	0.019	2.34 (1.13 – 4.83)	0.022
HLNR	—	—	—	—	1.07 (0.98 – 1.17)	0.140
LNR (per unit)	—	—	1.012 (0.998 – 1.026)	0.089	—	—
AUC	0.762	—	0.774	—	0.768	—
LR test vs. reference	Reference	—	$\chi^2 = 3.37$	0.066	$\chi^2 = 2.38$	0.123

HLNR and LNR were entered separately. Pathological T stage and concomitant CIS were not included because they were obtained from the same TURBT specimen as tumor grade. Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; LR, likelihood ratio; OR, odds ratio.

Internal Validation and Calibration

Bootstrap internal validation yielded optimism-corrected AUCs of 0.743, 0.753, and 0.747 for Models A, B, and C, respectively.

The corresponding optimism-corrected calibration slopes were 0.908, 0.889, and 0.889, and the Brier scores were 0.178, 0.177, and 0.177 (Table 6). No external validation was performed.

Table 6. Model discrimination, internal validation, and calibration

Metric	Model A	Model B (+LNR)	Model C (+HLNR)
Apparent AUC (95% CI)	0.762 (0.679 – 0.844)	0.774 (0.698 – 0.852)	0.768 (0.686 – 0.843)
DeLong p vs. reference	Reference	0.313	0.535
Optimism-corrected AUC	0.743	0.753	0.747
Optimism-corrected calibration slope	0.908	0.889	0.889
Optimism-corrected Brier score	0.178	0.177	0.177

Ninety-five percent confidence intervals and optimism-corrected estimates were obtained using 1,000 bootstrap resamples. The DeLong test compared Models B and C with Model A. Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Component and Interaction Analysis

In the pre-pathology covariate set, the model containing hemoglobin and LNR as separate main effects had an AUC of 0.775. Addition of the centered hemoglobin × LNR interaction did not improve model fit (interaction OR = 0.997, 95% CI 0.989 – 1.004; p = 0.389; LR p = 0.383) or discrimination (AUC = 0.780; DeLong p = 0.216). Thus, HLNR did not demonstrate incremental information beyond hemoglobin and LNR entered separately.

Sensitivity Analysis Excluding T1 Low-Grade Tumors

After exclusion of 43 T1 low-grade tumors, 133 patients remained, including 57 with high-grade disease. LNR remained nonsignificant in Model B (OR = 1.006, 95% CI 0.993 – 1.020;

p = 0.366; AUC = 0.777), as did HLNR in Model C (OR = 1.03, 95% CI 0.94 – 1.13; p = 0.521; AUC = 0.777). Neither augmented model improved fit or discrimination compared with Model A (LNR: LR p = 0.339, DeLong p = 0.974; HLNR: LR p = 0.510, DeLong p = 0.933).

Assessment of Nonlinearity

Restricted cubic spline analyses provided no evidence of nonlinearity for LNR or HLNR in the pre-pathology models (LNR p = 0.896; HLNR p = 0.810). No nonlinearity was detected for tumor size (p = 0.904); the finding for age was borderline but did not reach statistical significance (p = 0.062). The prespecified linear terms were therefore retained.

Discussion

This study evaluated hematological indices within a model restricted to demographic and endoscopic variables available before histopathological assessment. LNR was associated with high-grade pathology in univariable analysis, but the association was attenuated after adjustment; HLNR was not significant in the adjusted model. Moreover, the hemoglobin $\times$ LNR interaction did not add information beyond hemoglobin and LNR entered separately, and exclusion of T1 low-grade tumors did not alter the adjusted findings. Collectively, these results do not support HLNR as a biologically distinct biomarker or either index as a clinically useful pre-pathology predictor.

Systemic inflammatory markers have been investigated extensively in urothelial carcinoma because they may reflect the interaction between tumor-related inflammation and host immune activity. Previous studies and pooled analyses have generally associated an elevated NLR with adverse pathological characteristics, recurrence, progression, or mortality in bladder cancer [4,7,9,11-13]. Studies evaluating circulating and tumor-associated neutrophils and lymphocytes have also demonstrated that the relationship between systemic cell counts, local immune-cell infiltration, and tumor behavior is complex and may vary according to disease stage and the outcome under investigation [5,6]. Most previous NMIBC studies have focused on time-dependent oncological outcomes rather than tumor grade at the index TURBT [9,12,13]. The present analysis therefore addresses a different question by examining the relationship between preoperative hematological indices and a pathological characteristic determined at resection.

Because HLNR equals hemoglobin multiplied by LNR/100, its incremental contribution was examined with a hemoglobin $\times$ LNR interaction; the interaction was nonsignificant in the pre-pathology model. Restricted cubic splines did not identify significant nonlinearity for HLNR or LNR, supporting retention of linear terms within this dataset. LNR and NLR are reciprocals; differences on their untransformed scales reflect functional-form assumptions rather than distinct biology.

HLPR was included to assess whether a hemoglobin-based index incorporating platelet count conveyed information comparable to that of the neutrophil-based HLNR. Platelets have been implicated in tumor-associated inflammation, angiogenesis, and metastatic dissemination, and hemoglobin- and platelet-based indices have previously demonstrated prognostic relevance in bladder and other urological malignancies [6,7,11]. In the present study, however, HLPR did not differ between grade groups, showed poor standalone discrimination, and was not significantly associated with high-grade pathology in univariable analysis. Although LNR and HLNR showed stronger univariable signals than HLPR, the present results do not establish that neutrophil-related pathways are biologically more important than platelet-related pathways in NMIBC.

Although LNR was associated with high-grade pathology in univariable analysis, neither LNR nor HLNR significantly improved model fit or discrimination after adjustment for the pre-pathology clinical variables. A significant univariable association does not by itself establish incremental predictive value or clinical usefulness. The results therefore do not justify using these indices to guide treatment or surveillance.

Several limitations should be considered. The retrospective, single-center design introduces selection bias, and the consecutive nature of the cohort could not be verified because the original screening log was unavailable. Only 57 high-grade events and 16 women were included. Pathology was based on routine reports without central re-review. Information on active urinary tract infection, hematuria-related blood loss, recent transfusion, corticosteroid or immunosuppressive therapy, chronic inflammatory disease, and hematological disorders was not systematically available. Because these conditions directly affect the components of the investigated indices, residual confounding could plausibly account for part of the observed associations. Three-knot spline analyses did not detect nonlinearity, but the sample size limited power to identify more complex functional forms.

A strength of this analysis is its restriction of the multivariable models to demographic and endoscopic variables available before histopathological assessment, together with component, sensitivity, nonlinearity, internal-validation, and calibration analyses. Future multicenter studies should use prospectively recorded cystoscopic and imaging variables, standardized pathological review, and external validation.

Conclusion

In conclusion, LNR was associated with high-grade pathology in univariable analysis, but this association was attenuated after adjustment for demographic and endoscopic tumor characteristics. Neither LNR nor HLNR significantly improved model fit or discrimination beyond the pre-pathology clinical model. HLNR did not improve a model containing hemoglobin and LNR separately, and the sensitivity and spline analyses did not change the main conclusion. These findings are exploratory and require validation in larger cohorts.

Ethical Approval

This study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Alanya Alaaddin Keykubat University Clinical Research Ethics Committee (Approval No: 10354421-2025/03-17).

Patient Consent

Informed consent forms were obtained from all patients.

Conflict of Interest

The authors confirm the absence of any conflicts associated with this work.

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References

1. Babjuk M, Burger M, Capoun O, et al. European Association of Urology Guidelines on non-muscle-invasive bladder cancer (Ta, T1, and Carcinoma in Situ). *Eur Urol*. 2022;81:75-94.
2. Compérat E, Wasinger G, Oszwald A, et al. Nonmuscle-invasive bladder cancer, old problems, new insights. *Curr Opin Urol*. 2022;32:352-7.
3. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140:883-99.
4. Wu S, Zhao X, Wang Y, et al. Pretreatment neutrophil-lymphocyte ratio as a predictor in bladder cancer and metastatic or unresectable urothelial carcinoma patients: a pooled analysis of comparative studies. *Cell Physiol Biochem*. 2018;46:1352-64.
5. Hassan WA, ElBanna AK, Noufal N, et al. Significance of tumor-associated neutrophils, lymphocytes, and neutrophil-to-lymphocyte ratio in non-invasive and invasive bladder urothelial carcinoma. *J Pathol Transl Med*. 2023;57:88-94.
6. Liu K, Zhao K, Wang L, Sun E. The prognostic values of tumor-infiltrating neutrophils, lymphocytes and neutrophil/lymphocyte rates in bladder urothelial cancer. *Pathol Res Pract*. 2018;214:1074-80.
7. Luo Y, Shi X, Li W, et al. Evaluation of the clinical value of hematological parameters in patients with urothelial carcinoma of the bladder. *Medicine (Baltimore)*. 2018;97:e0351.
8. Tang G, Zhen Y, Xie W, et al. Preoperative hemoglobin-platelet ratio can significantly predict progression and mortality outcomes in patients with T1G3 bladder cancer undergoing transurethral resection of bladder tumor. *Oncotarget*. 2018;9:18627-36.
9. Cantiello F, Russo GI, Vartolomei MD, et al. Systemic inflammatory markers and oncologic outcomes in patients with high-risk non-muscle-invasive urothelial bladder cancer. *Eur Urol Oncol*. 2018;1:403-10.
10. Peng D, Zhang CJ, Gong YQ, et al. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. *Sci Rep*. 2018;8:794.
11. Luo Y, She DL, Xiong H, et al. Pretreatment neutrophil to lymphocyte ratio as a prognostic predictor of urologic tumors: a systematic review and meta-analysis. *Medicine*. 2015;94:e1670.
12. Mano R, Baniel J, Shoshany O, et al. Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non-muscle-invasive bladder cancer. *Urol Oncol*. 2015;33:67.e1-7.
13. Kang M, Jeong CW, Kwak C, et al. Preoperative neutrophil-lymphocyte ratio can significantly predict mortality outcomes in patients with non-muscle invasive bladder cancer undergoing transurethral resection of bladder tumor. *Oncotarget*. 2017;8:12891-901.
14. Uçar M, Soyupek S, Oksay T, et al. Can we predict preoperative tumor aggressivity with hemogram parameters in renal cell carcinoma? A novel calculation method. *J Med Syst*. 2019;44:19.