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RESEARCH ARTICLE

Novel Hematologic Markers for Risk Stratification in Bladder Cancer Patients Receiving BCG Treatment

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Abstract

Objective: In order to evaluate the predictive role of novel hematologic markers in recurrence and progression among non-muscle invasive bladder cancer (NMIBC) patients undergoing intravesical BCG therapy.

Material and Methods: A total of 182 patients diagnosed with NMIBC and treated with transurethral resection of bladder tumor (TUR-BT) followed by BCG therapy were included. Patients were stratified into intermediate-, high- and very high-risk groups per the EAU 2024 guidelines. Preoperative hematologic parameters were recorded. In addition, CLR, CAR, and IBI were calculated. Recurrence and progression were assessed through follow-up cystoscopies. ROC curve analysis was used to determine the predictive value of the biomarkers.

Results: Recurrence and progression occurred in 15% and 8% of patients, respectively. Multifocal tumors showed a notable association with recurrence ($p = 0.006$), and carcinoma in situ (CIS) predicted progression ($p < 0.001$). CAR (AUC = 0.695, $p = 0.013$) and CLR (AUC = 0.660, $p = 0.040$) significantly predicted progression. IBI was a strong predictor in the very high-risk group (AUC = 0.920, $p < 0.001$).

Conclusion: CLR, CAR, and IBI are promising markers for identifying patients at higher risk of progression during BCG therapy. IBI shows strong prognostic utility in very high-risk NMIBC patients. Further prospective, multicenter studies are needed for clinical validation.

Keywords: BCG, hematologic inflammatory markers, non-muscle invasive bladder cancer, progression, recurrence

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INTRODUCTION

Approximately 75% of bladder cancer cases are non-muscle invasive (NMIBC), and 25% are muscle-invasive (MIBC). NMIBC patients typically undergo transurethral resection followed by intravesical therapies with various therapeutic agents. The specific treatment being chosen based on the patient's risk of progression (1). Accurate prediction of short- and long-term probabilities of disease recurrence and progression in NMIBC patients, post-transurethral resection is essential for guiding adjuvant treatment recommendations and organizing effective surveillance programs. Risk stratification has been widely employed to inform treatment strategies and estimate the likelihood of developing muscle-invasive bladder cancer (2). The European Organization for Research and Treatment of Cancer (EORTC) risk classification system consolidates six factors: previous recurrences, maximum tumor diameter, number of tumors, tumor stage, World Health Organization (WHO) 1973 and 2004/2016 grading classifications, and presence of concomitant carcinoma in situ. Additionally, three clinical risk factors are considered: age greater than 70 years, presence of multiple papillary tumors, and tumor diameter exceeding 3 cm (1-3).

The immune system, including both the inflammatory response and the tumor microenvironment, significantly influences the clinical course, biological features, and outcomes of bladder cancer (4). During an inflammatory response, various immune cells, including neutrophils, lymphocytes, monocytes, and platelets, undergo alterations alongside C-reactive protein (CRP) and albumin. Several of these inflammatory markers have demonstrated potential as valuable indicators for assessing cancer prognosis. Immune-related biomarkers, including the monocyte/lymphocyte ratio (MLR), the pan-immune inflammation value (PIV), systemic inflammatory response index (SIRI), neutrophil/lymphocyte ratio (NLR), systemic immune inflammation index (SII) and platelet/lymphocyte ratio (PLR), have been studied to forecast the prognosis of bladder cancer patients (5-7).

Current studies point out the prognostic significance of CRP to lymphocyte ratio (CLR), inflammatory burden index (IBI), and CRP to albumin ratio (CAR) in both non-metastatic and metastatic cancers. Elevated levels of these markers in colorectal and oral mucosal cancers have been linked to adverse cancer prognosis (8-10). To date, however, no studies or meta-analyses have investigated the association of CLR, CAR, and IBI with recurrence and progression in NMIBC. Our study endeavors to ascertain the correlation between CLR, CAR, and IBI and the risk of recurrence and progression in NMIBC patients undergoing Bacillus Calmette-Guérin (BCG) therapy.

MATERIAL AND METHODS

Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee Date: 29.02.2024 Land No: HNEAH/KAEK-2024/KK/9 Study activities adhered to the principles outlined in the Declaration of Helsinki. All participating patients signed the informed consent in writing and agreed to the anonymous use of their data.

Patients were selected based on the inclusion criteria, which required a diagnosis of NMIBC confirmed by histopathological evaluation. Eligible patients had received at least one induction cycle of BCG therapy and had a minimum follow-up period of 12 months post-BCG therapy with documented recurrence and progression status. Adequate BCG therapy is when a patient has received at least five of six induction installations and at least one maintenance (two of three installations) in 6 months (11). Patients were also required to have available preoperative hematologic laboratory data, including CRP, albumin, and complete blood count parameters. Two hundred fifty patients with primary bladder cancer undergoing transurethral resection of bladder tumor (TUR-BT) at our tertiary referral uro-oncology clinic between January 2015 and June 2023 were enrolled. Sixty-eight patients with a history of secondary malignancy (n=5), immune system failure (n=3), pathology results contraindicating BCG therapy (n=41), non-adherence to BCG follow-up protocols (n=14) or follow-up conducted at other centers (n=5) were excluded from the study. Following these exclusions, our study group comprised 182 patients.

Demographic information (age, sex, comorbidities, smoking status) and clinical parameters were collected. Pre- and postoperative biochemical markers, including CRP (mg/L), albumin (g/L), and complete blood count values (monocyte count, lymphocyte count, platelet count, neutrophil count) (10^9/L), were recorded within a two-week window surrounding surgery. The following calculated indices were

derived from the collected data: neutrophil/lymphocyte as NLR, CRP x NLR as IBI, CRP/albumin as CAR, CRP/lymphocyte as CLR**,** monocyte × neutrophil × platelet) / lymphocyte as PIV, monocyte/lymphocyte as MLR, platelet/lymphocyte as PLR, monocyte x NLR as SIRI, platelet x NLR as SII.

The date of TUR-BT surgery, postoperative pathology results, T stage, low-grade/high-grade (LG/HG) grade, and presence of carcinoma in situ (CIS) were retrieved from the hospital database. Patients were risk-stratified into three groups (intermediate, high, very high) based on the updated prognostic risk group for NMIBC according to the European Association of Urology (EAU) 2024 guidelines. Follow-up cystoscopies were performed at intervals determined by each patient's risk category in accordance with the surveillance schedule outlined in the follow-up section of the EAU guidelines for NMIBC. Tumor recurrence or progression observed during these evaluations was duly recorded.

Disease-free survival time, progression time (if applicable), and progression-free survival time were calculated in months. Patients were followed for a maximum of 114 months and a minimum of 12 months.

The association between the presence of postoperative recurrence and/or progression and the above-mentioned hematologic inflammatory variables was evaluated. The relationships between these variables and the outcomes of interest were examined to assess their prognostic significance.

Statistical analysis was carried out using IBM SPSS version 25 (IBM Corp, Armonk, NY, USA). Continuous variables were presented as medians with interquartile ranges (IQR), where appropriate. Categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables, based on normality distribution (assessed by the Shapiro-Wilk test). The predictive performance for recurrence and progression was evaluated using ROC curve analysis, and the optimal cut-off values were determined using the Youden Index. Statistical significance was set at $p < 0.05$.

RESULTS

In our study, 63% of patients were younger than 70 years old, and 87% were male. Smoking prevalence was 79%. Additionally, 33% of patients had diabetes, 45% had hypertension, and 9% had chronic obstructive pulmonary disease (COPD). CIS was observed in 15% of cases. Single tumor lesions were present in 59% of patients, while 41% had two or more lesions. Tumor size was ≥3 cm in 62% of patients. Risk categorization revealed that 27% had intermediate risk, 59% had high risk, and 14% had very high risk. Recurrence and progression rates were 15% and 8%, respectively. Detailed demographic and clinical characteristics are presented in Table 1.

The median follow-up duration was 52.2 ± 27 months (range: 12–114 months). Evaluation of recurrence and progression according to age, tumor size, tumor multiplicity, and presence of CIS revealed that age group, tumor size, and CIS were not significantly associated with recurrence ($p = 0.133$, $p = 0.268$, and $p = 0.929$, respectively). However, a statistically significant association was observed between recurrence and tumor multiplicity ($p = 0.006$). Recurrence was notably more frequent in patients with multifocal lesions (24.3%) than in those with unifocal disease (9.3%) (Table 2).

In the analysis of progression, only the presence of CIS demonstrated a significant association ($p < 0.001$) with progression observed in 25.9% of patients with CIS, compared to 5.2% in those without. Age group, tumor size, and number of lesions were not significantly associated with progression ($p = 0.058$, $p = 0.703$ and $p = 0.957$, respectively) (Table 2).

When stratified by EAU 2022 risk groups, recurrence rates were 8.2%, 18.5%, and 16% in intermediate-, high- and very high-risk groups, respectively. This difference was not statistically significant ($p = 0.248$). However, a significant difference in progression was noted among risk groups ($p = 0.029$), with progression rates of 2% in the intermediate-risk group, 8.3% in the high-risk group, and 20% in the very high-risk group, as demonstrated in Table 2**.**

Hematologic markers were assessed in relation to recurrence and progression. No statistically significant associations were found between any of the tested indices (CAR, CLR,

IBI, SIRI, SII, PIV, NLR, MLR, and PLR) and recurrence ($p > 0.05$ for all). However, CAR ($p = 0.013$) and CLR ($p = 0.040$) were significantly associated with progression in the overall cohort (Table 3). ROC analysis confirmed that CAR provided superior predictive accuracy compared to CLR, with an AUC of 0.695 versus 0.660. The cut-off value for CAR was determined to be 0.56 (sensitivity = 63.5%, specificity = 66.7%, $p = 0.013$). In comparison, CLR had a cut-off of 1.26 (sensitivity = 59.9%, specificity = 60%, $p = 0.040$), as presented in Table 4 and illustrated in Figure 1-A.

Among patients in the very high-risk group, CLR ($p = 0.025$) and IBI ($p = 0.004$) were significantly associated with progression (Table 3). ROC curve analysis demonstrated the superior discriminative performance of IBI with an AUC of 0.920, a cut-off value of 9.56, and sensitivity and specificity, both at 80% ($p < 0.001$). CLR yielded an AUC of 0.830, with a cut-off of 1.57, sensitivity and specificity of 80%, and a p-value of 0.032 (Table 4, Figure 1-B).

Table I. Patient Demographics and Clinical Characteristics

Variables		n (%)
Age Group	Age ≤ 70	114 (63)
	Age > 70	68 (37)
Sex	Female	24 (13)
	Male	158 (87)
Smoking	None	38 (21)
	Yes	144 (79)
DM	None	122 (67)
	Yes	60 (33)
HT	None	100 (55)
	Yes	82 (45)
COPD	None	166 (91)
	Yes	16 (9)
CIS	None	155 (85)
	Yes	27 (15)
Tumoral lesion	Solitary	108 (59)
	Multifocal	74 (41)
Tumor size	< 3 cm	69 (38)
	≥ 3 cm	113 (62)
Risk categories	Intermediate Risk	49 (27)
	High Risk	108 (59)
	Very High Risk	25 (14)
Recurrence	None	154 (85)
	Yes	28 (15)
Progression	None	167 (92)
	Yes	15 (8)

DM: Diabetes mellitus; HT: Hypertension; COPD: Chronic obstructive pulmonary disease; CIS: Carcinoma in situ

Table 2. EAU 2022 Statistical Evaluation of Risk Factors of NMIBC and Presence of CIS in Terms of Recurrence and Progression

Risk Factor		Recurrence	No Recurrence	p*	Progression	No Progression	p*
Age	≤ 70	14 (%12.3)	100 (%87.7)	0.133	6 (%5.3)	108 (%94.7)	0.058
	> 70	14 (%20.6)	54 (%79.4)		9 (%13.2)	59 (%86.8)	
Tumoral lesion	Solitary	10 (%9.3)	98 (%90.7)	**0.006**	9 (%8.3)	99 (%91.7)	0.957
	Multifocal	18 (%24.3)	56 (%75.7)		6 (%8.1)	68 (%91.9)	
Tumor Size	< 3 cm	8 (%11.6)	61 (%88.4)	0.268	5 (%7.2)	64 (%92.8)	0.703
	≥ 3cm	20 (%17.7)	93 (%82.3)		10 (%8.8)	103 (%91.2)	
CIS	None	24 (%15.5)	131 (%84.5)	0.929	8 (%5.2)	147 (%94.8)	**<0.001**
	Yes	4 (%14.8)	23 (%85.2)		7 (%25.9)	20 (%74.1)	
Risk Groups	Intermediate Risk	4 (%8.2)	45 (%91.8)	0.248	1 (%2)	48 (%98)	**0.029**
	High Risk	20 (%18.5)	88 (%81.5)		9 (%8.3)	99 (%91.7)	
	Very High Risk	4 (%16)	21 (%84)		5 (%20)	20 (%80)	

*: Chi-square, CIS: Carcinoma in situ

Table 3. Analysis of Hematologic Parameters and Statistical Evaluation in Terms of Recurrence and Progression

	Overall Group			Very High-Risk Group			High- and Very High-Risk Group		
	Mean (IQR)	p*	p**	Mean (IQR)	p*	p**	Mean (IQR)	p*	p**
CAR	0.89 (0.43-0.96)	0.529 [a]	**0.013 [a]**	1.18 (0.44-1.13)	0.138 [a]	0.077 [a]	0.92 (0.43-0.97)	0.372 [a]	**0.017 [a]**
CLR	1.67 (1.06-1.62)	0.205 [a]	**0.040 [a]**	2.07 (0.86-2.48)	0.088 [a]	**0.025 [a]**	1.73 (0.71-1.74)	0.224 [a]	0.092 [a]
IBI	9.01 (3.16-8.66)	0.950 [a]	0.088 [a]	11.32 (3.32-10.59)	0.630 [a]	**0.004 [a]**	9.28 (3.17-9.17)	0.872 [a]	**0.036 [a]**
SIRI	1.39 (0.72-1.58)	0.246 [a]	0.114 [a]	1.75 (0.69-1.93)	0.683 [a]	0.185 [a]	1.39 (0.73-1.65)	0.348 [a]	0.225 [a]
SII	590.62 (342.46-739.05)	0.801 [a]	0.139 [a]	759.47 (366.41-964.21)	0.999 [a]	0.541 [a]	606.27 (355.85-762.28)	0.888 [a]	0.294 [a]
PIV	360.06 (161.08-374.52)	0.530 [a]	0.157 [a]	523.36 (174.70-526.80)	0.882 [a]	0.497 [a]	363.03 (173.79-387.29)	0.972 [a]	0.199 [a]
NLR	2.36 (1.54-2.80)	0.450 [a]	0.248 [a]	2.83 (1.39-3.74)	0.795 [a]	0.197 [a]	2.41 (1.56-2.85)	0.431 [a]	0.562 [a]
MLR	0.24 (0.16-0.28)	0.977 [a]	0.147 [a]	0.27 (0.19-0.34)	0.710 [a]	0.276 [a]	0.24 (0.17-0.28)	0.812 [a]	0.297 [a]
PLR	114.61 (83.79-137-32)	0.215 [a]	0.409 [a]	134.64 (93.13-156.80)	0.154 [a]	0.541 [a]	115.58 (86.71-141.19)	0.361 [a]	0.676 [a]

*: Statistical analysis by recurrence, **: Statistical analysis by progression, [a]: Mann-Whitney U Test. IQR: Interquartile range. CAR: Crp albumin ratio, IBI: Inflammation burden index, SIRI: Systemic inflammatory response index, SII: Systemic immune-inflammation index, PIV: Pan immune inflammation value, NLR: Neutrophil lymphocyte ratio, MLR: Monocyte lymphocyte ratio, PLR: Platelet lymphocyte ratio, CLR: Crp lymphocyte ratio

Table 4. ROC Analysis Results for Predicting Progression

	AUC (95%)	Cut-Off	p	Sensitivity (%)	Specificity (%)
Overall Group					
CAR	0.695(0.572-0.817)	0.56	**0.013**	63.5	66.7
CLR	0.660(0.508-0.812)	1.26	**0.040**	59.9	60
Very High-Risk Group					
IBI	0.920(0.802-1.000)	9.56	**<0.001**	80	80
CLR	0.830(0.529-1.000)	1.57	**0.032**	80	80
High- and Very High-Risk Group					
IBI	0.672(0.526-0.817)	6.66	**0.021**	63.9	64.3
CAR	0.696(0.566-0.825)	0.56	**0.003**	63.9	64.3

AUC: Area under curve; CAR: Crp albumin ratio; CLR: Crp lymphocyte ratio; IBI: inflammation burden index.

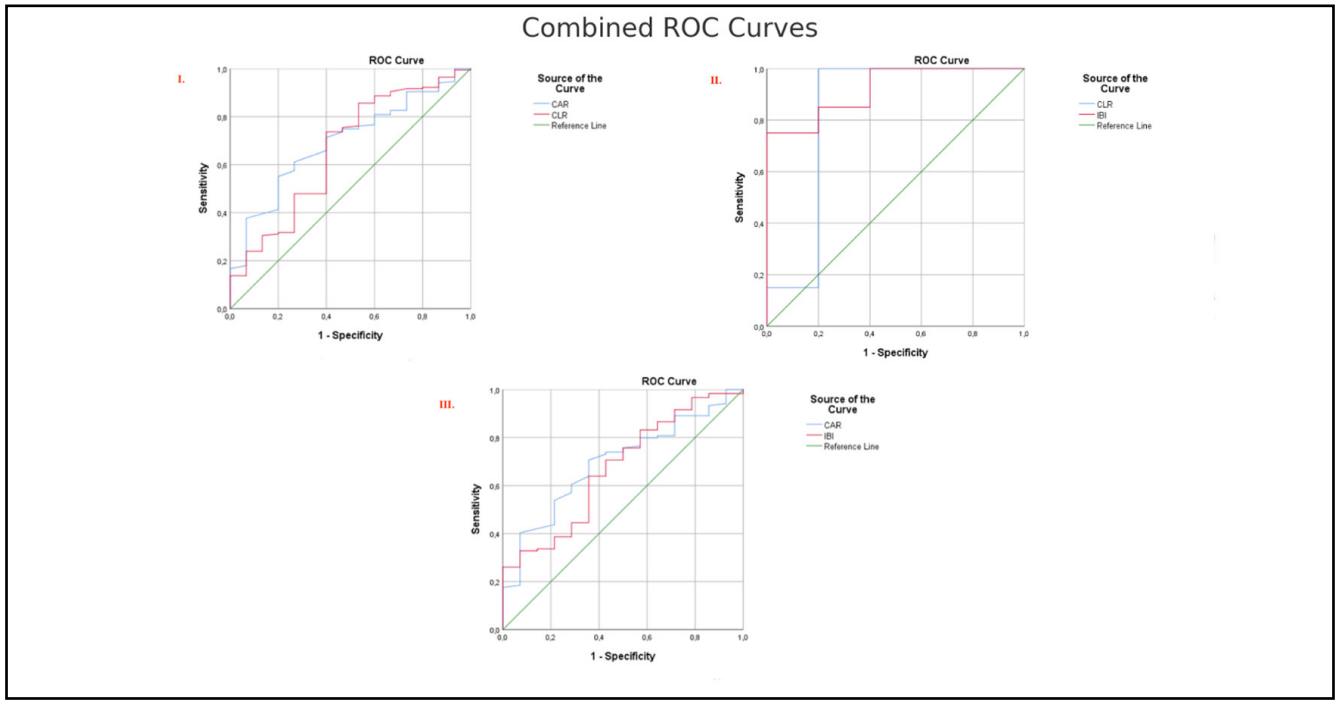

Figure 1. ROC Curve Analysis of Inflammatory Markers for Predicting Progression **(A)** CAR and CLR in the overall cohort (AUC: CAR = 0.695; CLR = 0.660). **(B)** IBI and CLR in the very high-risk subgroup (AUC: IBI = 0.920; CLR = 0.830). **(C)** IBI and CAR in the combined high- and very high-risk cohort (AUC: IBI = 0.672; CAR = 0.696). Dashed diagonal line represents the reference (AUC = 0.5).

In the combined high- and very high-risk cohort, both CAR (p = 0.017) and IBI (p = 0.036) were significantly associated with progression (Table 3). ROC analysis showed comparable predictive value for both parameters. CAR had an AUC of 0.696, a cut-off of 0.56, a sensitivity of 63.9%, and a specificity of 64.3% (p = 0.003). IBI demonstrated an AUC of 0.672, with a cut-off of 6.66, sensitivity of 63.9%, specificity of 64.3%, and a p-value of 0.021 (Table 4, Figure 1-C).

DISCUSSION

This study investigated the prognostic value of novel hematologic indices—CAR, CLR, and IBI—in predicting recurrence and progression in NMIBC patients undergoing BCG therapy. Among these, CAR and CLR emerged as relevant predictors of progression across the entire cohort, while IBI emerged as a particularly strong predictor in the very high-risk group.

While evaluating patient- and tumor-related factors as predictors of recurrence, the presence of a multifocal tumor was notably linked with increased recurrence risk (p = 0.006). At the same time, no statistically significant differences were observed for advanced age, increased tumor size, or CIS (p = 0.133, p = 0.268, p = 0.929, respectively). In predicting progression, as demonstrated by Daher et al. in 2010, the presence of CIS was a significant predictor (p = 0.000). In contrast, advanced age, multifocality, and increased tumor size did not demonstrate meaningful associations (p = 0.058, p = 0.957, p = 0.703, respectively) (12). As noted by Sylvester et al., when defining the current risk classification, progression rates in the very high-risk patient group were observed to increase from 12% to 40-44% in 5-year follow-up compared to the high-risk group in the previous classification (2). In our study, progression rates were 2% in the medium-risk group, 8.3% in the high-risk group, and 20% in the very high-risk group, demonstrating a significant difference (p=0,029).

Our findings align partially with prior literature evaluating systemic inflammatory markers in bladder cancer. While indices such as NLR, SII, and PLR have been linked to recurrence or progression in earlier studies (5, 13, 14), these associations were not observed in our cohort. This discrepancy may reflect differences in study population characteristics, BCG regimen consistency, or inflammatory marker thresholds. Notably, Deng-Xiong et al. identified SII as a predictor during BCG induction, whereas we found no significant role for SII in any subgroup (13). Similarly, Kun Ye et al. highlighted SIRI as a predictive factor that did not reach significance in our analysis (7).

The most compelling result of our study was the high predictive accuracy of IBI in very high-risk patients (AUC: 0.920). As a composite index reflecting CRP and NLR, IBI appears to reflect the systemic inflammatory burden more effectively than individual components (9). To our knowledge, this is the first study to assess IBI in the context of intravesical BCG therapy for NMIBC. Its predictive power in high-risk settings suggests potential utility in refining patient stratification beyond current risk models.

The role of CLR, a ratio combining CRP and lymphocyte count, has been validated in various malignancies, including colorectal and gastric cancer (15-17). In our study, CLR was significantly elevated among patients with disease progression, particularly in the very high-risk group. These findings echo previous reports linking CLR to tumor aggressiveness and immune evasion (18).

CAR also demonstrated prognostic value for progression, consistent with studies in pancreatic and muscle-invasive bladder cancer (19, 20). However, its lack of association with recurrence underscores that distinct inflammatory profiles may underpin early recurrence versus invasive transformation.

To the best of our knowledge, this is the first study to comprehensively evaluate IBI, CLR, and CAR in the context of intravesical BCG therapy among NMIBC patients stratified according to the updated 2024 EAU risk groups. While prior studies have assessed inflammatory markers such as NLR, SII, and PLR (5, 13, 14), the application of IBI—a composite index integrating CRP and NLR—in very high-risk NMIBC patients has not been previously reported. This novel approach provides a low-cost, accessible prognostic tool that may complement traditional risk classification systems and improve individualized follow-up strategies.

Importantly, none of the markers evaluated in our study were predictive of recurrence, including the more widely used indices such as NLR and PLR (21). This observation aligns with previous evidence suggesting that recurrence may be influenced more by tumor biology or localized immunologic factors in the bladder microenvironment rather than systemic inflammation (22).

Our study has several limitations. Its retrospective design and single-center setting limit generalizability. In addition, despite an adequate overall sample size, subgroup analyses—particularly for the very high-risk group—may be underpowered. Nonetheless, the consistent association of IBI and CLR with progression highlights the potential of these markers in supplementing current risk stratification models.

In clinical practice, integrating such low-cost, readily accessible biomarkers could aid in tailoring surveillance intensity and therapeutic strategies, especially in patients at heightened risk of progression. Prospective multicenter validation is warranted to confirm these findings and to

explore their role in guiding treatment decision-making.

CONCLUSION

Accurate estimation of bladder cancer prognosis is essential for guiding treatment decisions and improving patient outcomes. Preoperative inflammatory markers offer a cost-effective and non-personalized approach to prognostication. This study provides valuable insights that may inform future prospective, multicenter studies with larger patient groups, contributing to a more comprehensive understanding of prognostic markers in non-muscle invasive bladder cancer.

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Conflict of Interest: The authors declare no conflict of interest.

Data Availability Statement: The data that support the findings of this study are available from all authors, upon reasonable request.

Ethical Approval: Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee Date: 29.02.2024 Land No: HNEAH/KAEK-2024/KK/9

Authorship Contribution: KK: Conceptualization; methodology; data analysis; statistical analysis; manuscript writing. RK: Conceptualization; methodology; data analysis; statistical analysis; manuscript writing. BBÖ: Data acquisition. İA: Data acquisition, resources. ET: Manuscript writing and editing, critical supervision. ÇT: Manuscript editing. MİÖ: Critical Supervision. ÖEY: Supervision.

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