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ORIGINAL RESEARCH ARTICLE

Association between creatinine-to-hemoglobin ratio and advanced disease features in bladder cancer

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Abstract

Introduction: Bladder cancer (BC) is frequently marked by high recurrence and progression rates, making close follow-up essential. Cystoscopy remains the standard method for surveillance; however, it is invasive, costly, and uncomfortable for patients. Given these limitations, there is increasing interest in identifying minimally invasive biomarkers to support clinical management.

Objectives: This study aims to assess the potential prognostic role of the creatinine-to-hemoglobin ratio (CHR) in individuals with BC.

Methods: A retrospective study was performed on 148 patients with BC treated at the Urology Department of Mureș Clinical County Hospital. Patients' clinical, pathological, and laboratory data were collected. CHR was calculated from routine blood test parameters. The association between CHR and tumor-related parameters was assessed using statistical testing, primarily employing non-parametric methods and Spearman's rank correlation analysis.

Results: Elevated CHR values were significantly associated with more advanced tumor stages (median CHR: 0.10 in pT2 vs. 0.07 in pTa; $p < 0.001$), lower hematocrit levels, and higher tumor grades. CHR demonstrated weak but statistically significant correlations with tumor stage ($r = 0.274$), grade ($r = 0.274$), and patient age ($r = 0.16$). No significant association was observed between CHR and tumor size.

Conclusion: As a marker derived from routine laboratory tests, CHR may provide useful information for the assessment of BC patients, particularly those with advanced disease features. CHR appears to be associated with adverse pathological characteristics and may serve as a supportive indicator of disease burden. These preliminary findings emphasize the need for further prospective studies to determine whether CHR could be integrated into existing risk assessment tools and follow-up strategies.

Keywords: Non-muscle–invasive bladder cancer; Muscle-invasive bladder cancer; Blood-based biomarkers; Risk stratification; Creatinine-to-hemoglobin ratio

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1. Introduction

Bladder cancer (BC) is recognized as a major global health issue, with marked epidemiological differences between genders.[1] BC is the 10th most frequently diagnosed malignancy worldwide, accounting for approximately 573,000 new cases each year.[2] Two principal pathological entities are recognized in BC: non-muscle–invasive BC (NMIBC) and muscle-invasive BC (MIBC), each with distinct features.[3] Compared to NMIBC, MIBC is associated with a higher mutational burden, contributing to more aggressive behavior and unfavorable clinical outcomes.[4]

Approximately one-fourth to one-third of newly diagnosed BC cases are classified as MIBC, with incidence varying geographically and influenced primarily by occupational exposures, aging populations, and tobacco use. A marked male predominance is observed in MIBC, with an incidence ratio of approximately 3:1. This condition is most commonly diagnosed in individuals over 65 years.[5] A recent concern is the increasing number of BC cases observed in younger individuals. Nevertheless, this trend may be associated with a reduced risk of disease-specific mortality.[6,7]

Timely detection is crucial for improving outcomes in BC, underscoring the need for minimally invasive diagnostic strategies that facilitate accurate and early identification.[8] Therapeutically, transurethral resection of bladder tumor (TURBT) represents the standard initial treatment, complemented by intravesical therapy to reduce, or at least limit, relapse and disease progression. Achieving optimal patient outcomes necessitates a multidisciplinary approach that incorporates clinical, pathological, and molecular parameters to enable individualized treatment strategies.[9]

Bladder cancer follow-up protocols mainly depend on regular white-light cystoscopy in conjunction with urinary cytology. However, these techniques have limited sensitivity for detecting low-grade recurrent disease. Therefore, more precise tools are essential for improving diagnostic accuracy.[10] Several factors are associated with relapse and progression risk in NMIBC, including tumor multifocality, tumor size, prior recurrence history, T stage, the presence of carcinoma in situ, and tumor grade (defined by the 1973 World Health Organization [WHO] system).[11]

Despite appropriate treatment, NMIBC is associated with high rates of recurrence and, ultimately, disease progression. Consequently, patients require intensive, long-term surveillance to facilitate early detection of recurrence. However, current surveillance strategies remain insufficiently standardized and are largely based on limited empirical data.[12] Although urinary biomarkers have been investigated for several decades, none have achieved widespread adoption in routine clinical practice. Recent advances in molecular diagnostics—particularly in the field of epigenetics—have led to the development of novel urinary biomarkers with the potential to enhance diagnostic performance and disease monitoring.[13]

Bladder cancer, particularly NMIBC, remains a persistent clinical challenge, largely driven by its high rates of recurrence and progression.[14] In this context, the development of reliable, minimally invasive prognostic and predictive biomarkers remains a priority for optimizing patient management and follow-up strategies.[15] In recent years, peripheral blood-based inflammatory and nutritional ratios have emerged as potential prognostic indicators across a broad spectrum of tumors, including urothelial carcinoma.[16] These ratios, derived from routinely available hematological and biochemical parameters, offer a pragmatic and cost-effective means of quantifying systemic inflammatory status and host-immune response, both of which are established prognostic factors in cancer patients.[17]

A range of hematological ratios reflecting systemic inflammation—including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), hemoglobin-to-platelet ratio, and albumin-to-globulin ratio—have attracted considerable attention as potential prognostic indicators.[18,19] These biomarkers have been evaluated for their associations with recurrence risk and survival outcomes in patients with BC, underscoring the significant role of the immune response in tumor pathogenesis.[20] Additional biomarkers currently under investigation include the systemic immune–inflammation index and the C-reactive protein–to–albumin ratio, both of which incorporate nutritional and metabolic components to assess prognostic value in BC.[21]

Common comorbidities in this patient population include anemia and impaired renal function. In this context, one of the most recently explored biomarkers is the creatinine-to-hemoglobin ratio (CHR). Although none of these markers have yet been integrated into clinical guidelines or formal prognostic scoring systems, the body of evidence supporting their potential prognostic value continues to expand.

Creatinine is a low-molecular-weight (113 Da), nitrogen-containing end product of protein and muscle metabolism, derived from the degradation of creatine in muscle tissue. CHR remains an understudied biomarker in BC. Nevertheless, evidence suggests that renal impairment is linked to poorer prognosis in BC patients, especially those with MIBC undergoing radical cystectomy.[22–24]

The CHR has recently been proposed as a potential prognostic biomarker in BC; however, current scientific evidence supporting its clinical utility—particularly in NMIBC—remains limited. CHR may act as a composite marker reflecting both renal function and hematologic status, two parameters typically altered in BC patients and associated with a poor prognosis. Given these considerations, our study aims to address these gaps in the literature by exploring the clinical significance of CHR in BC. Specifically, this study aims to determine whether CHR is associated with tumor characteristics and to establish its association with advanced disease features, under the hypothesis that elevated CHR levels correlate with more aggressive disease features and potentially adverse clinical outcomes.

2. Methodology

2.1. Study design and patient selection

We conducted a retrospective cross-sectional analysis of clinical data from 161 patients with BC treated at Mureș Clinical County Hospital over a six-month period (July 2023 to December 2023). Inclusion criteria comprised patients with de novo bladder tumors admitted to the Urology Department with a clinical diagnosis of urothelial carcinoma. Only cases with histopathological confirmation of urothelial bladder cancer were included in the final analysis. Patients with non-urothelial histological findings were excluded.

After exclusions, the final study cohort comprised 148 patients who met the predefined inclusion criteria. All excluded cases are illustrated in the flow diagram (Figure 1).

Demographic information, clinical parameters, and pathological data were collected for each patient and entered into a structured database. Tumor specimens were assessed by a single pathologist at the same institution, ensuring consistency. Tumor staging was performed in accordance with the 8th edition of the American Joint Committee on Cancer Staging Manual. Grading was based on the 1973 WHO classification system: G1 (well-differentiated), G2 (moderately differentiated), and G3 (poorly differentiated). According to the WHO 2004/2016 grading system, G1 tumors were considered "low grade," while G2 and G3 tumors were grouped as "high grade," in line with current clinical practice and prognostic stratification.[25]

Cross-sectional imaging (e.g., computed tomography, magnetic resonance imaging) was not consistently available

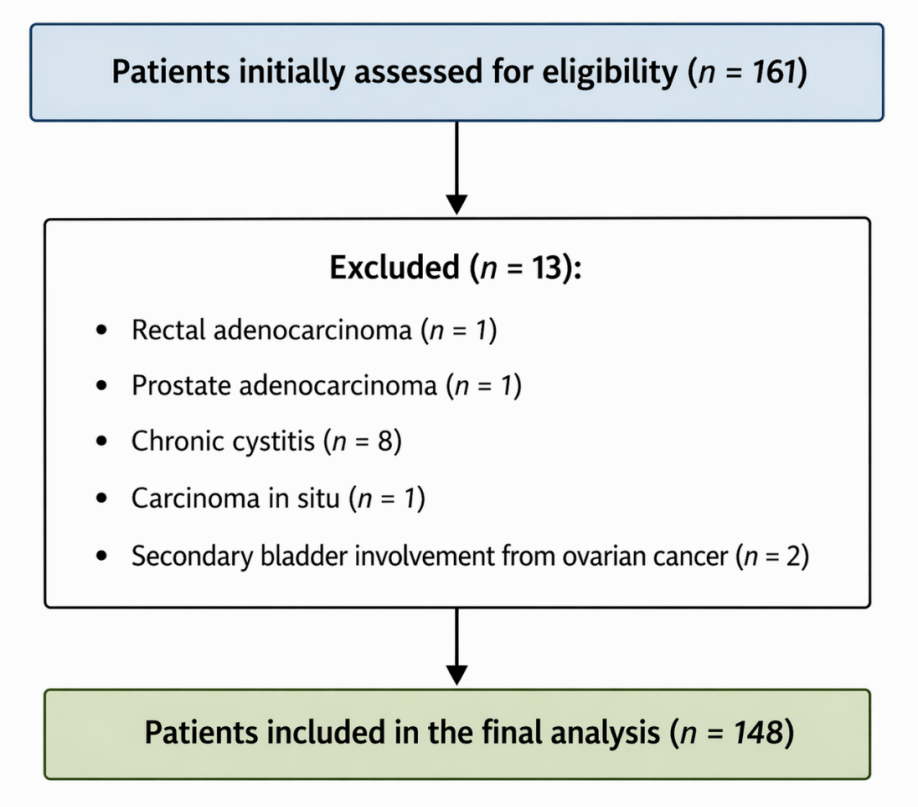

Figure 1. Patient selection flow diagram

for all patients, reflecting variability in clinical indications and the retrospective design of the study. A proportion of patients were subsequently referred to tertiary centers outside our institution, where further evaluation, including follow-up and complete tumor–node–metastasis staging, was performed. Data on nodal and metastatic status were incomplete for a subset of patients. Therefore, tumor staging in this study was based on histopathological findings following TURBT, in accordance with routine clinical practice.

2.2. Clinical and laboratory assessments

As part of the clinical and paraclinical evaluation, the presence of macroscopic hematuria—an early and common presenting symptom of BC—was recorded at the time of initial consultation. Renal function was assessed via serum creatinine levels, while hemoglobin concentration was used to quantify anemia status.

All laboratory tests were conducted in a single accredited facility to ensure consistency and reduce inter-laboratory variability. Baseline laboratory parameters were assessed from routine blood tests obtained prior to TURBT, minimizing the potential influence of prior treatment or medication.

Anemia was classified into four categories based on hemoglobin values: mild (10–12 g/dL), moderate (8–10 g/dL), severe (6.5–7.9 g/dL), and life-threatening (<6.5 g/dL). Anemia and renal dysfunction, both recognized as important prognostic factors in BC, were included as key variables in the analysis.[26]

Ethical approval was obtained from the institutional review board of our hospital in May 2025. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval covered the retrospective analysis of routinely collected patient data, including histopathological and laboratory results.

2.3. Statistical analysis

Data processing and statistical evaluation were conducted using SPSS (version 26.0.0, IBM, USA). Continuous variables were examined using graphical methods (e.g., histograms, Q–Q plots) and the Shapiro–Wilk test. Based on these results, all subsequent analyses were performed using non-parametric methods.

Numerical variables are expressed as median values and interquartile ranges (IQRs), while categorical variables are presented as counts and corresponding proportions. Differences between groups were analyzed using rank-based tests (Mann–Whitney *U* test and Kruskal–Wallis test). Relationships between categorical variables were assessed using the chi-square (χ^2) test. Statistical significance was defined as a two-sided p-value < 0.05. Correlation analysis was performed using Spearman's rank coefficient, interpreted according to predefined intervals (weak, moderate, or strong).

To evaluate whether CHR represents an independent predictor of adverse pathological features, multivariate logistic regression models were constructed. The models included established inflammatory biomarkers such as NLR, PLR, and LMR. In the multivariate analysis, neither CHR nor the inflammatory ratios NLR, PLR, and LMR demonstrated independent predictive value for advanced disease features.

Due to the absence of comprehensive follow-up data, survival analyses such as overall survival and progression-free survival were not feasible within this retrospective cohort, as many patients continued oncological management at tertiary centers outside our institution. Post-treatment urological follow-up, including cystoscopic monitoring and intravesical therapy (chemotherapy or immunotherapy), was frequently conducted in external healthcare centers. For this reason, reliable long-term survival data were not consistently available. Therefore, no statistical analysis of overall survival and progression-free survival was performed.

3. Results

3.1. Demographic and comorbidity analysis

A total of 148 patients met the eligibility criteria and were therefore included in the analysis. The median patient age was 68 years (IQR = 51–75). Of these, 115 (77.5%) were male. This demographic distribution is consistent with the known epidemiology of BC, which shows a higher incidence in older males.

3.2. Tumoral characteristics

Of the 148 patients included in the study, 88 (59.5%) had multifocal tumors. The median tumor diameter was 15 mm, reflecting a predominance of small, non-muscle–invasive lesions. Pathological staging showed that most tumors were classified as pTa (n = 78, 52.7%), indicating superficial involvement of the urothelium.

Regarding tumor grade, G3 (poorly differentiated) was the most frequently observed, present in 77 patients (52%). These results underscore the heterogeneity of BC, where superficial tumors may still exhibit high-grade histological features associated with increased risk of recurrence and progression. The study cohort included patients across different pathological stages, comprising both NMIBC and MIBC, with a predominance of NMIBC cases.

3.3. Laboratory and creatinine-to-hemoglobin ratio

All patients underwent peripheral blood sampling, which was subsequently analyzed in the institutional Department of Laboratory Medicine. Hemoglobin and serum creatinine levels were measured, and the CHR was subsequently calculated for each patient. CHR was calculated as the ratio of serum creatinine (mg/dL) to hemoglobin (g/dL), without any additional normalization.

As previously described, anemia severity was classified based on hemoglobin concentration as follows: mild (10–12 g/dL), moderate (8–10 g/dL), severe (6.5–7.9 g/dL), and life-threatening (<6.5 g/dL).

3.4. Association of CHR with clinicopathological features

Patients were stratified according to tumor stage and grade to assess potential differences in demographic characteristics and comorbidities. These comparisons are detailed in Table 1.

As shown in Table 2, patients with more advanced tumor stages (pT2) exhibited significantly larger tumors, with a median diameter of 30 mm compared to 15 mm in earlier-stage disease ($p < 0.01$). Moreover, high-grade histology was significantly more frequent among patients with pT2 tumors. In contrast, the presence of multifocal tumors did not differ significantly across tumor stages ($p = 0.26$). These findings underscore the importance of tumor size and grade as key indicators of tumor aggressiveness.

Laboratory parameters and calculated ratios were analyzed across tumor stages, as presented in Table 3. Patients with pT2 tumors exhibited significantly higher serum creatinine levels (median = 1.28 mg/dL) compared to those with pTa tumors (median = 0.98 mg/dL; $p < 0.001$), suggesting a progressive impairment of renal function with advancing disease.

Table 1. Comparison of demographic characteristics and comorbidities across tumor stages

Characteristic	Tumor stage			*p*
	pTa	pT1	pT2	
Age (years; median [IQR])	68 (61–76)	68 (59–75)	67.5 (63–73)	0.75[b]
Male (*n* [%])	59 (75.6%)	40 (80.0%)	16 (80.0%)	0.81[a]
Arterial hypertension (*n* [%])	21 (26.9%)	15 (30.0%)	6 (30.0%)	0.91[a]
Hematuria (*n* [%])	33 (42.3%)	20 (40.0%)	4 (20.0%)	0.18[a]
Anemia (*n* [%])				
Negative	50 (64.1%)	24 (48.0%)	7 (35.0%)	
Mild	13 (16.7%)	17 (34.0%)	8 (40.0%)	
Moderate	8 (10.3%)	4 (8.0%)	4 (20.0%)	0.11[a]
Severe	5 (6.4%)	5 (10.0%)	1 (5.0%)	
Life-threatening	2 (2.6%)	0 (0%)	0 (0%)	

Notes: [a]Chi-square test. [b]Kruskal–Wallis test.
Abbreviation: IQR: Interquartile range.

Table 2. Comparison of tumor characteristics across tumor stages

Characteristic	Tumor stage			*p*
	pTa	pT1	pT2	
Multifocal tumor (*n* [%])	46 (59.0%)	33 (66.0%)	9 (45.0%)	0.26[a]
Tumor size (mm; median [IQR])	15 (5–20)	15 (8.75–30)	30 (15–40)	<0.01[b]
Tumor grade (*n* [%])				
G1	2 (2.6%)	0 (0%)	0 (0%)	<0.001[a]
G2	59 (75.6%)	9 (18.0%)	1 (5.0%)	
G3	17 (21.8%)	41 (82.0%)	19 (95.0%)	

Notes: [a]Chi-square test. [b]Kruskal–Wallis test.
Abbreviation: IQR: Interquartile range.

Table 3. Comparison of laboratory findings across tumor stages

Parameters	Tumor stage			*p*
	pTa	pT1	pT2	
Hemoglobin (g/dL; median [IQR])	13.25 (10.77–14.90)	11.85 (11.00–14.60)	11.05 (9.90–12.81)	0.08[a]
Creatinine (mg/dL; median [IQR])	0.98 (0.80–1.23)	1.20 (0.88–1.63)	1.28 (1.05–1.86)	<0.001[a]
Hematocrit (%; median [IQR])	40 (34–44)	36.8 (33.7–43.4)	32.4 (31.2–39.1)	0.04[a]
Creatinine-to-hemoglobin ratio (median [IQR])	0.07 (0.05–0.10)	0.09 (0.07–0.15)	0.10 (0.09–0.18)	<0.001[a]

Notes: [a]Kruskal–Wallis test.
Abbreviation: IQR: Interquartile range.

Hematocrit levels were also significantly lower for pT2 patients (32.4%) versus pTa (40%; $p = 0.04$), consistent with a higher prevalence of anemia in more advanced stages (Figure 2). A decline in hemoglobin levels was observed; however, the difference was not statistically significant ($p = 0.08$).

Importantly, the CHR showed significant stage-dependent variation. The CHR was significantly higher in pT2 compared with pTa (0.10 vs. 0.07; $p < 0.001$) (Table 3). These findings support the potential role of CHR as a prognostic marker in BC, reflecting the combined impact of anemia and renal dysfunction on tumor behavior.

Table 4 outlines the correlations between CHR and clinicopathological variables. CHR showed a weak but significant positive correlation with age, suggesting an association with patient comorbidity burden. No meaningful relationship was identified between CHR and tumor size. In contrast, tumor stage and grade were weak but significantly associated with CHR ($r = 0.274$, $p < 0.0001$). These results indicate that a more biologically aggressive disease is associated with a shift toward unfavorable hematologic and renal profiles (Figure 3).

Despite the modest correlation strength, these findings underscore the potential utility of CHR and related biomarkers as minimally invasive, cost-effective indicators of disease severity in BC. When integrated with other clinical and pathological factors, such ratios may facilitate improved risk stratification, particularly in resource-limited settings or where invasive diagnostics are not routinely feasible.

The selected CHR cut-off value of 0.097 was derived from the receiver operating characteristic (ROC) curve analysis, based on the optimal balance between sensitivity and specificity, corresponding to the maximum Youden index (Figure 4). This threshold provided the most clinically relevant trade-off for identifying muscle-invasive tumors (pT2) within our cohort. However, given the retrospective design and limited sample size, this cut-off should be interpreted with caution. No formal internal validation (e.g., bootstrapping or cross-validation) was performed, which represents an inherent limitation of the present study. Additionally, data heterogeneity may have influenced the stability of the identified threshold. Therefore, this cut-off value should be considered exploratory and hypothesis-generating, requiring further validation in larger, independent cohorts before clinical implementation.

Table 4. Spearman's rank correlation analysis between variables (Spearman's rho)

Variable	Creatinine-to-hemoglobin ratio
Age	$r = 0.169$, $p = 0.04$
Tumor size	$r = 0.042$, $p = 0.60$
Tumor grade	$r = 0.274$, $p < 0.0001$
Tumor stage	$r = 0.274$, $p < 0.0001$

Future studies should aim to validate and refine this threshold using prospective data and robust internal validation techniques. The ROC analysis yielded an area under the curve of 0.692, indicating moderate discriminative ability of CHR for identifying muscle-invasive tumors (pT2). While this level of accuracy does not support its use as a stand-alone predictor, it suggests that CHR may retain adjunctive value within multimodal risk stratification frameworks. Given its simplicity and availability, CHR could serve as a pragmatic complementary marker for identifying patients at higher risk of advanced disease. However, its performance is likely influenced by the limited sample size and data heterogeneity, warranting further validation in larger, well-characterized cohorts.

To further explore the clinical relevance of CHR, multivariate models were constructed to assess its potential role as an independent predictor of adverse pathological features. However, CHR did not retain independent predictive value for either high tumor grade (G3) or muscle-invasive tumor (pT2), as presented in Tables 5

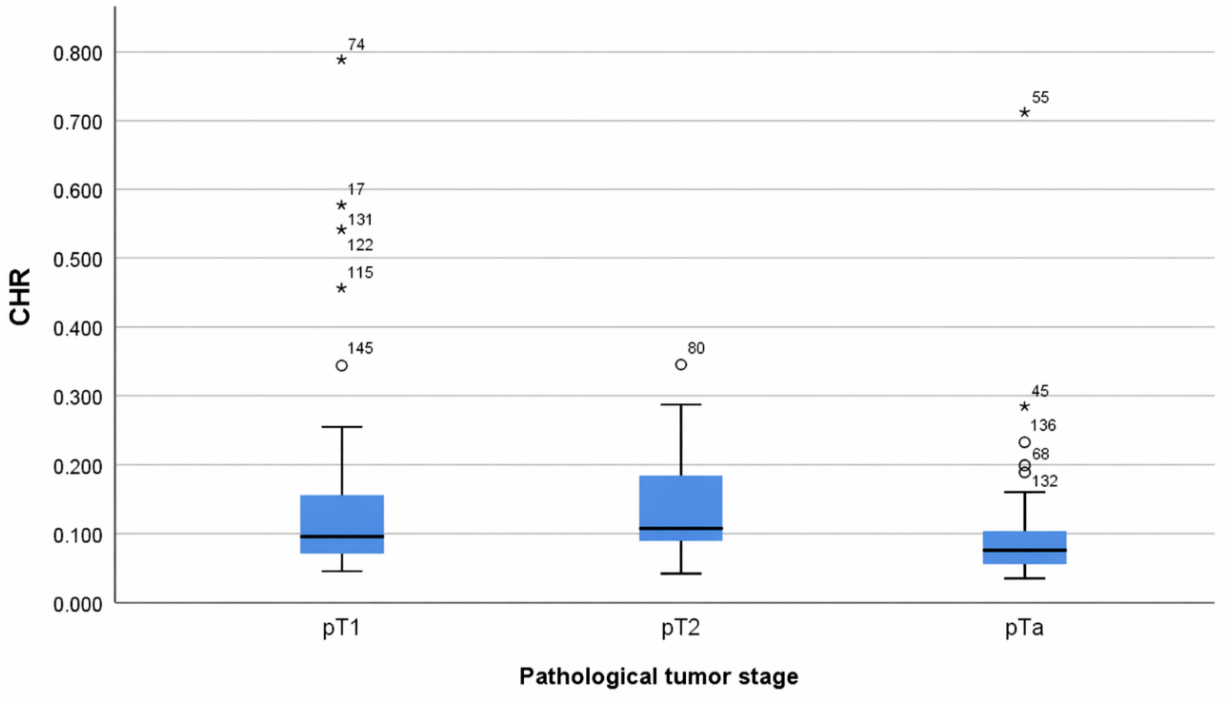

Figure 2. Boxplot of the creatinine-to-hemoglobin ratio (CHR) according to pathological tumor stage

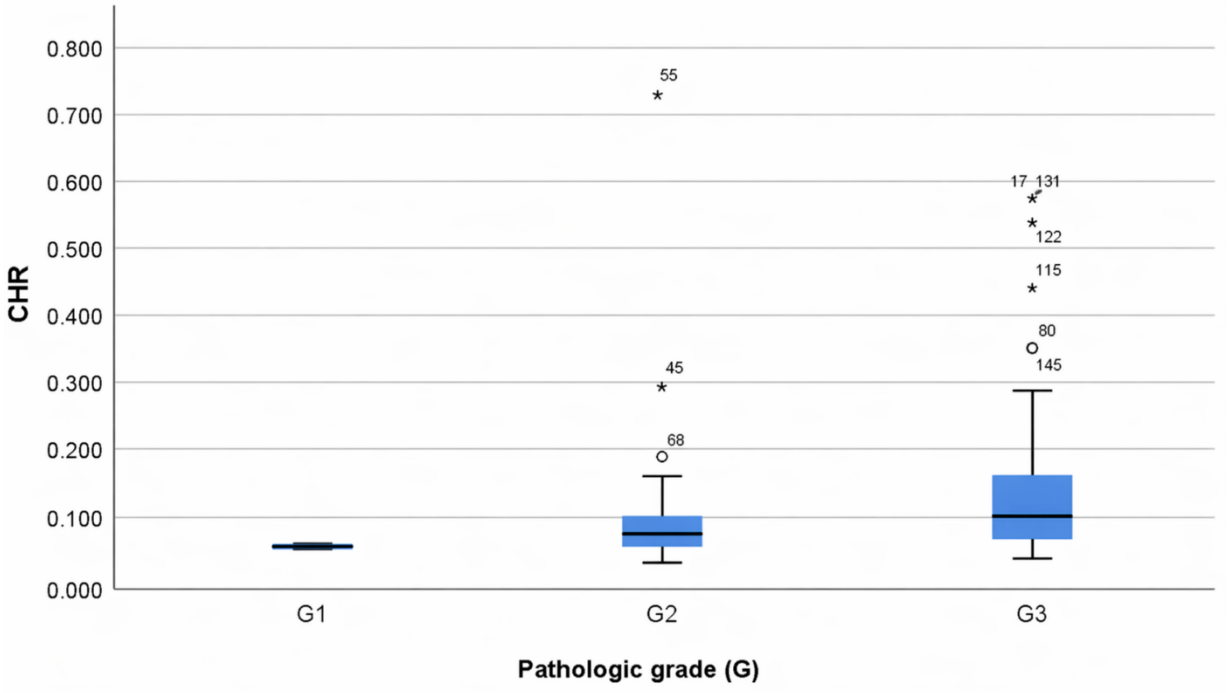

Figure 3. Boxplot of the creatinine-to-hemoglobin ratio (CHR) according to pathological grade

and 6. From a clinical perspective, this finding suggests that, although CHR is associated with more advanced disease characteristics, it may not directly reflect tumor aggressiveness or local invasion when considered alongside other patient- and disease-related factors. Rather, CHR likely captures a broader systemic profile, integrating the effects of anemia and renal dysfunction—both commonly encountered in patients with more advanced malignancy.

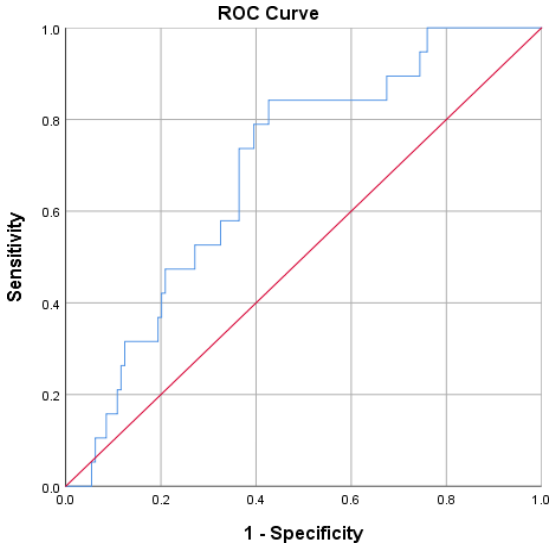

Figure 4. Receiver operating characteristic curve of the creatinine-to-hemoglobin ratio for predicting pathological tumor stage

The absence of independent predictive significance should be interpreted in the context of several important limitations. The relatively small sample size may have reduced the ability to detect subtle but clinically relevant associations. In addition, the inherent variability of the extracted clinical and laboratory data—reflecting real-world heterogeneity in patient characteristics and disease presentation—may have further attenuated the strength of these relationships. Consequently, the lack of independent predictive value does not necessarily negate the clinical relevance of CHR, but rather highlights the need for validation in larger, more homogeneous cohorts.

4. Discussion

Non-muscle–invasive BC is associated with frequent recurrences and carries a substantial risk of progression. Therefore, long-term monitoring is necessary. According to the European Association of Urology guidelines, repeated cystoscopies are the main follow-up measure. High-risk individuals may require lifelong cystoscopic follow-up.[27,28]

Although effective, this invasive approach poses several challenges, including increased patient burden, higher costs, reduced adherence, and significant resource consumption. Thus, there is a pressing need for reliable, cost-effective, and minimally invasive biomarkers to support or potentially replace certain aspects of traditional surveillance—especially in low and intermediate-risk populations—by improving early detection, reducing the frequency of invasive procedures, and optimizing risk-adapted follow-up strategies.[29,30]

In this context, systemic inflammation and immune status have emerged as promising domains for biomarker discovery in various cancers, including BC. Prior studies have demonstrated that peripheral blood-based ratios such as NLR, PLR, LMR, systemic immune–inflammation index, and albumin-to-globulin ratio correlate with prognosis and cancer-specific survival.[31,32] These markers, based on routine laboratory tests, are particularly attractive because they are easily accessible, cost-effective, and readily

Table 5. Multivariate logistic regression analysis of predictors of G3 tumor grade

Variable	*B*	SE	Wald statistic	df	*p*-value	OR (Exp[B])	95% CI	
							Lower	Upper
Age	0.012	0.017	0.529	1	0.467	1.012	0.979	1.047
NLR	0.009	0.030	0.101	1	0.751	1.010	0.952	1.070
LMR	−0.004	0.025	0.029	1	0.865	0.996	0.948	1.046
PLR	0.002	0.001	1.702	1	0.192	1.002	0.999	1.005
Hematuria	0.435	0.354	1.512	1	0.219	1.546	0.772	3.094
Anemia	0.697	0.641	1.180	1	0.277	2.007	0.571	7.056
CHR	0.005	0.020	0.059	1	0.808	1.005	0.967	1.044
Constant	−1.513	1.177	1.653	1	0.199	0.220	–	–

Abbreviations: CHR: Creatinine-to-hemoglobin ratio; CI: Confidence interval; df: Degrees of freedom; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PLR: Platelet-to-lymphocyte ratio; SE: Standard error.

Table 6. Multivariate logistic regression analysis of predictors of pT2 disease

Variable	*B*	SE	Wald statistic	df	*p*-value	OR (Exp[B])	95% CI	
							Lower	Upper
Age	0.001	0.025	0.003	1	0.958	1.001	0.953	1.053
NLR	0.110	0.059	3.534	1	0.060	1.117	0.995	1.253
LMR	0.010	0.037	0.066	1	0.797	1.010	0.939	1.086
PLR	0.000	0.002	0.000	1	0.989	1.000	0.996	1.004
Hematuria	0.685	0.615	1.241	1	0.265	1.984	0.594	6.620
Anemia	−0.872	1.099	0.629	1	0.428	0.418	0.049	3.604
CHR	−0.004	0.026	0.019	1	0.889	0.996	0.946	1.049
Constant	−3.114	1.839	2.868	1	0.090	0.044	–	–

Abbreviations: CHR: Creatinine-to-hemoglobin ratio; CI: Confidence interval; df: Degrees of freedom; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PLR: Platelet-to-lymphocyte ratio; SE: Standard error.

integrated into routine clinical practice.

This study adds to the existing literature by evaluating the prognostic relevance of CHR in BC patients. We proposed that CHR reflects the hematological and renal status of patients and may be associated with disease severity. CHR demonstrated a statistically significant, although weak, correlation with tumor stage and grade. This pattern may be explained by the systemic impact of advanced disease.

Importantly, CHR also showed a weak but significant positive correlation with patient age, further supporting its potential as an age-sensitive risk indicator. Although tumor size did not correlate with CHR, the associations with grade and stage suggest that CHR may reflect biological rather than purely anatomical aggressiveness.

However, the association between CHR and tumor stage should be interpreted cautiously and not assumed to be causal. Elevated values reflect a combination of systemic inflammation and organ dysfunction, which are commonly observed in patients with advanced disease.

Despite the relatively modest correlation coefficients (r = 0.17–0.27), the consistent directionality and statistical significance suggest that CHR may have value as part of a multifactorial risk stratification tool, especially in combination with other clinical, pathological, or molecular markers.

These observations are highly pertinent to the ongoing evolution of BC management paradigms, which emphasize the development of non-invasive tools to optimize cystoscopic follow-up.

Meagher *et al.*[33], in a study of 829 patients treated with radical nephroureterectomy, demonstrated the prognostic significance of CHR in urothelial malignancies. A CHR threshold above 0.15 was associated with higher rates of advanced stage (p = 0.016) and high-grade tumors (89.4% vs. 72.8%, p < 0.001). Multivariate analysis showed that elevated CHR was independently associated with poorer outcomes. Kaplan–Meier analysis demonstrated inferior five-year survival outcomes across all endpoints in this subgroup.

The present ROC analysis identified a CHR cut-off value of 0.097 for predicting muscle-invasive tumors. This threshold is lower than the value reported by Meagher *et al.*, who reported a cut-off value of 0.15 for upper tract urothelial carcinoma. In their cohort, CHR values above this threshold were associated with a higher prevalence of advanced-stage and high-grade tumors. While Meagher *et al.* evaluated long-term oncological outcomes in upper tract urothelial carcinoma, our analysis focused on the identification of locally advanced BC. Nevertheless, both studies demonstrate that higher CHR values are associated with more aggressive disease characteristics. As such, CHR may serve as a preoperative, low-cost biomarker to complement traditional risk stratification tools. The consistency of these findings across distinct urothelial cancer subtypes supports the broader integration of CHR into future risk models.

Evidence regarding the prognostic utility of CHR in BC remains limited. The observed associations with tumor stage and grade suggest that CHR may serve as a practical biomarker in this context. Its correlation with disease severity highlights its potential clinical relevance. These results offer a preliminary framework for validation in larger, prospective studies. Continued research in this area is essential to determine whether CHR can be reliably integrated into clinical practice as part of a multimodal

risk-stratification framework. This integration could enable more personalized, non-invasive, and cost-effective approaches for patient management.

Several limitations of this study should be acknowledged. Its retrospective, single-center design introduces potential sources of bias, thereby affecting the broader applicability of our findings. In addition, the small sample size limits statistical power and reduces the ability to detect subtle associations. The correlations between CHR and tumor grade and stage were modest—CHR may therefore not be sufficient as a stand-alone prognostic marker. Finally, the absence of a validated CHR threshold limits its clinical applicability.

The absence of survival analyses represents an additional limitation, along with incomplete follow-up data. A considerable proportion of patients were referred from other regions and continued their oncological treatment and surveillance in tertiary centers outside our institution. As a result, long-term outcome data could not be consistently collected. These findings should therefore be interpreted without survival endpoints and considered exploratory in nature. Incomplete information regarding nodal and metastatic staging represents an additional limitation. This is mainly attributable to the lack of cross-sectional imaging in all patients, caused by the retrospective nature of the study and heterogeneous follow-up. At the same time, this reflects routine clinical practice, where imaging is not always uniformly performed.

Within the expanding field of BC biomarkers, our findings complement existing molecular and urinary markers described in the literature. Matuszczak *et al.*[34] reviewed biomarkers such as CYFRA 21.1, ERCC1, *TP53*, *FGFR3*, and TATI, which primarily reflect tumor-specific molecular alterations. For example, *FGFR3* mutations are typically linked to low-grade NMIBC, while *TP53* alterations correlate with tumor aggressiveness. In contrast, *ERCC1* expression has been associated with chemotherapy response, indicating its role in treatment response. Although these markers are relevant, none have achieved widespread clinical adoption due to inconsistent results and limited standardization.

Unlike these tumor-centered markers, CHR represents a systemic indicator that integrates renal function and hematologic status in patients. Our study demonstrates that elevated CHR values are associated with tumor stage and grade, reflecting overall disease burden. In contrast to other relevant markers, CHR can be easily calculated from routine blood test results, offering a cost-effective and accessible option. Taken together, our findings are consistent with the concept that systemic biomarkers may provide complementary information about BC patients. While tumor-specific markers such as CYFRA 21.1, ERCC1, *TP53*, *FGFR3*, and TATI offer information about oncogenic mechanisms and therapeutic response, CHR may reflect the overall physiological impact of the disease. Therefore, integration of both biomarker categories into multimodal predictive models may improve management strategies in BC.

In the present study, CHR was not identified as an independent predictor of high tumor grade or muscle-invasive disease in multivariate analysis. Although initial associations were observed, these did not persist after adjustment for other clinical and pathological variables, suggesting that the relationship between CHR and adverse tumor characteristics may be confounded by other factors. Rather than directly reflecting tumor biology, CHR may capture the overall systemic condition of the patient, including renal impairment and hematological alterations. Accordingly, its role may be more appropriate as a complementary parameter within multifactorial risk models rather than as an isolated prognostic marker.

Future investigations are needed to confirm these preliminary findings in large, multicenter, prospective cohorts with greater demographic diversity. Moreover, the identification and external validation of standardized CHR cut-off values are essential to clarify their prognostic relevance.

Furthermore, CHR should be assessed in multivariable models alongside established clinical and pathological factors to evaluate its added predictive value for disease progression in BC. There is potential for CHR-related biomarkers to be incorporated into dynamic surveillance protocols, aiding clinicians in tailoring follow-up intensity, identifying high-risk patients earlier, or even serving as triage tools in settings where cystoscopy resources are limited. Furthermore, integration into machine-learning algorithms or risk calculators could enhance individualized patient management. If validated, these easily obtainable, low-cost ratios may become a practical adjunct supporting precision medicine approaches in NMIBC care.

5. Conclusion

This study retrospectively examined the prognostic role of CHR in BC, a relatively understudied area. Our results demonstrate that CHR values are significantly associated with tumor stage and grade, suggesting a relationship between these readily available blood parameters and tumor aggressiveness.

Patients with more advanced disease exhibited higher creatinine levels, lower hematologic parameters, and increased CHR values. Our findings reflect the impact

of systemic abnormalities (e.g., anemia, impaired renal function) in patients with advanced malignancy. ROC analysis demonstrated a moderate discriminative ability of CHR for identifying muscle-invasive disease (area under the curve = 0.692) with a cut-off value of 0.097. This level of accuracy does not support its use as an independent predictive marker; however, CHR may still have potential as an adjunctive parameter in preoperative risk assessment.

These findings should be interpreted with caution, given the retrospective design and limited sample size. The observed correlations, although statistically significant, were modest and may be influenced by unmeasured confounders. CHR was not an independent predictor in multivariate analysis, suggesting that it reflects systemic condition rather than tumor aggressiveness. In conclusion, our results should be considered exploratory and preliminary. CHR shows potential as a complementary biomarker in BC management; however, further validation in larger, prospective, multicenter studies is required.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Mureș Clinical County Hospital, Romania (approval no.: 7570; approval date: May 19, 2025), and was conducted in accordance with the Declaration of Helsinki. Although this was a retrospective study, informed consent had been routinely collected from all patients at the time of hospital admission, which also included authorization for the use of anonymized clinical data for educational and academic purposes, as specified in the institutional consent form.

Consent for publication

Consent obtained at hospital admission included permission for the use of anonymized clinical data for academic dissemination, as outlined in the institutional consent form.

Availability of data

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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