Research Article

Prognostic significance of red cell distribution width in bladder cancer: A retrospective analysis

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Abstract

Background: Bladder cancer (BC) remains a major global health concern because of its high recurrence and mortality rates. Accessible and reliable prognostic markers are crucial for improving patient outcomes. Red cell distribution width (RDW), a widely available parameter, has shown prognostic value in various malignancies, but its role in BC remains underexplored. **Objective:** This study aims to evaluate the association between pre-operative RDW and key clinicopathological features in BC, including tumor stage, grade, and overall survival, to assess its potential as an independent prognostic marker. **Methods:** We analyzed 125 patients diagnosed with BC between January and June 2021. Clinical and pathological data were recorded, and RDW was measured before the initial transurethral resection of the bladder tumor. The primary outcome was overall survival. Receiver operating characteristic curve analysis determined the optimal RDW threshold, and multivariate logistic regression assessed its independent prognostic value. **Results:** The median RDW was 14.0%. A cut-off value of 13.95% predicted mortality (area under the curve: 0.76; sensitivity: 80.4%, specificity: 65.8%), and patients with RDW ≥13.95% showed significantly higher mortality (p<0.001). Elevated RDW remained an independent predictor of death after adjusting for confounders (odds ratio: 1.205; 95% confidence interval: 1.025–1.416; p=0.02). RDW showed no significant association with tumor stage, grade, or gender; however, it correlated modestly with age. **Conclusion:** Elevated pre-operative RDW is an independent prognostic indicator of mortality in BC patients, reflecting systemic host-related factors rather than tumor-specific features. Given its cost-effectiveness and availability, RDW may serve as a valuable adjunct in the risk-stratification of BC patients.

Keywords: Red cell distribution width, Bladder cancer, Overall survival, Prognostic factor

1. Introduction

Bladder cancer (BC) is the 10th most commonly diagnosed malignancy globally and remains a significant public health issue due to its high rates of recurrence and mortality.[1] In 2023, BC was the fourth most common cancer among men, accounting for approximately 6% of all new cancer cases.[2] According to GLOBOCAN, there are approximately 573,000 new cases each year and 213,000 deaths.[3] At diagnosis, 70–75% of patients present with non-muscle invasive BC (NMIBC), 20–25% with muscle invasive disease (MIBC), and around 5% with metastatic disease.[4] The reported mortality rate is approximately 1.9/100,000 population. The highest incidence is observed in Southern Europe, with an age-standardized rate of 26.5 for men and 5.8/100,000 for women. The lowest rates of BC are reported in Central Africa for men and South-Central Asia for women.[5]

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Histologically, over 90% of BC cases are classified as urothelial carcinoma.[6] Recent studies highlight that up to 25% of cases exhibit variant histology, which can impact treatment strategies and clinical outcomes.[7] According to the World Health Organization (WHO) 2022 classification, all BC subtypes must be considered and treated as high-grade tumors.[8]

In addition to conventional urothelial carcinoma, a wide spectrum of variant histologic subtypes has been described, including squamous, glandular, micropapillary, nested, plasmacytoid, sarcomatoid, or small-cell neuroendocrine differentiation. The presence of abnormal histology is clinically relevant and often associated with a more aggressive biological behavior.[9] The second most common histologic subtype is squamous cell carcinoma, frequently associated with chronic irritation and, in endemic regions, with Schistosoma haematobium infection.[10] Adenocarcinoma of the bladder accounts for approximately 1–2% of all cases and can arise from cells of the urachal remnant. It is associated with poor prognosis due to diagnosis at an advanced stage.[11]

Present staging relies on the 2017 TNM classification (Union for International Cancer Control 8th edition), while grading systems vary between the 1973 WHO and the more recent 2016/2022 WHO classifications.[12,13]

Prognostic tools, such as the European Organisation for Research and Treatment of Cancer and the Spanish Urological Club for Oncological Treatment risk scores are routinely used to estimate recurrence and progression risk, particularly in patients treated with Bacillus Calmette–Guérin therapy.[14,15]

In 2023, Jubber *et al.*[16] conducted a comprehensive systematic review to assess the risk factors for BC. Tobacco, aromatic amines, and aromatic hydrocarbons were found to be the main risk factors in the development of BC. Other occupational exposures, such as X radiation, gamma radiation, or arsenic exposure, were secondary contributors to BC incidence.[17]

Chronic inflammation plays a critical role in bladder carcinogenesis by inducing DNA damage, promoting oxidative stress, and facilitating immune evasion and angiogenesis.[18,19] Consequently, several inflammatory markers—including neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune inflammation index—have been investigated for their prognostic relevance in BC.[20]

Molecularly, BC is highly heterogeneous. Common alterations in low-grade BC include *FGFR3* and *PIK3CA* mutations.[21] In contrast, MIBC frequently harbors alterations in *TP53*, *RB1*, and *ERBB2*.[22] Chromosomal losses, particularly on chromosome 9 and mutations in the telomerase reverse transcriptase promoter are among the most frequent events in urothelial carcinogenesis.

Among the inflammatory markers, red cell distribution width (RDW) has recently gained attention as a potential prognostic biomarker in oncology. RDW is a standard, inexpensive component of the complete blood count, typically expressed as a percentage (normal range: 11.5–14.5%) or in fL (30–46 fL). It reflects variability in erythrocyte size and is influenced by nutritional status, systemic inflammation, and oxidative stress—all of which may contribute to tumor progression.[23,24]

Although RDW has been associated with adverse outcomes in malignancies, such as breast, gastric, and upper tract urothelial cancers, its utility in BC remains underexplored. As a non-invasive, cost-effective, and readily available biomarker, RDW may improve risk stratification and guide individualized patient management. Therefore, this study aims to assess the prognostic significance of pre-operative RDW in patients with BC by examining its association with tumor stage, grade, disease progression, and overall survival, to determine its potential as an independent prognostic marker.

2. Methodology

2.1. Study population

This retrospective cohort study included 125 patients diagnosed with BC and treated at Târgu Mureș Clinical County Hospital between January and June 2021. Patients with non-urothelial or other histopathological diagnoses were excluded from the analysis, including those with rectal or prostate adenocarcinoma, chronic cystitis, carcinoma *in situ*, or secondary bladder involvement.

The study was approved by the Ethics Committee of the Târgu Mureș Clinical County Hospital, România (Nr. 7570/21.05.2025), for the retrospective analysis of patient data, and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

2.2. Data collection

For each patient, demographic data (including sex and age), clinical parameters, and pathological findings were collected and systematically recorded in a structured database for subsequent analysis. All pathological evaluations were performed at the same institution. Tumor staging was conducted in accordance with the 8th edition of the American Joint Committee on Cancer Staging Manual. Tumor grading was initially assessed using the 1973 WHO classification, which categorizes tumors as G1 (well-differentiated), G2 (moderately differentiated), and G3 (poorly differentiated). In alignment with the 2004/2016 WHO grading criteria and present clinical standards, G1 tumors were considered

"low-grade," while G2 and G3 tumors were grouped as "high-grade" for the purposes of prognostic stratification.

To ensure baseline values unaffected by therapeutic interventions or medications, all blood samples were obtained at a standardized time point—specifically, before transurethral resection of the bladder tumor (TURBT) at initial diagnosis. RDW was expressed as a percentage, with values between 11.5% and 14.5% considered within the normal reference range.

The observation period spanned from the date of diagnosis (January–June 2021) until the most recent follow-up, conducted in May 2025. Overall survival (OS) was defined as the time from the initial TURBT to death from any cause or last follow-up. Patients alive at the last contact were censored on May 31, 2025. The median follow-up duration for the entire cohort was approximately 46 months (interquartile range [IQR]: 40–50 months).

2.3. Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 26.0.0. In this study, the following statistical tests were used: Mann–Whitney U test; Chi-Square test; Receiver operating characteristic curve (ROC); Multivariate logistic regression analysis; and Spearman's rank correlation test. The significance threshold was set at $p<0.05$.

3. Results

A total of 125 patients met the inclusion criteria for this study. The median age at diagnosis was 68 years (IQR: 61–75 years), and the cohort exhibited a marked male predominance, with 97 male patients (77.6%) and 28 female patients (22.4%). The most frequently observed pathological stage was pTa, identified in 66 patients (52.8%), reflecting the predominance of NMIBC in our population. Regarding the tumor grade, G2 and G3 lesions were equally represented, with 62 cases in each category. Together, these high-grade tumors accounted for 69.6% of the entire cohort. The median pre-operative RDW value was 14.0% (IQR:13.10–15.26), consistent with the upper range of normal reference values.

Over the follow-up period, a total of 46 patients (36.8%) died from any cause. Comparative analysis between survivors and non-survivors revealed a statistically significant age difference, with deceased patients being older at diagnosis than those who survived (median age: 71 years vs. 66 years; $p=0.02$). Furthermore, RDW values were markedly higher in the non-survivor group compared with the survivor group (median RDW: 14.80 vs. 13.60%; $p<0.001$), indicating the potential relationship between elevated pre-operative RDW and increased mortality risk. The findings are summarized in Table 1, which includes detailed demographic, clinical, and pathological characteristics stratified by survival status.

To evaluate the prognostic utility of RDW in predicting overall mortality among patients with BC, a receiver operating characteristic (ROC) curve analysis was constructed. This method allowed the determination of an optimal RDW threshold that most effectively discriminated between survivors and non-survivors. The ROC curve analysis (Figure 1) identified a cut-off value of 13.95%, which demonstrated a sensitivity of 80.4% and a specificity of 65.8% (confidence interval [CI]: 95%). The ROC analysis demonstrated a favorable balance between correctly identifying patients at elevated risk of death and minimizing

Table 1. Patients' characteristics

Characteristics	Overall (*n*=125)	Survived (*n*=79)	Deceased (*n*=46)	*p*
Age (years), median (interquartile range)	68 (61–75)	66 (60–73)	71 (64–78)	0.02[a]
Male gender (%)	97 (77.6)	61 (77.2)	36 (78.3)	0.89[b]
Tumor stage (%)				
pTa	66 (52.8)	41 (51.9)	25 (54.3)	0.93[b]
pT1	41 (32.8)	26 (32.9)	15 (32.6)	
pT2	18 (14.4)	12 (15.2)	6 (13.0)	
Tumor grade (%)				
G1	1 (0.8)	0 (0)	1 (2.2)	0.27[b]
G2	62 (49.6)	37 (46.8)	25 (54.3)	
G3	62 (49.6)	42 (53.2)	20 (43.5)	
Red cell distribution width (%), median (interquartile range)	14.00 (13.10–15.26)	13.60 (12.90–14.60)	14.80 (14.00–16.61)	<0.001[a]

Note: [a]Mann–Whitney test; [b]Chi-square test. Data presented as *n* (%) unless stated otherwise.

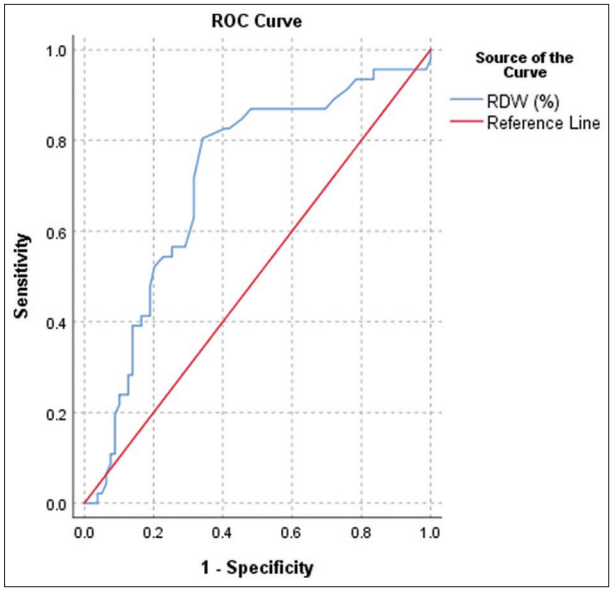

Figure 1. Receiver operating curve (ROC) and cut-off values of red cell distribution width (RDW)

the rate of false-positive classifications, supporting the clinical relevance of this cut-off point.

Furthermore, using this threshold, patients were stratified into two distinct groups: A high-RDW group (RDW ≥13.95) and a low-RDW group (RDW <13.95%). This division allowed a more detailed examination of associations between RDW levels and various demographic, clinical, and pathological parameters.

Of the total study population, 61 patients (48.8%) were categorized into the high RDW group, while the remaining 64 patients (51.2%) were classified as having low RDW. This stratification formed the basis for subsequent comparisons regarding tumor characteristics, comorbidities, and survival outcomes.

Subsequently, we analyzed the differences between the two RDW subgroups (high vs. low RDW) to identify potential associations with demographic and pathological characteristics. A statistically significant difference was observed in patient age, with individuals in the high RDW group being older than those in the low RDW group (median age: 70 vs. 66 years; p=0.03). However, no statistically significant differences were identified between the groups with respect to tumor stage, tumor grade, or gender distribution (Table 2)

To determine whether RDW was independently associated with mortality, a multivariate logistic regression analysis was performed. The model included RDW values along with other potential confounders, such as age, gender, tumor stage, and grade. The results demonstrated that elevated RDW remained an independent predictor of mortality, with an adjusted odds ratio of 1.205 (95% CI: 1.025–1.416; p=0.02). These findings suggest that RDW may serve as a valuable, non-invasive biomarker for predicting mortality in BC patients (Table 3).

Table 2. Comparison between high- and low-red cell distribution width groups

Variables	Overall (n=125)	High-RDW (n=64)	Low-RDW (n=61)	p
Age (years), median (interquartile range)	68 (61–75)	70 (63–76)	66 (58–73)	0.03[a]
Male gender (%)	97 (77.6)	47 (73.4)	50 (82.0)	0.25[b]
Tumor stage (%)				
pTa	66 (52.8)	32 (50.0)	34 (55.7)	0.49[b]
pT1	41 (32.8)	24 (37.5)	17 (27.9)	
pT2	18 (14.4)	8 (12.5)	10 (16.4)	
Tumor grade (%)				
G1	1 (0.8)	1 (1.6)	0 (0)	0.60[b]
G2	62 (49.6)	31 (48.4)	31 (50.8)	
G3	62 (49.6)	32 (50.0)	30 (49.2)	

Note: [a]Mann–Whitney test; [b]Chi-square test. Data presented as n (%) unless stated otherwise.

Abbreviation: RDW: Red cell distribution width.

To explore the potential associations between RDW and clinical parameters, correlation analyses were conducted. A statistically significant, albeit weak, positive correlation was observed between RDW and patient age (Spearman test r=0.176; p=0.04), suggesting a modest trend toward increasing RDW with advancing age. No other clinical parameters demonstrated a statistically significant correlation with RDW values (Table 4).

4. Discussion

In 2020, Yilmaz *et al.*[25] conducted a study to determine whether the hemoglobin-to-RDW ratio (HRR) measured before treatment could serve as a prognostic indicator in patients with MIBC. Their study comprised 152 patients diagnosed with MIBC and demonstrated that a lower pre-treatment HRR was associated with worse progression-free and OS. HRR was an independent prognostic factor for both progression-free survival and OS.

Another study was conducted to assess whether pre-operative RDW could predict recurrence and progression in primary NMIBC.[26] The researchers reported that a high pre-operative RDW (≥14.5%) was a strong, independent predictor of a shorter time to recurrence with a sub-distribution hazard ratio of 2.65 (95% CI: 1.83–3.84; p<0.001). They also observed that among patients treated with Bacillus Calmette–Guérin, a high RDW remained an independent prognostic factor for recurrence (sub-distribution hazard ratio = 2.0; 95% CI: 1.01–3.98; p=0.047).

Ma *et al.*[27] investigated patients treated with radical cystectomy for MIBC, using a cut-off value of 0.1395 for RDW. Patients from the high RDW group had significantly lower hemoglobin levels, higher C-reactive protein levels, lower RBC counts, and a higher T-stage disease (p<0.05 for all variables). Similar to our study, high RDW was independently associated with worse OS, cancer-specific survival, and disease-free survival on both univariate and multivariate analysis.

When compared with previous studies, our findings demonstrated similar trends in patient OS. The absence of significant correlations between RDW and tumor stage, grade, or patient gender suggests that RDW may be more reflective of systemic factors rather than tumor biology.

To the best of our knowledge, this is the first study to assess the prognostic significance of RDW in a contemporary cohort that includes both NMIBC and MIBC patients. However, it has several limitations that should be acknowledged. Its retrospective design may introduce selection biases. Second, our study was conducted at a single center, which may limit its generalizability to a more diverse population. Third, even if key confounders, such as age, gender, and tumor

Table 3. Multivariate regression regarding red cell distribution width as an independent predictor for mortality

Variables	*B*	Standard error	Wald	*p*	Adjusted odds ratio	Confidence interval 95% lower	Confidence interval 95% upper
Male gender	−0.220	0.484	0.207	0.649	0.803	0.311	2.072
Age	0.045	0.020	4.853	0.028	1.046	1.005	1.089
P stage	−0.017	0.334	0.002	0.960	0.984	0.511	1.892
G stage	−0.485	0.463	1.100	0.294	0.616	0.249	1.524
Red cell distribution width	0.186	0.082	5.117	0.024	1.205	1.025	1.416

Table 4. Spearman test for red cell distribution width and other clinical parameters

Variables	Male gender	Tumor stage	Tumor grade	Age
Red cell distribution width	r=0.114, p=0.20	r=0.125, p=0.16	r=0.033, p=0.71	r=0.176, p=0.04*

Note: *indicates statistically significance $p<0.05$

characteristics were included in our multivariate analysis, other potentially influential factors (inflammatory markers, nutritional status) were not assessed. These confounders could have an impact on our RDW values. In addition, we measured RDW at a single time point (before TURBT) and did not evaluate it over time. Finally, the lack of an external validation cohort limits the ability to confirm the reproducibility and robustness of our results.

Despite a growing body of evidence regarding RDW and its prognostic value in various malignancies, research that specifically addresses BC remains limited. Most existing studies focus on more established biomarkers, leaving a gap in the literature regarding the prognostic utility of RDW in this population. These observations underscore the need for further studies to expand our present understanding of RDW and its impact on BC patients.

Another important future direction may be the investigation of dynamic RDW measurements throughout treatment and follow-up. Serial RDW could provide insights into temporal changes in systemic inflammation, nutritional status, and overall physiological reserve of the body, potentially identifying patients with a higher risk of relapse or treatment-related complications. Linking these changes with treatment modalities (intravesical therapy, systemic chemotherapy, or immunotherapy) may help determine whether RDW could serve as an early response or toxicity marker.[28]

The absence of a significant association between RDW and tumor-related characteristics, such as pathological stage or grade, suggests that RDW may primarily reflect host-related systemic factors rather than tumor-specific factors. Elevated RDW levels have been linked to chronic inflammation, oxidative stress, and nutritional deficiencies, all of which can impair erythropoiesis and reduce the body's physiological reserve. These systemic alterations are known to contribute to frailty, impaired immune response, and reduced tolerance to oncologic therapies. These factors may together worsen OS independently of tumor aggressiveness. Therefore, RDW may serve as an integrative biomarker of the patient's global health status, reflecting systemic vulnerability and inflammatory burden rather than tumor-specific pathology.

To understand the confounders and their relationship with RDW values, more studies are needed to assess correlations between RDW and systemic inflammatory cytokines, oxidative stress markers, erythropoietic dysfunction, and nutritional biomarkers. Understanding these pathways may open new opportunities for targeted interventions, such as nutritional optimization or anti-inflammatory therapies.[29] Ultimately, these methods could enhance treatment response and tolerance, reduce complications, and improve survival outcomes in BC patients.

5. Conclusion

In our retrospective analysis, we demonstrated that pre-treatment RDW measured before any therapeutic intervention was an independent prognostic factor for overall mortality in patients with newly diagnosed BC. This association was observed regardless of the subsequent treatment strategies used after the initial TURBT.

The prognostic significance of RDW persisted after adjusting for established clinical and pathological confounders, including patient age, gender, pathological tumor stage, and histological tumor grade. Patients with elevated RDW values, defined by a cut-off of 13.95%, had a significant higher risk of death (13.60% in the survivor group vs. 14.80% in the non-survivor group; $p<0.001$)

From a clinical perspective, these findings indicate that a high pre-operative RDW (≥13.95%) at the time of primary diagnosis is associated with a greater likelihood of fatal outcomes over time. This prognostic association remained consistent regardless of the therapeutic approach undertaken (including intravesical Bacillus Calmette–Guérin, immunotherapy, radical cystectomy, or re-TURBT).

The RDW maintains its predictive value independently of oncologic parameters, suggesting that it reflects important host-related factors, such as systemic inflammation, impaired erythropoiesis, or other nutritional deficiencies.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Târgu Mureș Clinical County Hospital, România (Nr. 7570/21.05.2025), and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the subjects involved in the study.

Consent for publication

Written informed consent has been obtained from the patients to publish this paper.

Data availability statement

The data presented in this study are available on request from the corresponding author.

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