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Association of Preoperative Systemic Inflammatory Biomarkers with Pathological Tumor Stage in Bladder Cancer: A Retrospective Cohort Study

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Abstract

Background

Systemic inflammatory biomarkers have been increasingly investigated as potential indicators of tumor aggressiveness in bladder cancer. We evaluated the association between hemoglobin levels, systemic inflammatory markers, and pathological tumor stage in patients undergoing transurethral resection of bladder tumor (TUR-BT).

Methods

This retrospective study included 182 patients with primary bladder cancer who underwent TUR-BT between 2018 and 2026. Patients were classified according to pathological tumor stage as pTa, pT1, and pT2. Hemoglobin, red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and De Ritis ratio were analyzed. Group comparisons were performed using the Kruskal–Wallis test with Dunn–Bonferroni post-hoc analysis. Correlation analysis, ordinal logistic regression, and Jonckheere–Terpstra trend analysis were also performed.

Results

Significant differences in hemoglobin and inflammatory markers were observed across pathological tumor stages. Hemoglobin levels progressively decreased, whereas RDW, NLR, SII, SIRI, and De Ritis ratio increased with advancing tumor stage. Correlation analyses demonstrated significant associations between tumor stage and all evaluated markers. In multivariable ordinal logistic regression analysis, hemoglobin emerged as the only independent predictor of higher pathological stage (OR = 0.884, 95% CI = 0.825–0.947, $p < 0.001$). Trend analysis further confirmed progressive increases in systemic inflammatory activity across tumor stages.

Conclusions

Systemic inflammatory biomarkers are significantly associated with pathological tumor stage in bladder cancer. Increased inflammatory marker levels together with decreased hemoglobin levels may reflect more aggressive tumor biology. Routine hematological parameters may provide additional information for preoperative risk assessment in patients with bladder cancer.

BACKGROUND

Bladder cancer is one of the most common malignancies of the urinary tract worldwide and remains a major cause of cancer-related morbidity and healthcare burden. Approximately 70%–75% of patients

present with non–muscle-invasive bladder cancer at diagnosis, whereas the remaining patients have muscle-invasive disease with more aggressive clinical behavior (1, 2). Despite advances in diagnostic and therapeutic approaches, predicting tumor aggressiveness and progression remains challenging in clinical practice. Therefore, identification of novel biomarkers reflecting tumor biology has become increasingly important (3). Accumulating evidence indicates that chronic inflammation plays an important role in carcinogenesis and tumor progression through mechanisms including cytokine production, angiogenesis, immune dysregulation, and promotion of tumor invasion (4). In this context, systemic inflammatory biomarkers derived from routine blood tests have attracted increasing clinical interest because they are inexpensive, widely available, and easily reproducible (5). Among these biomarkers, the neutrophil-to-lymphocyte ratio (NLR) has been extensively investigated as a prognostic indicator in several malignancies, including bladder cancer (6). More recently, composite inflammatory indices such as the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) have been introduced to better reflect the interaction between inflammatory and immune pathways (7, 8). Previous studies have demonstrated that elevated inflammatory marker levels are associated with adverse oncological outcomes in bladder cancer patients (9, 10). In addition to inflammation-based indices, several routine hematological and biochemical parameters have also been investigated as potential biomarkers of tumor aggressiveness. Red blood cell distribution width (RDW) has been associated with systemic inflammatory activity and poor prognosis in various malignancies (11). Similarly, the aspartate aminotransferase/alanine aminotransferase ratio (De Ritis ratio) has been linked to tumor progression and unfavorable oncological outcomes in multiple solid tumors (12). Although previous studies have primarily focused on survival outcomes and recurrence, the relationship between systemic inflammatory biomarkers and pathological tumor stage in bladder cancer has not been fully clarified. Therefore, the present study aimed to evaluate the association between hemoglobin levels, systemic inflammatory biomarkers, and pathological tumor stage in patients undergoing transurethral resection of bladder tumor (TUR-BT). In addition, we investigated whether these routinely available laboratory parameters may provide clinically useful information regarding tumor aggressiveness.

METHODS

1. Study design and patient population

This retrospective single-center observational study included consecutive patients who underwent transurethral resection of bladder tumor (TUR-BT) for primary bladder cancer between January 2018 and January 2026 at our institution.Patients with available pathological findings and complete preoperative laboratory data were included in the study. Cases with incomplete laboratory variables were excluded by complete-case analysis. In addition, patients with active infection, hematological disorders, chronic inflammatory diseases, or significant hepatic dysfunction that could potentially affect systemic inflammatory biomarkers were excluded from the analysis. To minimize potential confounding, these exclusion criteria were applied before statistical analysis. A total of 247 patients who underwent transurethral resection of bladder tumor (TUR-BT) for primary bladder cancer between January 2018 and

January 2026 were initially screened for eligibility. Among them, 65 patients were excluded, including 28 patients with missing laboratory data, 12 patients with active infection, 8 patients with hematological disorders, 11 patients with chronic inflammatory diseases, and 6 patients with significant hepatic dysfunction. Consequently, the final study cohort consisted of 182 patients. The patient selection process and exclusion criteria are summarized in Fig. 1. According to pathological tumor stage, patients were classified as pTa, pT1, and pT2 based on histopathological examination of TUR-BT specimens.

2. Data collection and laboratory parameters

Demographic, clinical, and laboratory data were obtained from the electronic medical record system. Recorded demographic variables included age and sex. Preoperative laboratory parameters included hemoglobin, red blood cell distribution width (RDW), neutrophil count, lymphocyte count, monocyte count, platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Laboratory values were collected from routine blood tests performed preoperatively as close as possible to the date of surgery. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The systemic immune-inflammation index (SII) was calculated as platelet count × neutrophil count / lymphocyte count. The systemic inflammation response index (SIRI) was calculated as neutrophil count × monocyte count / lymphocyte count. The De Ritis ratio was defined as the serum AST/ALT ratio.

3. Statistical analysis

All statistical analyses were performed using R statistical software. Sample size estimation was conducted using G*Power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). A fixed-effects one-way analysis of variance model was used for sample size approximation across the three pathological tumor stage groups. Assuming a medium effect size (Cohen's $f = 0.25$), $\alpha = 0.05$, and statistical power of 80%, the minimum required sample size was calculated as 159 patients. The final cohort of 182 patients exceeded this threshold. Continuous variables were presented as median and interquartile range, whereas categorical variables were expressed as number and percentage. Comparisons among pathological tumor stage groups were performed using the Kruskal–Wallis test. Dunn–Bonferroni post-hoc analysis was applied for pairwise comparisons when significant overall differences were detected (13). Associations between pathological tumor stage and hematological parameters were evaluated using Spearman rank correlation analysis (14). Since pathological tumor stage was treated as an ordinal dependent variable, ordinal logistic regression analysis was performed to assess the association between the investigated markers and higher tumor stage (15). Ordinal logistic regression analysis was performed to identify independent predictors of higher pathological tumor stage. Odds ratio (OR), 95% confidence interval (CI), and p-values were reported. In addition, the Jonckheere–Terpstra trend test was used to evaluate monotonic trends across ordered pathological tumor stages. A two-sided p-value < 0.05 was considered statistically significant (16).

RESULTS

Baseline characteristics

A flow diagram demonstrating patient screening, exclusion criteria, and final cohort formation is presented in Fig. 1.

Figure 1. Study flowchart illustrating patient screening, exclusion criteria, and final cohort selection.

After application of the exclusion criteria, the final study cohort consisted of 182 patients who underwent transurethral resection of bladder tumor (TUR-BT) for primary bladder cancer.

According to pathological tumor stage, patients were classified as pTa, pT1, and pT2.

Baseline clinicopathological and laboratory characteristics according to tumor stage are summarized in Table 1.

Table 1
Baseline clinicopathological characteristics according to pathological tumor stage

Variable	pTa (n = 75)	pT1 (n = 69)	pT2 (n = 38)	p-value
Age (yr)	63 (55–70)	72 (66–77)	70.5 (63–78)	< 0.001
Hemoglobin (g/dL)	14.9 (13.6–16.1)	14.2 (12.7–15.2)	13.2 (11.6–14.7)	0.001
RDW (%)	14.1 (13.3–14.9)	14.3 (13.6–15.3)	14.7 (13.8–16.3)	0.033
NLR	2.23 (1.63–2.99)	2.60 (1.88–3.71)	3.28 (2.10–4.33)	< 0.001
SII	525.7 (377.0–753.1)	598.9 (413.1–896.0)	884.2 (479.9–1510.3)	0.004
SIRI	1.25 (0.87–1.81)	1.67 (1.02–2.33)	2.22 (1.31–3.81)	< 0.001
De Ritis ratio	1.10 (0.87–1.41)	1.28 (1.10–1.50)	1.42 (1.18–1.74)	0.002
Male sex	66 (88.0)	61 (88.4)	35 (92.1)	0.900
Female sex	9 (12.0)	8 (11.6)	3 (7.9)	

Values are presented as median (interquartile range) or number (%). RDW, red blood cell distribution width; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index. P-values were calculated using the Kruskal–Wallis test or Fisher exact test

Significant differences were observed among tumor stages regarding age, hemoglobin levels, RDW, NLR, SII, SIRI, and De Ritis ratio. Overall, hemoglobin levels decreased with advancing tumor stage, whereas systemic inflammatory markers demonstrated progressive increases. No significant difference was observed in sex distribution among the groups (Fig. 2).

Figure 2. Distribution of hemoglobin and systemic inflammatory markers according to pathological tumor stage.

Box plots represent the median and interquartile range, while jittered points represent individual patient values

Pairwise comparisons between tumor stages

Pairwise comparisons using the Dunn–Bonferroni post-hoc test demonstrated that the most prominent differences were observed between pTa and pT2 tumors. Hemoglobin levels were significantly lower in advanced tumor stages, whereas inflammatory markers including RDW, NLR, SII, SIRI, and De Ritis ratio were generally higher in pT2 tumors compared with pTa tumors. Detailed pairwise comparison results are presented in Table 2.

Table 2
Pairwise comparisons of inflammatory markers according to pathological tumor stage

Variable	pTa vs. pT1	pTa vs. pT2	pT1 vs. pT2
Hemoglobin	0.046	0.002	0.488
RDW	0.343	0.034	0.695
NLR	0.065	< 0.001	0.268
De Ritis ratio	0.033	0.004	0.883
SII	0.678	0.003	0.071
SIRI	0.198	< 0.001	0.092

Values represent adjusted p-values obtained from Dunn–Bonferroni post-hoc analysis. RDW, red blood cell distribution width; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

NOTE

Remove Z statistics from the table. ICUrology tables are generally cleaner and avoid unnecessary statistical clutter.

Correlation analysis

Spearman correlation analysis demonstrated significant associations between pathological tumor stage and several hematological and inflammatory markers. Tumor stage showed negative correlation with hemoglobin levels and positive correlations with RDW, NLR, SII, SIRI, and De Ritis ratio. The detailed correlation coefficients are summarized in Table 3.

Table 3
Correlation between inflammatory biomarkers and pathological tumor stage

Variable	Spearman ρ	p-value
Hemoglobin	−0.27	< 0.001
RDW	0.17	0.030
NLR	0.28	< 0.001
De Ritis ratio	0.26	< 0.001
SII	0.24	0.001
SIRI	0.28	< 0.001

RDW, red blood cell distribution width; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

Ordinal logistic regression analysis

Ordinal logistic regression analysis was performed to identify independent predictors of higher pathological tumor stage. Among the evaluated variables, only hemoglobin remained a significant independent predictor in the multivariable model, whereas the remaining inflammatory markers did not retain statistical significance. Detailed regression results are presented in Table 4 and Fig. 3.

Table 4
Ordinal logistic regression analysis for prediction of higher pathological tumor stage

Variable	OR	95% CI	p-value
Hemoglobin	0.884	0.825–0.947	< 0.001
RDW	1.004	0.935–1.078	0.920
NLR	0.933	0.692–1.259	0.651
SII	1.001	0.999–1.002	0.058
SIRI	0.993	0.741–1.330	0.960
De Ritis ratio	1.255	0.735–2.141	0.407

OR, odds ratio; CI, confidence interval; RDW, red blood cell distribution width; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

NOTE

Do not bold p-values. ICUrology usually prefers cleaner statistical presentation.

Figure 3. Forest plot of ordinal logistic regression analysis for pathological tumor stage.

Points represent odds ratios and horizontal bars represent 95% confidence intervals. The vertical dashed line indicates OR = 1.

Trend analysis across tumor stages

The Jonckheere–Terpstra trend analysis demonstrated significant monotonic trends across pathological tumor stages. Hemoglobin levels showed a progressive decreasing trend, while inflammatory markers demonstrated increasing trends with advancing tumor stage. Detailed trend analysis results are shown in Table 5 and Fig. 4.

Table 5
Jonckheere–Terpstra trend analysis across pathological tumor stages

Variable	JT statistic	p-value
Hemoglobin	3915.5	< 0.001
RDW	6323.0	0.004
NLR	6773.5	< 0.001
SII	6538.0	< 0.001
SIRI	6732.5	< 0.001
De Ritis ratio	6591.0	< 0.001

JT, Jonckheere–Terpstra; RDW, red blood cell distribution width; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

Figure 4. Median trends of hemoglobin and systemic inflammatory markers across pathological tumor stages.

Points represent median values for each marker, and lines illustrate the monotonic trend from pTa to pT2 tumors.

DISCUSSION

In the present study, we investigated the association between systemic inflammation-related hematological biomarkers and pathological tumor stage in patients with bladder cancer. The results demonstrated a progressive increase in inflammatory markers, including NLR, SII, SIRI, RDW, and De Ritis ratio, with advancing pathological stage, whereas hemoglobin levels gradually decreased. Although

several inflammatory markers showed significant associations with tumor stage in correlation and trend analyses, hemoglobin remained the only independent predictor of higher pathological stage in the multivariable ordinal logistic regression model.

Bladder cancer is characterized by considerable biological heterogeneity and exhibits a broad spectrum of clinical behavior. Despite substantial advances in diagnostic modalities and therapeutic strategies, accurately identifying patients with aggressive disease before definitive pathological evaluation remains challenging in daily clinical practice (1–3). For this reason, increasing attention has been directed toward the identification of inexpensive, reproducible, and easily obtainable biomarkers that may improve preoperative risk stratification and facilitate clinical decision-making. Among these, systemic inflammatory biomarkers derived from routine blood tests have attracted significant interest because they are widely available and can be readily incorporated into routine clinical assessment (4, 5).

The relationship between inflammation and cancer progression has been extensively documented. Chronic inflammation contributes to tumor development through several biological mechanisms, including cytokine-mediated signaling, angiogenesis, immune dysregulation, and enhancement of tumor invasion and metastatic potential (4, 17, 18). In bladder cancer specifically, inflammatory processes within the tumor microenvironment have been associated with aggressive pathological characteristics and disease progression (19). Consequently, systemic inflammatory markers may provide indirect information regarding the biological behavior of the tumor and the interaction between the host immune system and malignant cells.

Among the evaluated biomarkers, NLR demonstrated a significant positive association with increasing pathological stage. This finding is consistent with previous studies reporting that elevated pre-treatment NLR is associated with adverse oncological outcomes, advanced disease, and poorer survival among patients with bladder cancer (20, 21). The observed relationship may reflect the combined effects of neutrophil-mediated tumor-promoting inflammation and relative suppression of lymphocyte-mediated antitumor immune responses. Therefore, increasing NLR values may indicate a shift toward a biological environment that favors tumor progression.

Similarly, both SII and SIRI increased significantly across pathological tumor stages. These indices integrate multiple components of the systemic inflammatory response and may therefore provide a broader representation of the balance between inflammation and host immunity. Previous studies and meta-analyses have demonstrated the prognostic value of SII in bladder cancer and have linked elevated SII levels with unfavorable oncological outcomes (9, 10, 22). Our findings extend these observations by demonstrating a clear association between increasing SII and SIRI values and advancing pathological tumor stage. The progressive increase observed across ordered pathological stages further supports the hypothesis that systemic inflammatory activity intensifies as bladder cancer becomes more advanced.

In addition to the composite inflammatory indices, RDW and De Ritis ratio were also associated with higher pathological stage. RDW has been recognized as a marker of chronic systemic inflammation and has previously been linked to poor prognosis in several malignancies (12). Likewise, the De Ritis ratio

has been associated with alterations in tumor metabolism and more aggressive cancer behavior across multiple solid tumors (11). The associations identified in the present study suggest that both inflammatory and metabolic changes may accompany disease progression in bladder cancer. Although the exact biological mechanisms underlying these relationships remain incompletely understood, the findings support the concept that routine laboratory parameters may reflect clinically relevant aspects of tumor biology.

One of the most notable observations of the present study was the independent association between lower hemoglobin levels and higher pathological stage. While several inflammatory markers demonstrated significant correlations with tumor stage, hemoglobin was the only variable that retained significance in the multivariable model. Cancer-related anemia is a multifactorial condition that may arise from chronic inflammation, nutritional deficiencies, impaired erythropoiesis, or increased tumor burden (29). Therefore, declining hemoglobin levels may reflect the cumulative biological impact of progressive disease. The present findings suggest that hemoglobin, a routinely measured laboratory parameter, may provide clinically meaningful information regarding tumor aggressiveness and could potentially contribute to preoperative risk assessment.

The trend analysis performed using the Jonckheere–Terpstra test further strengthened the study findings. A significant monotonic decrease in hemoglobin levels and significant monotonic increases in inflammatory markers were observed across the ordered pathological stages. These results indicate that systemic inflammatory activation and anemia-related alterations are not isolated phenomena but rather demonstrate a progressive relationship with tumor advancement. Such findings support the biological plausibility of the observed associations and reinforce the potential clinical relevance of these biomarkers.

Prospective investigations have similarly emphasized the role of inflammation in bladder cancer progression (30). Collectively, the available evidence suggests that inflammatory pathways contribute substantially to disease development and progression. Consequently, systemic inflammatory biomarkers may represent useful adjunctive tools for identifying patients who are more likely to harbor aggressive pathological disease.

Several limitations should be considered when interpreting the findings of the present study. First, the retrospective single-center design may have introduced selection bias. Second, despite the application of strict exclusion criteria, systemic inflammatory markers may have been influenced by unrecognized inflammatory conditions that could not be completely excluded. Third, although the overall sample size exceeded the calculated minimum requirement, subgroup analyses may still have been affected by limited statistical power. In addition, while ordinal logistic regression was selected because pathological stage represents an ordered outcome, the proportional odds assumption was not formally tested. Finally, external validation of the findings was not available, which may limit generalizability.

Despite these limitations, the study possesses several strengths. Multiple inflammation-related biomarkers were evaluated simultaneously within the same cohort, allowing direct comparison of their

associations with pathological stage. Furthermore, the consistency of findings across correlation analyses, ordinal regression models, and trend analyses increases confidence in the robustness of the observed relationships. The use of routinely available laboratory parameters also enhances the potential clinical applicability of the results. These biomarkers may assist clinicians in identifying patients at higher risk of harboring advanced pathological disease before definitive pathological evaluation.

CONCLUSIONS

Systemic inflammatory biomarkers are significantly associated with pathological tumor stage in bladder cancer. Progressive increases in NLR, SII, SIRI, RDW, and De Ritis ratio, together with decreasing hemoglobin levels, were observed with advancing tumor stage. Although several inflammatory markers demonstrated significant associations with pathological stage, hemoglobin emerged as the only independent predictor of higher-stage disease in multivariable analysis. These findings suggest that routinely available hematological parameters may provide valuable information regarding tumor aggressiveness and could contribute to improved preoperative risk assessment and risk stratification in patients with bladder cancer. Further prospective multicenter studies are warranted to validate these observations and to clarify the potential role of these biomarkers in clinical decision-making.

Abbreviations

ALT – Alanine Aminotransferase

AST – Aspartate Aminotransferase

CI – Confidence Interval

NLR – Neutrophil-to-Lymphocyte Ratio

OR – Odds Ratio

RDW – Red Cell Distribution Width

SII – Systemic Immune-Inflammation Index

SIRI – Systemic Inflammation Response Index

TUR-BT – Transurethral Resection of Bladder Tumor

Declarations

Ethics statement

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Elazığ Fethi Sekin City Hospital (Decision No: 2026/27-07). The study was conducted in accordance with the

principles of the Declaration of Helsinki.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Author Contributions

Mehmet Sezai Oğraş contributed to the study conception and design, statistical analysis, data interpretation, manuscript drafting, critical revision of the manuscript, and supervision of the study.

Eyüp Andaç Karataş contributed to the study design, data collection, manuscript drafting, and administrative and technical support.

Erdoğan Ağlamış contributed to data collection, data interpretation, critical revision of the manuscript, and administrative support.

Fatih Yıldırım contributed to data collection, statistical analysis, and critical revision of the manuscript.

All authors reviewed and approved the final version of the manuscript.

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Figures

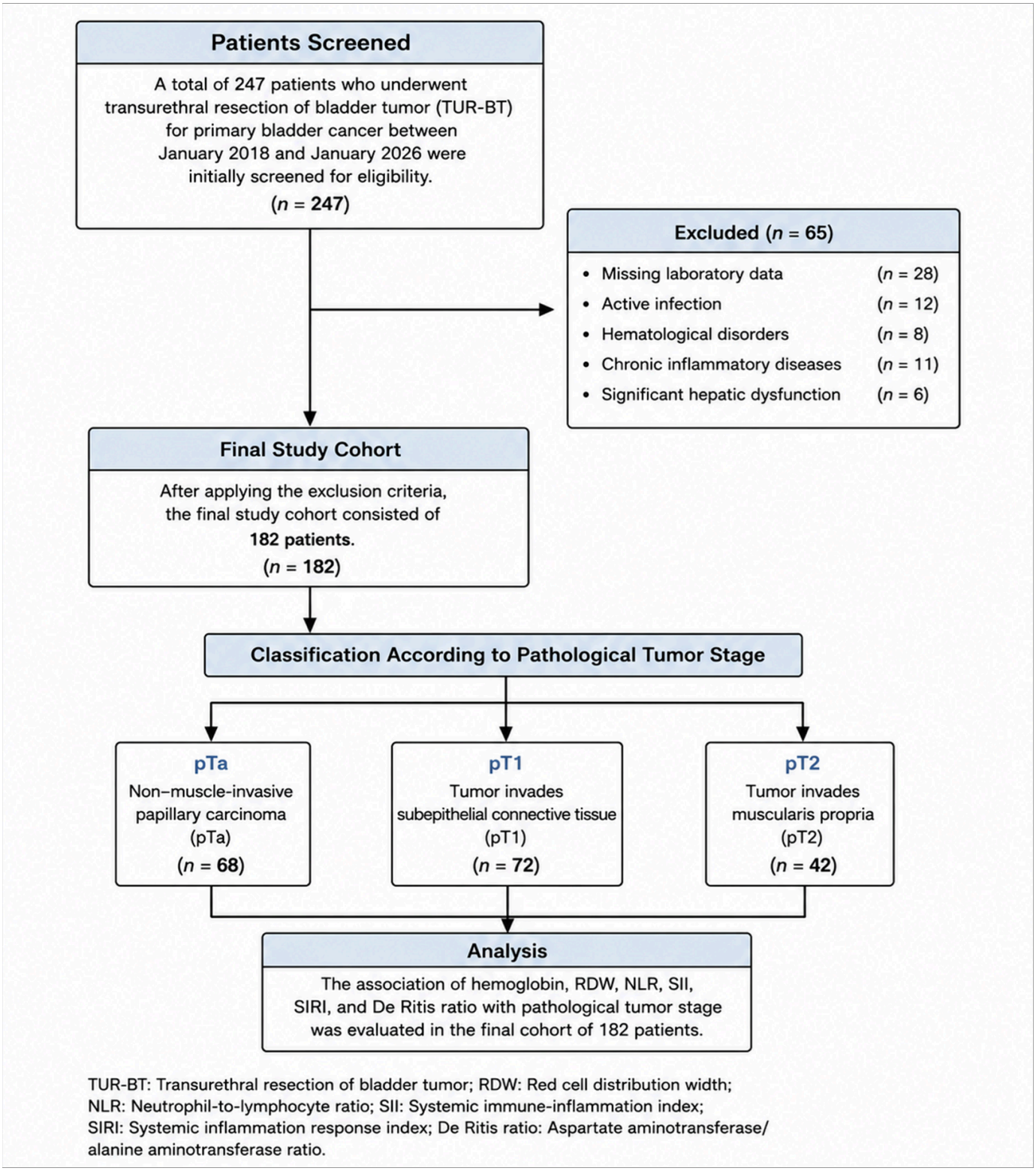


Figure 1

Study flowchart illustrating patient screening, exclusion criteria, and final cohort selection.

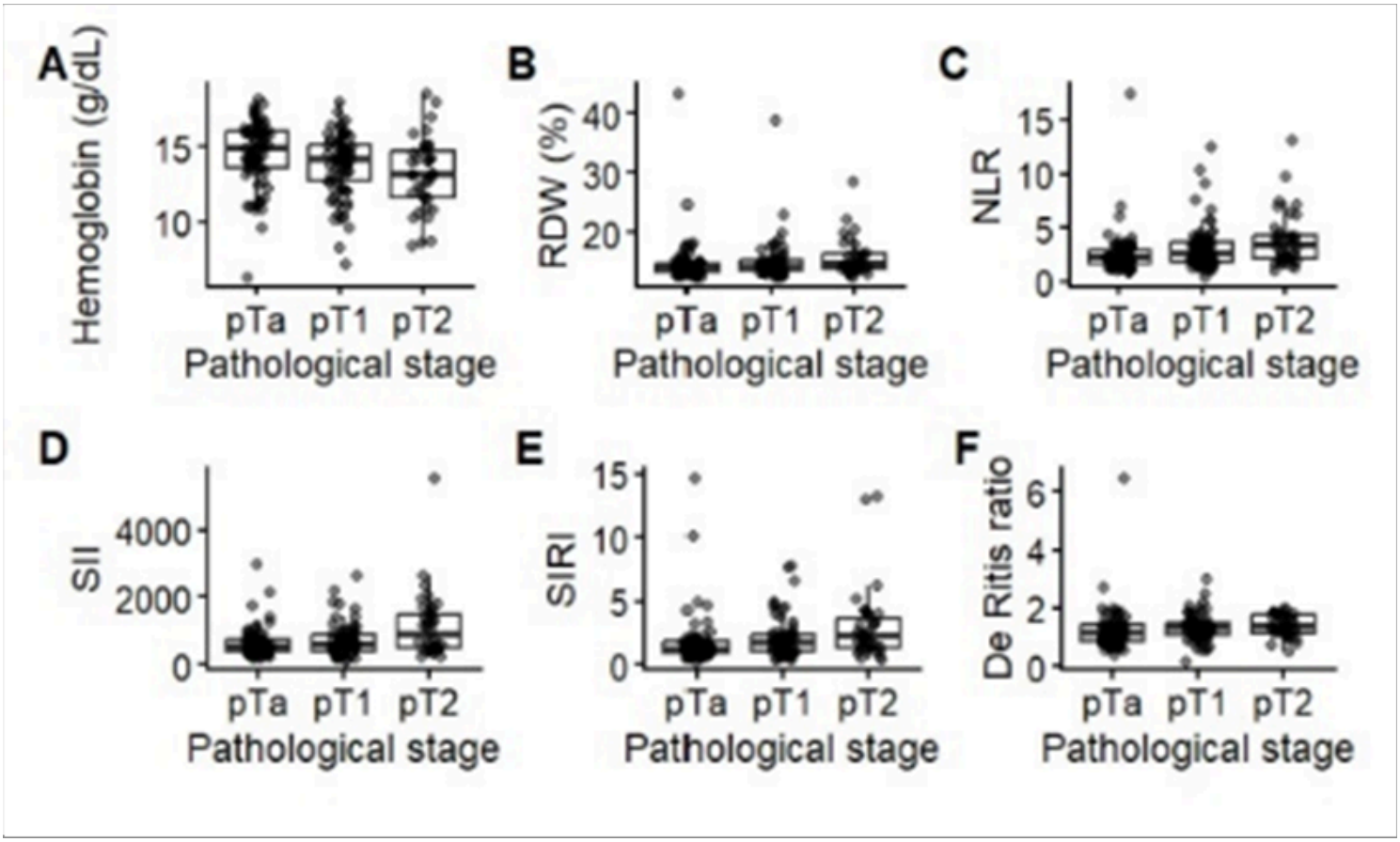


Figure 2

Distribution of hemoglobin and systemic inflammatory markers according to pathological tumor stage.

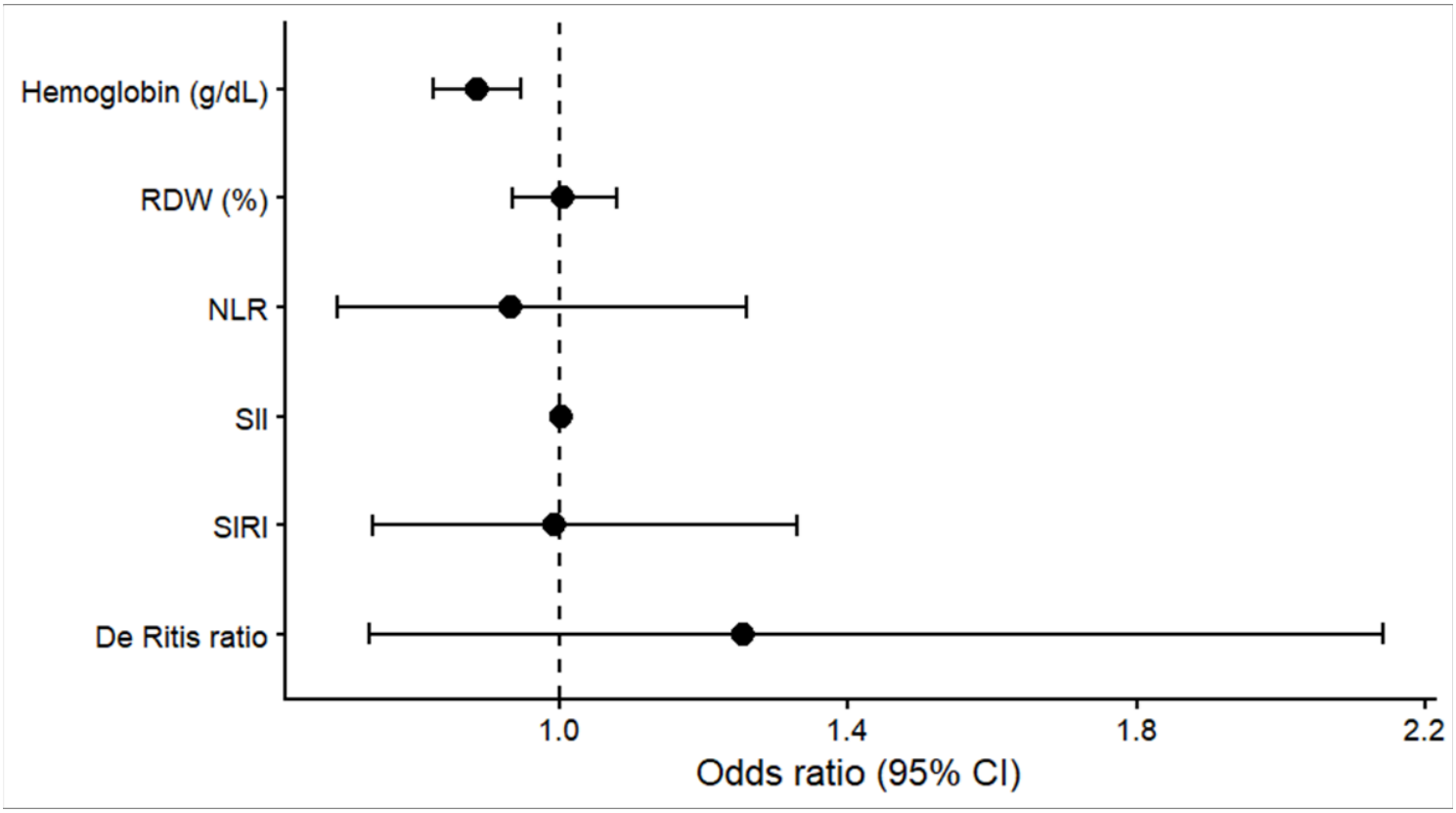


Figure 3

Forest plot of ordinal logistic regression analysis for pathological tumor stage.

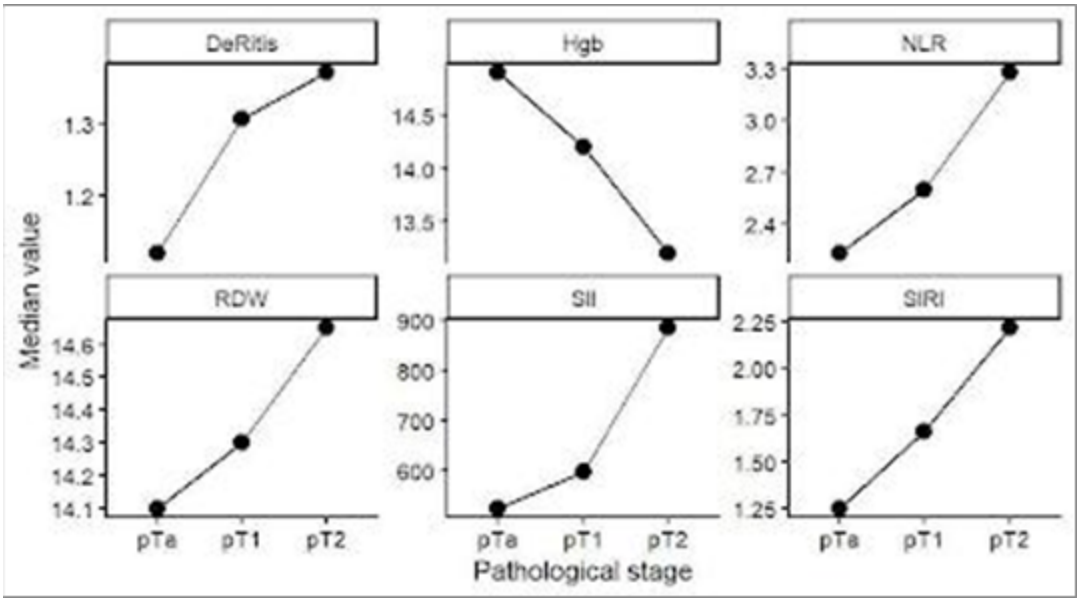


Figure 4

Median trends of hemoglobin and systemic inflammatory markers across pathological tumor stages.