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Factors Influencing Recurrence After Initial Transurethral Resection of Bladder Tumor (TURBT) in Stage T2 Bladder Cancer and the Development of a Predictive Model

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【Abstract】

Background: Patients with stage T2 muscle-invasive bladder cancer (MIBC) have a high risk of intravesical recurrence following transurethral resection of bladder tumor (TURBT); however, there is currently a lack of precise tools for predicting intravesical recurrence in this population, particularly for stage T2 patients who are unsuitable for or refuse radical cystectomy due to advanced age or comorbidities. This study aims to develop and validate a multifactorial predictive model that integrates tumor pathological characteristics with the host's inflammatory status, thereby providing a basis for personalized clinical management, particularly for stage T2 patients who are unsuitable for or refuse radical cystectomy due to advanced age or comorbidities.

Methods: This retrospective study included 239 patients with stage T2 MIBC who were treated at the Affiliated Hospital of Zunyi Medical University from January 2013 to December 2024. Univariate and multivariate Cox proportional hazards models were used to identify independent risk factors for postoperative recurrence, and a nomogram prediction model was developed based on the results. The model's discriminatory power, calibration, and clinical utility were systematically evaluated in

the training set (n = 167, 69.87%) and validation set (n = 72, 30.13%) using time-dependent receiver operating characteristic (ROC) curves, the C-index, calibration curves, and decision curve analysis (DCA).

Results: The median follow-up period was 41 months; 72 patients experienced intravesical recurrence, resulting in an overall intravesical recurrence rate of 30.13%. Multivariate Cox regression analysis showed that tumor number (multiple vs. single: HR = 3.59, 95% CI: 1.74–7.42, P < 0.001), tumor size (≥3 cm vs. <3 cm: HR = 3.13, 95% CI: 1.67–5.87, P < 0.001), histological grade (high-grade vs. low-grade: HR = 2.34, 95% CI: 1.17–4.68, P = 0.017), absolute neutrophil count (continuous variable: HR = 1.48, 95% CI: 1.04–2.11, P = 0.031), and red blood cell count (continuous variable: HR = 1.87, 95% CI: 1.20–2.93, P = 0.006) were independent risk factors for postoperative intravesical recurrence. The log-line model constructed based on the above five significant variables (with white blood cell count included to maintain model completeness) had C-indices of 0.807 (95% CI: 0.74–0.85) and 0.72 (95% CI: 0.61–0.82) in the training and validation sets, respectively. At 12 months post-surgery, the model achieved time-dependent AUC values of 0.85 and 0.72 on the training and validation sets, respectively. The calibration curves showed a high degree of agreement between the predicted probability and the actual probability of intravesical recurrence (Brier score: 0.12/0.15). DCA analysis indicated that the model provided significant clinical net benefit within a risk threshold range of 0.2 – 0.8.

Conclusion: This study successfully developed and validated a multifactorial predictive model for intravesical recurrence following TURBT in patients with stage T2 MIBC. The model is intended for patients who are unsuitable for or refuse radical cystectomy due to advanced age or comorbidities. The model integrates tumor-specific characteristics with host inflammation and red blood cell levels. It demonstrated good predictive performance and clinical utility during short-term follow-up, providing a practical tool for the precise identification of high-risk patients and the development of individualized follow-up and postoperative adjuvant treatment strategies.

Keywords: Stage T2 Bladder Cancer;Transurethral Resection Of Bladder;

Intravesical Tumor Recurrence；Nomograms; Red Blood Cells.

1. Introduction

Bladder cancer is a common malignant tumor of the urinary system worldwide, ranking among the leading causes of both morbidity and mortality [1]. Against the backdrop of an aging population, the disease burden of bladder cancer continues to rise both globally and in China, making it a significant public health issue that threatens human urological health [2]. Urothelial carcinoma is the predominant histological type of bladder cancer, accounting for over 90% of cases. It exhibits highly heterogeneous biological behavior, and pathological staging and histological grading of the tumor serve as crucial references for formulating clinical management plans [3].

Based on the depth of tumor invasion into the bladder wall, bladder cancer can be classified into two major types: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) (see Figure 1). These two types differ fundamentally in terms of incidence, biological behavior, and prognosis [4]. Specifically, NMIBC accounts for approximately 70%–75% of all newly diagnosed cases, while MIBC accounts for approximately 25%–30% [5]. Stage T2 tumors (involving the bladder muscle layer) are typical examples of MIBC. These tumors are more aggressive and metastatic; patients have a higher risk of intravesical recurrence after surgery, and such recurrence is often accompanied by local disease progression or distant metastasis. The overall prognosis is significantly worse than that of NMIBC [6].

Transurethral resection of bladder tumors (TURBT) is a core therapeutic approach for the diagnosis and initial treatment of bladder cancer [7]. For patients with stage T2 muscle-invasive bladder cancer (MIBC), TURBT not only determines the pathological stage and histological grade of the tumor—providing a basis for subsequent treatment—but also enables macroscopic resection of the tumor, making it a crucial treatment modality for preserving bladder function [8]. However, despite continuous advances in surgical techniques in recent years and the increasing

refinement of adjuvant regimens such as intravesical chemotherapy [9-11] and immunotherapy [12-14], the rate of intravesical recurrence following initial TURBT in patients with stage T2 MIBC remains high. Some patients ultimately require radical cystectomy due to intravesical tumor recurrence, which severely impacts their quality of life and survival [15]. Therefore, identifying the key factors influencing intravesical recurrence in patients with stage T2 MIBC following TURBT and developing a precise predictive tool for intravesical recurrence hold significant clinical importance for implementing risk-stratified management and formulating individualized treatment and follow-up strategies.

Currently, clinical predictions of intravesical recurrence in bladder cancer primarily focus on the NMIBC population and are mainly based on prognostic tools such as the European Organization for Research and Treatment of Cancer (EORTC) score and the Spanish Club of Urological Oncology (CUETO) score [16-19]. However, the applicability of these scoring systems to patients with muscle-invasive bladder cancer (MIBC) is limited; studies on patients with stage T2 MIBC are relatively scarce, and existing research mostly analyzes the predictive value of tumor characteristics or laboratory markers in isolation, without comprehensively considering the interaction between tumor characteristics and the host’s systemic status. Existing evidence indicates that tumor characteristics such as number, size, and histological grade [20,21] are closely associated with intravesical recurrence of bladder cancer, while laboratory markers reflecting systemic inflammation, coagulation function, and nutritional status [22-25] have also been shown to be significantly associated with the prognosis of various solid tumors; however, their predictive value for postoperative intravesical recurrence in stage T2 MIBC remains unclear. Furthermore, there is currently a lack of systematic comparative analysis to determine whether differences between NMIBC and MIBC in tumor biology and host response can provide insights for assessing the risk of intravesical recurrence in MIBC.

In light of this, this study conducted a retrospective analysis of clinical data from 831 patients with bladder cancer to systematically compare the clinical characteristics of NMIBC and MIBC. The study focused specifically on 239 patients with stage T2

MIBC who underwent initial TURBT; these patients were deemed unsuitable for radical cystectomy due to advanced age, severe cardiopulmonary insufficiency, or other comorbidities, or had refused radical surgery. Univariate and multivariate Cox proportional hazards models were used to identify independent risk factors for postoperative intravesical recurrence. Based on these findings, a multivariate predictive model for intravesical recurrence risk (bar chart) was developed, integrating tumor pathological characteristics with host inflammation and red blood cell levels. This model aims to provide clinicians with a practical tool for quantitatively assessing the risk of postoperative intravesical recurrence in patients with stage T2 MIBC, thereby facilitating personalized clinical management and ultimately improving patient prognosis. It should be emphasized that the findings of this study cannot be generalized to patients who undergo standard radical cystectomy or triple-modality therapy.

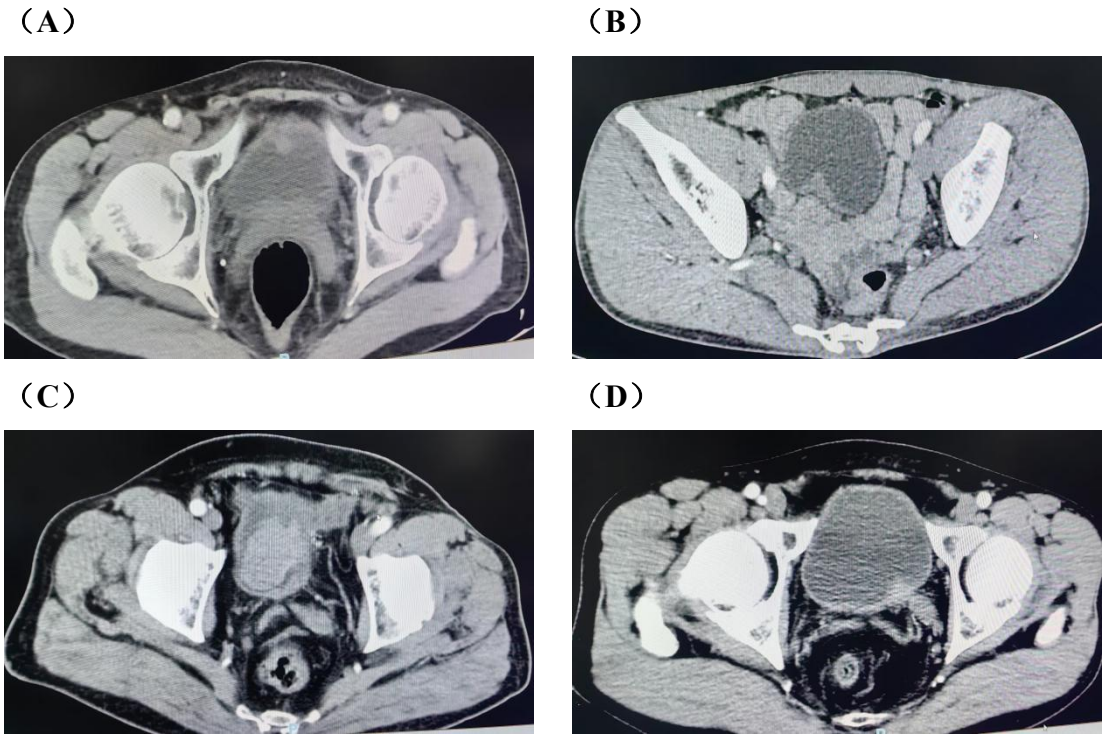


Figure 1: Non-muscle-invasive bladder cancer (A, B) and muscle-invasive bladder cancer (C, D)

2. Materials and Methods

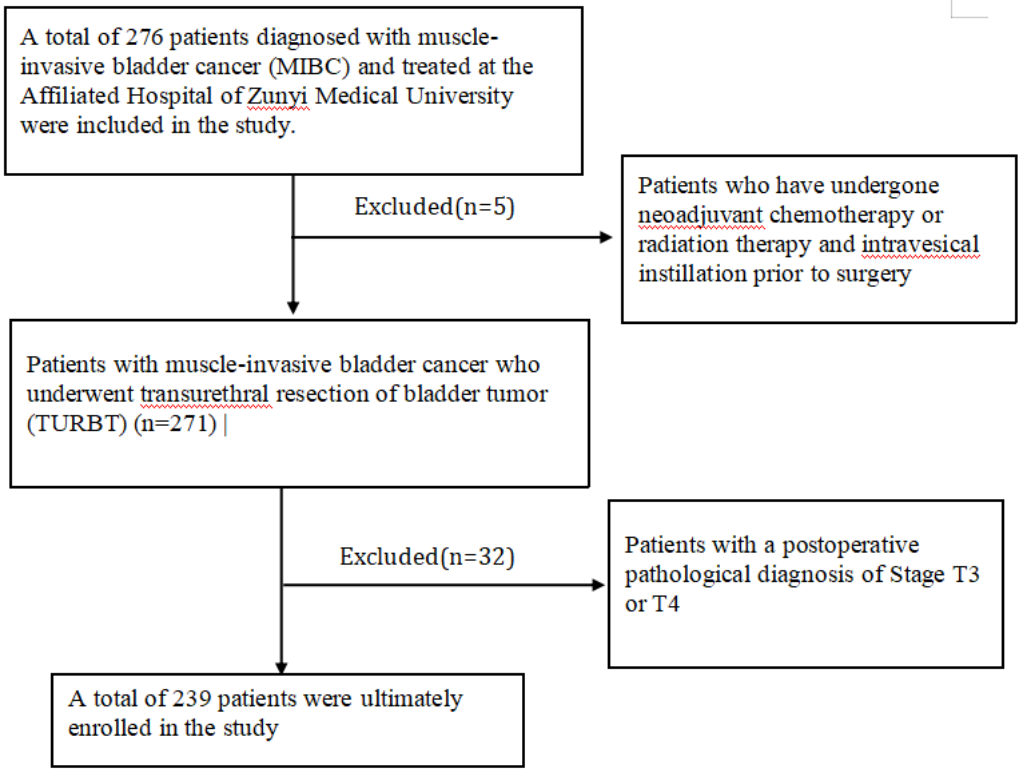
2.1 Study Design and Study Population

This study is a single-center, retrospective cohort study approved by the Medical Ethics Committee of the Affiliated Hospital of Zunyi Medical University (Approval No.: KLLY-2025-054) and complies with the relevant ethical requirements of the Declaration of Helsinki. As this is a retrospective observational study that collects only existing clinical data and does not involve any additional interventions, the Ethics Committee granted an exemption from informed consent.

This study collected clinical data from bladder cancer patients treated at the Affiliated Hospital of Zunyi Medical University from January 2013 to December 2024. A total of 831 bladder cancer patients were initially enrolled and classified according to postoperative pathological staging into the non-muscle-invasive bladder cancer group (NMIBC group, n = 592, 71.24%) and the muscle-invasive bladder cancer group (MIBC group, n = 239, 28.76%). Within the MIBC group, the analysis focused on the 239 patients with stage T2 bladder cancer who underwent their first TURBT procedure.

The inclusion criteria for patients with stage T2 disease were: (1) postoperative pathological confirmation of stage T2 bladder urothelial carcinoma; (2) undergoing initial TURBT treatment; (3) ineligible for radical cystectomy due to advanced age (≥75 years), severe cardiopulmonary insufficiency, or other comorbidities, or refusal of radical surgery by the patient; (4) complete clinical data; (5) follow-up duration of ≥3 months. Exclusion criteria were: (1) history of previous surgery for bladder cancer; (2) history of other malignant tumors; (3) preoperative neoadjuvant chemotherapy or radiation therapy; (4) incomplete follow-up data. The case selection flowchart is shown in Figure 2.

It should be noted that this study did not include the following important clinical variables: TURBT integrity (whether en bloc resection was achieved), repeat TURBT procedures, residual muscle-invasive disease, T2a/T2b substaging, coexisting carcinoma in situ (CIS), lymphovascular invasion (LVI), variant histological subtypes, hydronephrosis, and clinical lymph node status. The absence of these variables constitutes a significant limitation of this study and may, to some extent, affect the predictive accuracy of the model.



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Figure 2: Case Screening Flowchart

2.2 Data Collection

The data collected falls into three major categories: ① General information: age, sex, smoking history, and history of diabetes and hypertension; ② Clinical and pathological characteristics: number of tumors, size, location, growth pattern, types of intravesical chemotherapy drugs (camptothecin, epirubicin), frequency and duration of instillations, pathological stage, and histological grade; ③ Laboratory test results: Peripheral blood parameters from 1 week before surgery (blood glucose, creatinine, uric acid, albumin, globulin, total protein, A/G ratio, platelets, hemoglobin, red blood cell distribution width, prothrombin time, activated partial thromboplastin time, etc.) and urine parameters from 1 week before surgery (urinary white blood cells, occult blood, nitrites, etc.).

2.3 Follow-up and Definition of Outcomes

Follow-up is conducted through the outpatient medical record system or by telephone. Follow-up protocol: Cystoscopy is performed once every 3 months for the

first 2 years postoperatively; once every 6 months starting in the third year; and once a year starting in the fifth year postoperatively. Follow-up includes bladder instillation, cystoscopy, abdominal ultrasound, and CT/MRI scans to assess for intravesical tumor recurrence. The follow-up period ends on December 31, 2024.

Criteria for recurrence: (1) Detection of a new intravesical neoplasm by cystoscopy, confirmed by pathological biopsy; (2) CT/MRI findings indicating a new intravesical tumor lesion, or a suspicious intravesical lesion confirmed by pathological biopsy. Recurrence-free survival (RFS) is defined as the time from the date of TURBT surgery to the first intravesical tumor recurrence. For patients without recurrence, RFS is defined as the time from the date of surgery to the time of the last follow-up or death. As this study cohort consists primarily of elderly patients, death is a potential competing event for intravesical recurrence. In the current analysis, patients who died were censored, and death was not treated as a competing event; this may introduce bias in the recurrence estimates.

2.4 Sample Size Calculation

According to previous literature reports, the intravesical recurrence rate at 2 years following TURBT in patients with stage T2 MIBC is approximately 30%–40%. This study ultimately included 5 predictive variables; based on the principle that each variable requires at least 10–15 endpoint events (Events Per Variable, EPV), it was estimated that at least 50–75 intravesical recurrence events would be needed. Based on an estimated intravesical recurrence rate of 30%, the required sample size was calculated to be 167–250 cases. This study ultimately enrolled 239 patients, of whom 72 experienced intravesical recurrence, resulting in an EPV of 14.4, which met the statistical requirements.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS 26.0 and R 4.2.0 software. Continuous variables were expressed as the median (interquartile range) based on the results of normality tests, and comparisons between groups were performed using the Mann-Whitney U test; categorical variables were expressed as frequencies (percentages), and comparisons between groups were performed using the chi-square

test or Fisher's exact test. Survival curves were plotted using the Kaplan-Meier method, and the Log-rank test was used to compare differences in recurrence-free survival rates among different groups. A univariate Cox proportional hazards model was used to screen for potential risk factors. Variables with $P < 0.10$ in the univariate analysis were included in a multivariate Cox regression analysis to identify independent risk factors for recurrence, and the hazard ratio (HR) and its 95% confidence interval (CI) were calculated. A predictive model was constructed based on the results of the multivariate Cox regression analysis, and a contour plot was created to facilitate clinical application. Time-dependent receiver operating characteristic (ROC) curves and the C-index were used to evaluate the model's discriminatory power, while calibration curves were used to assess the model's calibration. Decision curve analysis (DCA) was used to evaluate the model's clinical utility. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant.

3. Results

3.1 Comparative Analysis of Non-Muscle-Invasive and Muscle-Invasive Bladder Cancer

Among the 831 bladder cancer patients, 592 were in the NMIBC group and 239 in the MIBC group. Significant differences ($P < 0.05$) were observed between the two groups across 20 clinical indicators, covering demographic characteristics, tumor characteristics, laboratory indicators related to immunity, nutrition, and coagulation, and urine test results. However, no statistically significant differences ($P > 0.05$) were found for indicators such as gender, diabetes, number of tumors, and bladder instillation drugs. See Table 1 for specific results.

Table 1 General Clinical Characteristics of Non-Muscle-Invasive and Muscle-Invasive Bladder Cancer

Variables	Total (n = 831)	Non-muscle-invasive bladder cancer (n = 592)	Muscle-invasive bladder cancer (n = 239)	Statistic	*P*

Variables	Total (n = 831)	Non-muscle-invasive bladder cancer (n = 592)	Muscle-invasive bladder cancer (n = 239)	Statistic	*P*
White blood cell count, M (Q_1, Q_3)	5.93 (4.87, 7.17)	5.94 (4.90, 7.13)	5.93 (4.80, 7.32)	Z=-0.05	0.957
Absolute neutrophil count M (Q_1, Q_3)	3.54 (2.76, 4.51)	3.54 (2.80, 4.46)	3.54 (2.69, 4.75)	Z=-0.30	0.763
Absolute lymphocyte count, M (Q_1, Q_3)	1.53 (1.22, 1.96)	1.57 (1.25, 1.98)	1.47 (1.16, 1.88)	Z=-2.63	**0.009**
Absolute monocyte count, M (Q_1, Q_3)	0.47 (0.37, 0.61)	0.46 (0.36, 0.59)	0.49 (0.40, 0.64)	Z=-2.91	**0.004**
Red blood cell count, M (Q_1, Q_3)	4.35 (3.93, 4.71)	4.39 (4.01, 4.76)	4.16 (3.75, 4.57)	Z=-4.76	**<.001**
Platelet count, M (Q_1, Q_3)	190.00 (157.00, 226.00)	191.50 (157.75, 226.00)	188.00 (154.00, 226.00)	Z=-0.82	0.413
Hemoglobin, M (Q_1, Q_3)	133.00 (120.00, 145.00)	135.00 (122.00, 146.00)	129.00 (114.50, 140.00)	Z=-4.37	**<.001**
Red blood cell distribution width, M (Q_1, Q_3)	13.20 (12.70, 13.90)	13.20 (12.60, 13.90)	13.20 (12.80, 13.90)	Z=-1.25	0.212
Activated partial thromboplastin time, M (Q_1, Q_3)	27.40 (25.30, 32.30)	27.50 (25.10, 32.30)	27.20 (25.50, 32.60)	Z=-0.53	0.595
Fibrinogen, M (Q_1, Q_3)	2.82 (2.34, 3.41)	2.78 (2.31, 3.31)	2.94 (2.41, 3.51)	Z=-2.53	**0.011**
Thrombin time(TT), M (Q_1, Q_3)	18.60 (17.30, 20.60)	18.60 (17.30, 20.60)	18.30 (17.10, 20.60)	Z=-1.20	0.232
AST/ALT, M (Q_1, Q_3)	1.31 (1.00, 1.68)	1.29 (1.00, 1.64)	1.36 (1.03, 1.79)	Z=-2.08	**0.037**
Blood glucose, M (Q_1, Q_3)	4.88 (4.44, 5.54)	4.87 (4.42, 5.58)	4.95 (4.47, 5.53)	Z=-0.87	0.382
Total protein, M (Q_1, Q_3)	64.70 (60.30, 68.90)	65.30 (60.80, 69.10)	63.50 (58.75, 67.65)	Z=-3.52	**<.001**
Albumin, M (Q_1, Q_3)	39.00 (36.40,	39.40 (37.10, 42.20)	37.90 (35.00, 40.55)	Z=-5.57	**<.001**

Variables	Total (n = 831)	Non-muscle-invasive bladder cancer (n = 592)	Muscle-invasive bladder cancer (n = 239)	Statistic	*P*
	41.80)				
Globulin, M (Q_1, Q_3)	25.10 (22.75, 28.35)	25.25 (22.80, 28.30)	24.90 (22.65, 28.65)	Z=-0.24	0.807
A/G, M (Q_1, Q_3)	1.54 (1.37, 1.73)	1.57 (1.40, 1.75)	1.50 (1.31, 1.71)	Z=-2.92	**0.003**
Creatinine, M (Q_1, Q_3)	81.00 (71.00, 93.00)	81.00 (72.00, 92.00)	82.00 (70.50, 97.50)	Z=-1.05	0.293
Uric acid, M (Q_1, Q_3)	340.00 (290.00, 400.00)	339.50 (288.75, 398.00)	341.00 (293.50, 407.56)	Z=-1.01	0.314
Recurrence time (months), M (Q_1, Q_3)	44.00 (18.00, 79.00)	46.00 (21.00, 79.00)	38.00 (14.00, 79.00)	Z=-1.50	0.135
Gender, n(%)				χ^2=0.18	0.673
Female	157 (18.89)	114 (19.26)	43 (17.99)		
Male	674 (81.11)	478 (80.74)	196 (82.01)		
Age, n(%)				χ^2=25.39	**<.001**
＜60 years	251 (30.20)	209 (35.30)	42 (17.57)		
⩾60 years	580 (69.80)	383 (64.70)	197 (82.43)		
Smoking history, n(%)				χ^2=9.86	**0.002**
No	567 (68.23)	423 (71.45)	144 (60.25)		
Yes	264 (31.77)	169 (28.55)	95 (39.75)		
Hypertension, n(%)				χ^2=5.04	**0.025**
No	592 (71.24)	435 (73.48)	157 (65.69)		
Yes	239 (28.76)	157 (26.52)	82 (34.31)		
Diabetes mellitus, n(%)				χ^2=0.25	0.620
No	744 (89.53)	532 (89.86)	212 (88.70)		
Yes	87 (10.47)	60 (10.14)	27 (11.30)		
Number of tumors on cystoscopy, n(%)				χ^2=0.00	0.978
Solitary tumor	397 (47.77)	283 (47.80)	114 (47.70)		

Variables	Total (n = 831)	Non-muscle-invasive bladder cancer (n = 592)	Muscle-invasive bladder cancer (n = 239)	Statistic	*P*
Common tumors	434 (52.23)	309 (52.20)	125 (52.30)		
Tumor size as observed during cystoscopy, n(%)				χ^2=46.06	**<.001**
＜3cm	612 (73.65)	475 (80.24)	137 (57.32)		
⩾3cm	219 (26.35)	117 (19.76)	102 (42.68)		
Anterior wall, n(%)				χ^2=5.91	**0.015**
No	755 (90.85)	547 (92.40)	208 (87.03)		
Yes	76 (9.15)	45 (7.60)	31 (12.97)		
Posterior lateral wall, n(%)				χ^2=0.21	0.646
No	621 (74.73)	445 (75.17)	176 (73.64)		
Yes	210 (25.27)	147 (24.83)	63 (26.36)		
Left lateral wall, n(%)				χ^2=9.30	**0.002**
No	509 (61.25)	382 (64.53)	127 (53.14)		
Yes	322 (38.75)	210 (35.47)	112 (46.86)		
Right lateral wall, n(%)				χ^2=5.03	**0.025**
No	495 (59.57)	367 (61.99)	128 (53.56)		
Yes	336 (40.43)	225 (38.01)	111 (46.44)		
Trigone, n(%)				χ^2=2.03	0.154
No	724 (87.12)	522 (88.18)	202 (84.52)		
Yes	107 (12.88)	70 (11.82)	37 (15.48)		
Bladder neck, n(%)				χ^2=0.48	0.488
No	740 (89.05)	530 (89.53)	210 (87.87)		
Yes	91 (10.95)	62 (10.47)	29 (12.13)		
Other locations, n(%)				χ^2=2.55	0.110
No	675 (81.23)	489 (82.60)	186 (77.82)		
Yes	156 (18.77)	103 (17.40)	53 (22.18)		
Intravesical instillation drugs, n(%)				χ^2=1.56	0.211
Hesperidin	562 (67.63)	408 (68.92)	154 (64.44)		
Doxorubicin	269 (32.37)	184 (31.08)	85 (35.56)		

Variables	Total (n = 831)	Non-muscle-invasive bladder cancer (n = 592)	Muscle-invasive bladder cancer (n = 239)	Statistic	*P*
Pathological grade, n(%)				χ^2=301.91	**<.001**
lower level	614 (73.89)	537 (90.71)	77 (32.22)		
High-level	217 (26.11)	55 (9.29)	162 (67.78)		
Urinary nitrite, n(%)				χ^2=0.09	0.770
Negative	731 (87.97)	522 (88.18)	209 (87.45)		
Positive	100 (12.03)	70 (11.82)	30 (12.55)		
Urinary leukocyte, n(%)				χ^2=37.89	**<.001**
Negative	379 (45.61)	310 (52.36)	69 (28.87)		
Positive	452 (54.39)	282 (47.64)	170 (71.13)		
Urinary occult blood, n(%)				χ^2=56.92	**<.001**
Negative	300 (36.10)	261 (44.09)	39 (16.32)		
Positive	531 (63.90)	331 (55.91)	200 (83.68)		
Tumor recurrence, n(%)				χ^2=2.63	0.105
No	613 (73.77)	446 (75.34)	167 (69.87)		
Yes	218 (26.23)	146 (24.66)	72 (30.13)		
Tumor growth pattern, n(%)				χ^2=20.05	**0.001**
Nipple-like	154 (19.30)	112 (20.04)	42 (17.57)		
Varieties of cauliflower	217 (27.19)	150 (26.83)	67 (28.03)		
Coral-like	86 (10.78)	67 (11.99)	19 (7.95)		
Carpet samples	44 (5.51)	25 (4.47)	19 (7.95)		
Aquatic plant-like	116 (14.54)	94 (16.82)	22 (9.21)		
Other types	181 (22.68)	111 (19.86)	70 (29.29)		

Note: Z value was calculated by Mann-Whitney U test; χ^2 value was calculated by Chi-square test. M = Median; Q_1 = 1st Quartile; Q_3 = 3rd Quartile.

3.1.1 Differences in Demographic Characteristics

A comparative analysis revealed significant differences in demographic characteristics between the NMIBC and MIBC groups. The proportion of patients

aged ≥60 years was significantly higher in the MIBC group than in the NMIBC group ($P < 0.001$), suggesting that advancing age is associated with an increased risk of muscle-invasive bladder cancer, which is consistent with the findings of previous studies [26]. In addition, the proportion of patients with a history of smoking was significantly higher in the MIBC group than in the NMIBC group (39.75% vs. 28.55%, $P = 0.002$), and the proportion with a history of hypertension was also higher (34.31% vs. 26.52%, $P = 0.025$). These factors may promote tumor invasion and metastasis by contributing to chronic inflammation and alterations in the microenvironment.

3.1.2 Differences in Tumor Characteristics

In terms of tumor characteristics, there were highly significant differences between the two groups. The proportion of patients with tumor sizes ≥3 cm was significantly higher in the MIBC group than in the NMIBC group (42.68% vs. 19.76%, $P < 0.001$). More importantly, the proportion of patients with high-grade histological classification was as high as 67.78% in the MIBC group, compared with only 9.29% in the NMIBC group; this difference was extremely statistically significant ($P < 0.001$), directly reflecting the greater biological aggressiveness of MIBC.

3.1.3 Differences in Laboratory Indicators

A comparative analysis of laboratory parameters revealed significant differences between the two patient groups in terms of immune status, nutritional status, and coagulation function: (1) Immune parameters: The absolute lymphocyte count in the MIBC group was significantly lower than that in the NMIBC group (1.47 vs. 1.57, $P = 0.009$), while the absolute monocyte count was significantly higher than that in the NMIBC group (0.49 vs. 0.46, $P = 0.004$), suggesting an immunosuppressed state in MIBC patients [27]; (2) Nutritional status indicators: The MIBC group had significantly lower levels of red blood cells, hemoglobin, albumin, total protein, and the A/G ratio compared to the NMIBC group ($P < 0.05$), suggesting that MIBC patients are more likely to experience malnutrition and a state of chronic wasting; (3) Coagulation function indicators: Fibrinogen levels in the MIBC group were significantly higher than those in the NMIBC group (2.94 vs. 2.78, $P = 0.011$),

suggesting a hypercoagulable state in MIBC patients; (4) Liver function indicators: The AST/ALT ratio in the MIBC group was significantly higher than that in the NMIBC group (1.36 vs. 1.29, P = 0.037), suggesting that MIBC patients may have abnormal liver metabolism.

3.1.4 Differences in Urinalysis

In the MIBC group, the prevalence of leukocytes in urine (71.13% vs. 47.64%) and the prevalence of occult blood in urine (83.68% vs. 55.91%) were both significantly higher than in the NMIBC group (P < 0.001), which may be related to the larger tumor volume in MIBC and its tendency to invade surrounding tissues and blood vessels.

3.1.5 Analysis of Time to Recurrence

The median time to recurrence was 46 months (21.00–79.00) in the NMIBC group and 38 months (14.50–81.00) in the MIBC group; the difference between the two groups was not statistically significant (Z = −1.50, P = 0.135).

3.2 Baseline Characteristics of Patients with Stage T2 Bladder Cancer

Among the 239 patients in the MIBC group, 72 (30.13%) were in the recurrence group and 167 (69.87%) were in the non-recurrence group. The median age of the patients was 72 years (range: 64–76 years), and 196 (82.01%) were male.

The median follow-up duration was 41.0 months (interquartile range: 14.5–81.0 months; range: 1.0–143.0 months). The median time to recurrence in the recurrence group was 12.0 months, while the median follow-up duration in the non-recurrence group was 66.0 months; the difference between the two groups was statistically significant (P < 0.001).

There were no statistically significant differences between the two groups in terms of age, sex, smoking history, blood type, hypertension, diabetes, tumor location, type of intravesical instillation drug (with yohimbine as the reference; epirubicin: HR = 1.08, 95% CI: 0.59–1.98, P = 0.812), urinalysis results, or other laboratory indicators (P > 0.05). See Table 2 for details.

Table 2 General Clinical Characteristics of Patients with Stage T2 Bladder Cancer

Variables	Total (n = 239)	Non-relapse group (n = 167)	Relapse group(n = 72)	Statistic	*P*
Age, M (Q_1, Q_3)	71.00 (63.50, 76.00)	72.00 (64.50, 77.00)	68.00 (63.00, 75.00)	Z=-1.70	0.089
White blood cell count, M (Q_1, Q_3)	5.93 (4.80, 7.32)	5.85 (4.89, 7.32)	6.12 (4.74, 7.36)	Z=-0.42	0.674
Absolute neutrophil count M (Q_1, Q_3)	3.54 (2.69, 4.75)	3.52 (2.58, 4.49)	3.67 (2.89, 5.07)	Z=-1.59	0.112
Absolute lymphocyte count, M (Q_1, Q_3)	1.47 (1.16, 1.88)	1.43 (1.15, 1.84)	1.48 (1.18, 1.90)	Z=-0.34	0.737
Absolute monocyte count, M (Q_1, Q_3)	0.49 (0.40, 0.64)	0.49 (0.40, 0.64)	0.48 (0.38, 0.64)	Z=-0.01	0.993
Red blood cell count, M (Q_1, Q_3)	4.16 (3.75, 4.57)	4.12 (3.69, 4.49)	4.28 (3.87, 4.68)	Z=-1.52	0.130
Platelet count, M (Q_1, Q_3)	188.00 (154.00, 226.00)	189.00 (155.00, 230.00)	186.50 (148.50, 212.75)	Z=-0.92	0.358
Hemoglobin, M (Q_1, Q_3)	129.00 (114.50, 140.00)	128.00 (113.00, 139.90)	130.50 (115.00, 140.25)	Z=-0.90	0.368
Red blood cell distribution width, M (Q_1, Q_3)	13.20 (12.80, 13.90)	13.30 (12.90, 13.90)	13.20 (12.70, 13.93)	Z=-0.54	0.590
Activated partial thromboplastin time, M (Q_1, Q_3)	27.20 (25.50, 32.60)	27.20 (25.60, 32.60)	27.35 (25.28, 32.47)	Z=-0.20	0.843
Fibrinogen, M (Q_1, Q_3)	2.94 (2.41, 3.51)	2.97 (2.41, 3.62)	2.75 (2.41, 3.31)	Z=-1.72	0.085
Thrombin time(TT), M (Q_1, Q_3)	18.30 (17.10, 20.60)	18.10 (16.90, 20.03)	19.30 (17.38, 21.33)	Z=-2.17	**0.030**
AST/ALT, M (Q_1, Q_3)	1.36 (1.03, 1.79)	1.36 (1.03, 1.81)	1.36 (1.04, 1.71)	Z=-0.57	0.571
Blood glucose, M (Q_1, Q_3)	4.95 (4.47, 5.53)	5.04 (4.50, 5.78)	4.85 (4.36, 5.33)	Z=-2.25	**0.024**
Total protein, M (Q_1, Q_3)	63.50 (58.75, 67.65)	62.90 (57.80, 67.80)	64.25 (60.77, 67.60)	Z=-1.27	0.204
Albumin, M (Q_1, Q_3)	37.90 (35.00, 40.55)	37.70 (34.65, 40.45)	38.20 (35.60, 40.92)	Z=-0.98	0.326
Globulin, M (Q_1, Q_3)	24.90 (22.65,	24.70 (22.25,	25.35 (23.00,	Z=-0.56	0.575

Variables	Total (n = 239)	Non-relapse group (n = 167)	Relapse group(n = 72)	Statistic	*P*
	28.65)	28.65)	28.70)		
A/G, M (Q_1, Q_3)	1.50 (1.31, 1.71)	1.50 (1.30, 1.71)	1.50 (1.32, 1.70)	Z=-0.27	0.785
Creatinine, M (Q_1, Q_3)	82.00 (70.50, 97.50)	81.00 (68.00, 98.50)	83.00 (75.75, 93.75)	Z=-1.28	0.201
Uric acid, M (Q_1, Q_3)	341.00 (293.50, 407.56)	343.00 (302.00, 415.50)	333.50 (281.00, 397.50)	Z=-0.81	0.419
Gender, n(%)				χ^2=0.12	0.726
Female	43 (17.99)	31 (18.56)	12 (16.67)		
Male	196 (82.01)	136 (81.44)	60 (83.33)		
Smoking history, n(%)				χ^2=0.03	0.858
No	144 (60.25)	100 (59.88)	44 (61.11)		
Yes	95 (39.75)	67 (40.12)	28 (38.89)		
Hypertension, n(%)				χ^2=1.21	0.271
No	157 (65.69)	106 (63.47)	51 (70.83)		
Yes	82 (34.31)	61 (36.53)	21 (29.17)		
Diabetes mellitus, n(%)				χ^2=1.95	0.163
No	212 (88.70)	145 (86.83)	67 (93.06)		
Yes	27 (11.30)	22 (13.17)	5 (6.94)		
Number of tumors on cystoscopy, n(%)				χ^2=32.97	**<.001**
Solitary tumor	114 (47.70)	100 (59.88)	14 (19.44)		
Common tumors	125 (52.30)	67 (40.12)	58 (80.56)		
Tumor size as observed during cystoscopy, n(%)				χ^2=33.39	**<.001**
＜3cm	137 (57.32)	116 (69.46)	21 (29.17)		
⩾3cm	102 (42.68)	51 (30.54)	51 (70.83)		
Anterior wall, n(%)				χ^2=0.08	0.781
No	208 (87.03)	146 (87.43)	62 (86.11)		
Yes	31 (12.97)	21 (12.57)	10 (13.89)		
Posterior lateral wall, n(%)				χ^2=0.42	0.518
No	176 (73.64)	125 (74.85)	51 (70.83)		
Yes	63 (26.36)	42 (25.15)	21 (29.17)		
Left lateral wall, n(%)				χ^2=0.41	0.523
No	127 (53.14)	91 (54.49)	36 (50.00)		
Yes	112 (46.86)	76 (45.51)	36 (50.00)		

Variables	Total (n = 239)	Non-relapse group (n = 167)	Relapse group(n = 72)	Statistic	*P*
Right lateral wall, n(%)				χ^2=1.66	0.197
No	128 (53.56)	94 (56.29)	34 (47.22)		
Yes	111 (46.44)	73 (43.71)	38 (52.78)		
Trigone, n(%)				χ^2=0.00	0.954
No	202 (84.52)	141 (84.43)	61 (84.72)		
Yes	37 (15.48)	26 (15.57)	11 (15.28)		
Bladder neck, n(%)				χ^2=0.30	0.585
No	210 (87.87)	148 (88.62)	62 (86.11)		
Yes	29 (12.13)	19 (11.38)	10 (13.89)		
Other locations, n(%)				χ^2=0.12	0.726
No	186 (77.82)	131 (78.44)	55 (76.39)		
Yes	53 (22.18)	36 (21.56)	17 (23.61)		
Intravesical instillation drugs, n(%)				χ^2=1.13	0.288
Hesperidin	154 (64.44)	104 (62.28)	50 (69.44)		
Doxorubicin	85 (35.56)	63 (37.72)	22 (30.56)		
Pathological grade, n(%)				χ^2=11.41	**<.001**
lower level	77 (32.22)	65 (38.92)	12 (16.67)		
High-level	162 (67.78)	102 (61.08)	60 (83.33)		
Urinary nitrite, n(%)				χ^2=0.17	0.682
Negative	209 (87.45)	147 (88.02)	62 (86.11)		
Positive	30 (12.55)	20 (11.98)	10 (13.89)		
Urinary leukocyte, n(%)				χ^2=0.31	0.578
Negative	69 (28.87)	50 (29.94)	19 (26.39)		
Positive	170 (71.13)	117 (70.06)	53 (73.61)		
Urinary occult blood, n(%)				χ^2=0.01	0.924
Negative	39 (16.32)	27 (16.17)	12 (16.67)		
Positive	200 (83.68)	140 (83.83)	60 (83.33)		
Tumor growth pattern, n(%)				χ^2=6.64	0.248
Nipple-like	42 (17.57)	33 (19.76)	9 (12.50)		
Varieties of cauliflower	67 (28.03)	48 (28.74)	19 (26.39)		
Coral-like	19 (7.95)	14 (8.38)	5 (6.94)		
Carpet samples	19 (7.95)	9 (5.39)	10 (13.89)		
Aquatic plant-like	22 (9.21)	16 (9.58)	6 (8.33)		

Variables	Total (n = 239)	Non-relapse group (n = 167)	Relapse group(n = 72)	Statistic	*P*
Other types	70 (29.29)	47 (28.14)	23 (31.94)		

Note: Z value was calculated by Mann-Whitney U test; χ^2 value was calculated by Chi-square test. M = Median; Q_1 = 1st Quartile; Q_3 = 3rd Quartile.

3.3 Univariate Cox Regression Analysis of Postoperative Recurrence in Patients with Stage T2 MIBC Following TURBT

Analysis using a univariate Cox proportional hazards model revealed that factors significantly associated with recurrence following the first TURBT procedure in patients with stage T2 MIBC included (all $P < 0.05$): number of tumors, tumor size, histological grade, absolute neutrophil count, white blood cell count, and red blood cell count. Detailed results are shown in Table 3.

Age, sex, smoking history, blood type, hypertension, diabetes, tumor location, intravesical chemotherapy, pathological stage, and other laboratory and urine parameters were not significantly associated with postoperative recurrence (all $P > 0.05$).

Table 3: Results of the univariate Cox proportional hazards model for postoperative recurrence in patients with stage T2 MIBC following TURBT

Variables	β	S.E	Z	*P*	HR (95%CI)
Gender, n(%)					
Female					1.00 (Reference)
Male	-0.01	0.37	-0.03	0.980	0.99 (0.48 ~ 2.04)
Smoking history, n(%)					
No					1.00 (Reference)
Yes	-0.13	0.29	-0.44	0.663	0.88 (0.50 ~ 1.56)
Hypertension, n(%)					
No					1.00 (Reference)
Yes	0.05	0.30	0.16	0.875	1.05 (0.58 ~ 1.89)
Diabetes mellitus, n(%)					
No					1.00 (Reference)
Yes	-0.81	0.60	-1.36	0.174	0.45 (0.14 ~ 1.43)
Number of tumors on cystoscopy, n(%)					

Variables	β	S.E	Z	*P*	HR (95%CI)
Solitary tumor					1.00 (Reference)
Common tumors	1.62	0.35	4.57	**<.001**	5.04 (2.52 ~ 10.09)
Tumor size as observed during cystoscopy, n(%)					
＜3cm					1.00 (Reference)
⩾3cm	1.34	0.31	4.33	**<.001**	3.80 (2.08 ~ 6.97)
Anterior wall, n(%)					
No					1.00 (Reference)
Yes	-0.79	0.60	-1.33	0.183	0.45 (0.14 ~ 1.45)
Posterior lateral wall, n(%)					
No					1.00 (Reference)
Yes	-0.20	0.34	-0.58	0.559	0.82 (0.42 ~ 1.60)
Left lateral wall, n(%)					
No					1.00 (Reference)
Yes	0.17	0.28	0.60	0.550	1.18 (0.68 ~ 2.05)
Right lateral wall, n(%)					
No					1.00 (Reference)
Yes	0.28	0.28	1.00	0.315	1.32 (0.77 ~ 2.29)
Trigone, n(%)					
No					1.00 (Reference)
Yes	0.08	0.41	0.19	0.847	1.08 (0.49 ~ 2.40)
Bladder neck, n(%)					
No					1.00 (Reference)
Yes	0.51	0.41	1.26	0.209	1.67 (0.75 ~ 3.70)
Other locations, n(%)					
No					1.00 (Reference)
Yes	0.45	0.31	1.46	0.144	1.57 (0.86 ~ 2.87)
Intravesical instillation drugs, n(%)					
Hesperidin					1.00 (Reference)
Doxorubicin	0.07	0.31	0.24	0.812	1.08 (0.59 ~ 1.98)
Pathological grade, n(%)					
lower level					1.00 (Reference)
High-level	0.87	0.34	2.54	**0.011**	2.38 (1.22 ~ 4.65)
Urinary nitrite, n(%)					

Variables	β	S.E	Z	*P*	HR (95%CI)
Negative					1.00 (Reference)
Positive	0.11	0.41	0.27	0.787	1.12 (0.50 ~ 2.48)
Urinary leukocyte, n(%)					
Negative					1.00 (Reference)
Positive	0.34	0.32	1.04	0.296	1.40 (0.74 ~ 2.63)
Urinary occult blood, n(%)					
Negative					1.00 (Reference)
Positive	-0.20	0.37	-0.56	0.577	0.81 (0.40 ~ 1.67)
Age, M (Q_1, Q_3)	-0.01	0.01	-1.10	0.271	0.99 (0.97 ~ 1.01)
Tumor growth pattern, n(%)		0.07	0.83	0.409	1.06 (0.92 ~ 1.22)
White blood cell count, M (Q_1, Q_3)	0.09	0.04	2.14	**0.033**	1.09 (1.01 ~ 1.18)
Absolute neutrophil count M (Q_1, Q_3)	0.11	0.04	2.55	**0.011**	1.11 (1.03 ~ 1.21)
Absolute lymphocyte count, M (Q_1, Q_3)	0.22	0.19	1.17	0.243	1.25 (0.86 ~ 1.82)
Absolute monocyte count, M (Q_1, Q_3)	0.62	0.52	1.20	0.231	1.86 (0.67 ~ 5.14)
Red blood cell count, M (Q_1, Q_3)	0.35	0.19	1.81	0.070	1.42 (0.97 ~ 2.07)
Platelet count, M (Q_1, Q_3)	-0.00	0.00	-0.20	0.838	1.00 (1.00 ~ 1.00)
Hemoglobin, M (Q_1, Q_3)	0.01	0.01	1.36	0.173	1.01 (1.00 ~ 1.02)
Red blood cell distribution width, M (Q_1, Q_3)	0.02	0.04	0.62	0.538	1.02 (0.95 ~ 1.10)
Activated partial thromboplastin time, M (Q_1, Q_3)	-0.02	0.03	-0.88	0.381	0.98 (0.93 ~ 1.03)
Fibrinogen, M (Q_1, Q_3)	-0.13	0.17	-0.78	0.435	0.88 (0.63 ~ 1.22)
Thrombin time(TT), M (Q_1, Q_3)	0.04	0.05	0.72	0.469	1.04 (0.94 ~ 1.16)
Blood glucose, M (Q_1, Q_3)	-0.19	0.13	-1.49	0.136	0.83 (0.65 ~ 1.06)
Total protein, M (Q_1, Q_3)	0.01	0.02	0.40	0.686	1.01 (0.97 ~ 1.04)
Albumin, M (Q_1, Q_3)	0.02	0.03	0.72	0.470	1.02 (0.97 ~ 1.08)
Globulin, M (Q_1, Q_3)	0.03	0.03	0.89	0.374	1.03 (0.97 ~ 1.09)
Creatinine, M (Q_1, Q_3)	-0.00	0.00	-0.53	0.594	1.00 (0.99 ~ 1.00)
Uric acid, M (Q_1, Q_3)	-0.00	0.00	-0.36	0.716	1.00 (1.00 ~ 1.00)

HR: Hazard Ratio, CI: Confidence Interval

3.4 Multivariate Cox Regression Analysis of Recurrence After TURBT in Patients with Stage T2 MIBC

Variables with P < 0.10 in the univariate analysis were included in the multivariate Cox regression analysis (including: number of tumors, tumor size, histological grade, absolute neutrophil count, white blood cell count, and red blood cell count), and the stepwise regression method was used to identify independent risk factors.

The multivariate analysis ultimately identified the following five factors as independent risk factors for recurrence after the first TURBT procedure for stage T2 bladder cancer (Table 4):

Table 4: Results of the multivariate Cox proportional hazards model for recurrence after TURBT in patients with stage T2 MIBC

Variables	β	S.E	Z	*P*	OR (95%CI)
Number of tumors on cystoscopy, n(%)					
Solitary tumor					1.00 (Reference)
Common tumors	1.28	0.37	3.46	**<.001**	3.59 (1.74 ~ 7.42)
Tumor size as observed during cystoscopy, n(%)					
＜3cm					1.00 (Reference)
⩾3cm	1.14	0.32	3.56	**<.001**	3.13 (1.67 ~ 5.87)
Pathological grade, n(%)					
lower level					1.00 (Reference)
High-level	0.85	0.35	2.40	**0.017**	2.34 (1.17 ~ 4.68)
White blood cell count, M (Q_1, Q_3)	-0.28	0.17	-1.65	0.099	0.76 (0.55 ~ 1.05)
Absolute neutrophil count M (Q_1, Q_3)	0.39	0.18	2.16	**0.031**	1.48 (1.04 ~ 2.11)
Red blood cell count, M (Q_1, Q_3)	0.63	0.23	2.74	**0.006**	1.87 (1.20 ~ 2.93)

HR: Hazards Ratio, CI: Confidence Interval

1. Number of tumors (multiple vs. single: HR = 3.59, 95% CI: 1.74–7.42, P < 0.001)

2. Tumor size (≥3 cm vs. <3 cm: HR = 3.13, 95% CI: 1.67–5.87, P < 0.001)

3. Pathological grade (high-grade vs. low-grade: HR = 2.34, 95% CI: 1.17–4.68, P = 0.017)

4. Absolute neutrophil count (continuous variable: HR = 1.48, 95% CI: 1.04–2.11,

P = 0.031)

5. Red blood cells (continuous variable: HR = 1.87, 95% CI: 1.20–2.93, P = 0.006)

Among these factors, the predictive value of tumor number was the most significant: the risk of intravesical recurrence for multiple tumors was 3.59 times higher than that for a single tumor. Red blood cells emerged as a new independent predictor; elevated levels were associated with an increased risk of intravesical recurrence, suggesting that the host's nutritional status and overall health have a significant impact on intravesical tumor recurrence. White blood cell count was significant in univariate analysis but did not emerge as an independent risk factor in multivariate analysis (HR = 0.76, 95% CI: 0.55–1.05, P = 0.099), suggesting that its predictive role may be masked by other variables. Table 4 also lists white blood cell count (P = 0.099); although it did not reach the conventional level of significance, it was included in the line plot and SHAP analysis to maintain model completeness.

3.5 Development and Validation of a Predictive Model for Postoperative Recurrence in Stage T2 MIBC

A line chart prediction model for intravesical recurrence following the first TURBT procedure in patients with stage T2 MIBC was constructed using the five significant variables identified through multivariate Cox regression analysis, along with white blood cell count. The model's discriminatory power, calibration, and clinical utility were evaluated using a multidimensional indicator system.

3.5.1 Construction of the Scorecard Model

The line chart integrates six indicators: number of tumors, tumor size, histological grade, absolute neutrophil count, and red blood cell and white blood cell counts. Each indicator is assigned a specific score based on its value; after summing these scores to obtain a total score, the probability of intravesical recurrence at 12, 24, and 36 months post-surgery can be directly determined: see Figure 3.

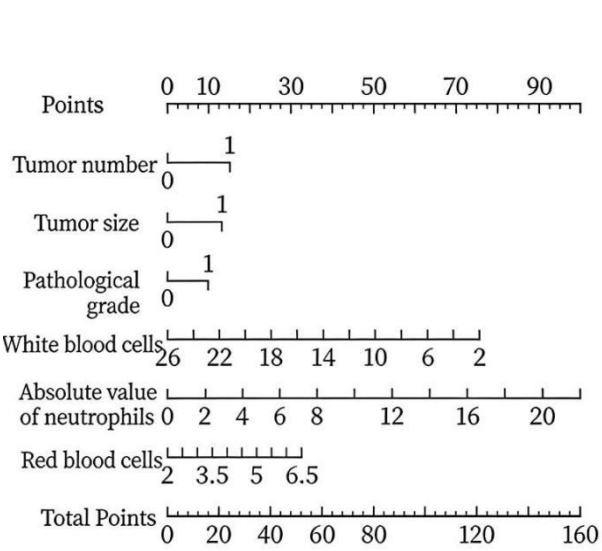


Figure 3: Line-graph model

Number of tumors: Single (0 points), Multiple (10 points)

Tumor size: <3 cm (0 points), ≥3 cm (9 points)

Pathological grade: Low grade (0 points), High grade (6 points)

Absolute neutrophil count: Scored 0–10 points based on actual value

White Blood Cell Count: Assign a score of 0–6 based on the actual value

Red blood cell count: Scored 0–8 points based on actual value

The total score ranges from 0 to 160; the higher the score, the higher the risk of intravesical recurrence. You can directly look up the probability of intravesical recurrence at 12, 24, and 36 months post-surgery.

3.5.2 Discrimination Assessment

To evaluate the discriminatory power of the Cox prognostic model, we plotted time-dependent ROC curves (Figure 4). In the training set, the model achieved high

AUC values at multiple time points (6 months, 12 months, 18 months, 24 months, 30 months, and 36 months), ranging from 0.77 to 0.95, demonstrating excellent predictive ability. Specifically, the AUC reached 0.95 at the 6-month time point; it declined slightly over time but remained consistently above 0.77. The AUC was approximately 0.85 at the 12-month time point, approximately 0.80 at the 24-month time point, and approximately 0.78 at the 36-month time point. ; In the validation set, the time-dependent ROC curves also demonstrated good predictive performance, with AUC values ranging from 0.62 to 0.93. Although the AUC values were slightly lower than those in the training set, the model's discriminative ability in the validation set remained within a good range, indicating that the model possesses a certain degree of generalization ability. To visually compare the predictive performance between the training set and the validation set, we overlaid the two time-dependent ROC curves. The results show that the C-index for the training set is 0.84, while that for the validation set is 0.73. The overall AUC for the training set is 0.80 (95% CI: 0.74–0.86), and the overall AUC for the validation set is 0.73 (95% CI: 0.62–0.84). The two curves show a good fit graphically, confirming the model's stability and reliability.

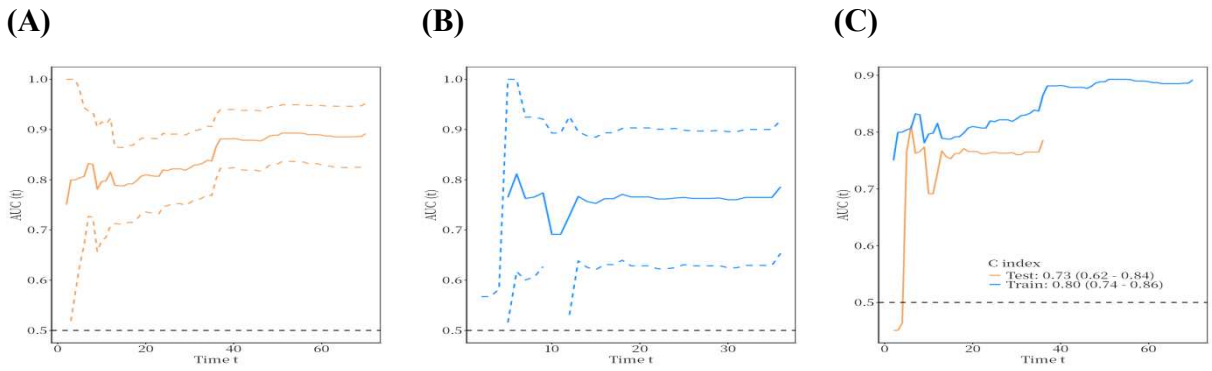


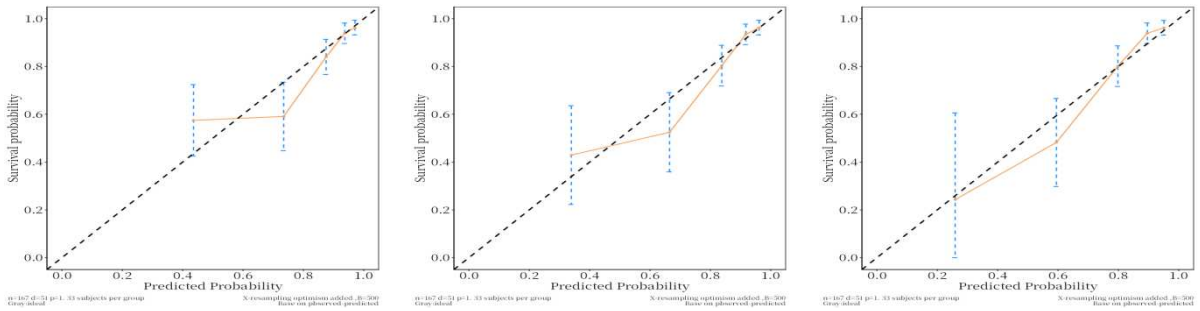
Figure 4: Time-dependent ROC curves: (A) Training set, (B) Validation set, (C) Overlay of ROC curves

3.5.3 Assessment of Calibration

Calibration curves are an important tool for evaluating the calibration of predictive models; by comparing the consistency between the model's predicted probabilities and the actual observed probabilities, they provide a visual representation of the

model's predictive accuracy. We plotted calibration curves for both the training set and the validation set at three key time points: 12 months, 24 months, and 36 months (Figure 5). Analysis of the training set calibration curve shows that, among n = 167 patients, d = 51 experienced intravesical recurrence events. The calibration curve closely follows the ideal diagonal line (the 45-degree line), indicating a high degree of consistency between the model's predicted probabilities and the actual probabilities of intravesical recurrence. The low Brier score (prediction error) suggests that the model has high predictive accuracy. At the 12-month time point, the calibration curve fit the ideal line almost perfectly; at the 24-month time point, the curve deviated slightly but remained within an acceptable range; at the 36-month time point, the calibration curve maintained a good fit, validating the model's reliability in medium- to long-term predictions. Analysis of the validation set calibration curve showed: n = 72 patients, including d = 21 intravesical recurrence events. The calibration curves for the validation set also closely followed the ideal diagonal line, with good calibration observed at all time points, indicating that the model maintained high predictive accuracy during internal validation. The results of the calibration curve analysis strongly demonstrate that the Cox prognostic model established in this study exhibits good calibration, and its predictions of individual risk of intravesical recurrence can be trusted.

(A) **(B)** **(C)**



(D) **(E)** **(F)**

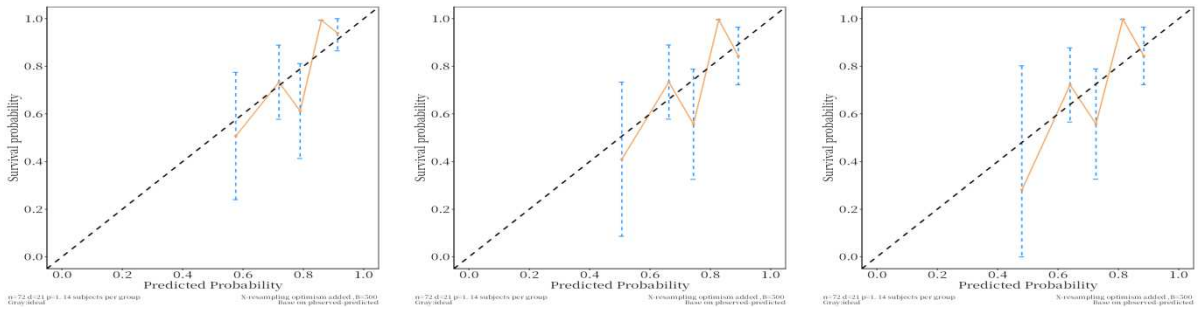


Figure 5: Calibration curves for the training sets at 12 months (A), 24 months (B), and 36 months (C), and for the validation sets at 12 months (D), 24 months (E), and 36 months (F). The blue curves represent the predicted curves, and the dashed lines represent the reference curves.

3.5.4 Assessment of Clinical Utility

Decision Curve Analysis (DCA) evaluates the practical value of a model in guiding clinical decision-making by calculating the clinical net benefit at different risk thresholds. The wider the range in which the model's curve lies above the "full intervention" and "no intervention" curves, the higher the net benefit, and the greater the clinical utility.

At 12 months, the training set model curve was significantly higher than the "full intervention" and "no intervention" curves across a wide range of risk thresholds from 0.2 to 0.8, with a maximum net benefit of approximately 0.22 occurring between thresholds of 0.4 and 0.6; The validation set model curve maintained a positive net benefit within the threshold range of 0.3–0.7 (Figures 6A and D); although slightly lower than that of the training set, it was significantly superior to traditional strategies. These results indicate that the first year postoperatively represents a critical window for clinical intervention. Model-based screening of high-risk patients for stratified management helps optimize the allocation of follow-up resources while avoiding overtreatment of low-risk patients. It should be noted that the DCA analysis evaluates the decision utility of the model at different thresholds and does not imply that model-guided interventions can reduce the rate of intravesical recurrence; clinical actions corresponding to specific risk thresholds have not yet been defined.

At 24 months, the effective threshold range for the training set narrowed to 0.25–0.75, the maximum net benefit decreased to approximately 0.18, and the net benefit in the high-threshold region (>0.75) turned negative; the effective threshold range for the validation set narrowed to 0.35–0.65 (Figures 6B and E), and the net benefit decreased overall. At this stage, individual heterogeneity in medium- to long-term recurrence risk increases, making it difficult for the model to precisely define intervention thresholds. Furthermore, the effectiveness of postoperative adjuvant therapy is no longer as significant as in the short term, leading to a reduction in clinical net benefit and rendering the model applicable only to patient decision-making within the medium threshold range.

At 36 months, the effective threshold range in the training set further narrowed to 0.3–0.7, with a maximum net benefit of only approximately 0.13; in the validation set, outside the threshold range of 0.4–0.6 (Figures 6C and F), the model curve fell below the “full intervention” curve, and the clinical net benefit was negative. In long-term follow-up, clinicians tend to opt for routine follow-up rather than intensive intervention; the model’s value as a decision-making guide is diminished, and the uncertainty surrounding the long-term risk of intravesical recurrence increases, making it difficult for model-based intervention strategies to achieve ideal clinical benefits and severely limiting their applicability.

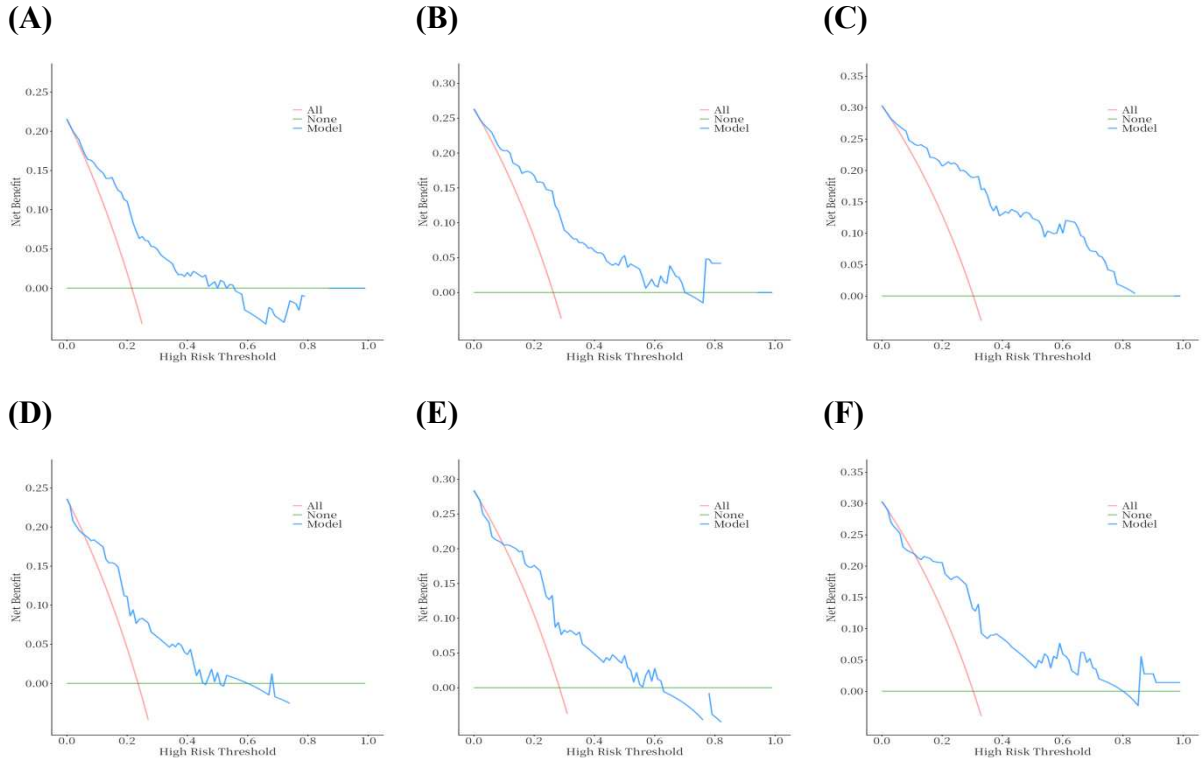


Figure 6: DCA curves for the training sets at 12 months (A), 24 months (B), and 36 months (C), and DCA calibration curves for the validation sets at 12 months (D), 24 months (E), and 36 months (F).

3.5.5 Model Interpretability Analysis

Based on a comprehensive evaluation of various indicators, the predictive model developed in this study demonstrated good stability and clinical utility in both the training and validation sets. Twelve months post-surgery is the optimal time point for applying the model, as it offers the strongest discriminatory power, the best calibration, and the highest clinical net benefit. At 24 months post-surgery, although the model still possesses some predictive value, it requires adjustment based on the patient's postoperative dynamic indicators. At 36 months post-surgery, the model's predictive performance declines significantly, and it is not recommended for use as a standalone tool for assessing the risk of intravesical recurrence.

3.5.6 Comprehensive Evaluation of Model Performance

Based on a comprehensive analysis of all indicators, the predictive model developed in this study demonstrated good stability and clinical utility in both the training and validation sets. Twelve months post-surgery was identified as the optimal time point for model application, as it exhibited the strongest discriminatory power, optimal calibration, and the highest clinical net benefit. Although the model still

possessed some predictive value at 24 months post-surgery, it required adjustment based on patients' postoperative dynamic indicators. By 36 months post-surgery, the model's predictive performance declines significantly, and it is not recommended for use as a standalone tool for assessing recurrence risk.

3.6 Association Between Intravesical Chemotherapy and Recurrence

All 239 patients received intravesical chemotherapy postoperatively; the drugs administered included hydroxycamptothecin (n=154, 64.4%) and epirubicin (n=85, 35.6%). There were 50 recurrences (32.5%) in the oxytetracycline group and 22 recurrences (25.9%) in the epirubicin group; the difference in recurrence rates between the two groups was not statistically significant (χ^2 = 1.13, P = 0.288). Univariate Cox regression analysis showed that, with hydroxycamptothecin as the reference, epirubicin was not significantly associated with the risk of intravesical recurrence (HR = 1.08, 95% CI: 0.59–1.98, P = 0.812). Due to the inclusion of only two drugs and the limited sample size, we were unable to further analyze the effects of perfusion frequency and treatment duration on intravesical recurrence.

4. Discussion

Through a systematic comparative analysis of 831 patients with bladder cancer, this study found significant differences between NMIBC and MIBC in terms of general clinical characteristics, laboratory parameters, tumor characteristics, and prognosis. An in-depth analysis of 239 patients with stage T2 bladder cancer identified the number of tumors in the bladder, tumor size, histological grade, preoperative absolute neutrophil count, and red blood cell count as independent risk factors for intravesical recurrence following the first TURBT procedure. The predictive model constructed based on these factors demonstrated good predictive performance and clinical utility.

4.1 Differences in Clinical Characteristics Between NMIBC and MIBC and Their Clinical Significance

This study confirms that there are fundamental differences in the clinical characteristics between NMIBC and MIBC [1], including 21 indicators such as general clinical characteristics, tumor characteristics, immunological parameters, nutritional status, coagulation parameters, and urinalysis results. These differences directly

reflect the distinct biological behaviors and host response states of the two tumor types and provide important guidance for the risk assessment and clinical management of MIBC. Regarding general clinical characteristics, the MIBC group had a significantly higher proportion of patients aged ≥60 years, with a history of smoking, and a history of hypertension. This suggests that these factors may promote tumor invasion into the muscularis layer by inducing chronic inflammation and altering the tumor microenvironment, which is consistent with previous findings on risk factors for bladder cancer [3,28,29]; Regarding tumor characteristics, the MIBC group had a significantly higher proportion of tumors ≥3 cm and high-grade histological classifications compared to the NMIBC group, directly reflecting the greater invasiveness and malignancy of MIBC [30]; Differences in laboratory test indicators revealed significant differences in the host status between the two patient groups: at the immunological level, the MIBC group exhibited reduced absolute lymphocyte counts and elevated absolute monocyte counts, suggesting a marked state of immunosuppression; the tumor may promote progression by inducing immune evasion and immune tolerance [31,32];In terms of nutrition, the MIBC group showed significantly lower levels of red blood cells, hemoglobin, albumin, and other indicators, reflecting a greater susceptibility to malnutrition and chronic wasting. Malnutrition further weakens the body's antitumor immune function [33], creating a vicious cycle. Regarding coagulation, the MIBC group had higher fibrinogen levels, suggesting a hypercoagulable state; fibrinogen can accelerate tumor invasion and metastasis through mechanisms such as constructing a scaffold for tumor cell migration and promoting angiogenesis [34]. Additionally, the MIBC group exhibited significantly higher rates of urinary leukocytes and positive urinary occult blood tests, which are associated with larger tumor volumes and a greater tendency to invade the blood vessels of surrounding tissues. There was no statistically significant difference in the median time to recurrence between the two groups; however, the MIBC group exhibited greater individual heterogeneity in time to recurrence. This may be related to the high biological heterogeneity of MIBC tumors [35] and also indicates that a one-size-fits-all follow-up strategy cannot be applied to MIBC patients; instead,

individualized risk stratification based on multiple indicators is required.

4.2 Analysis of Independent Risk Factors for Recurrence After TURBT in Patients with Stage T2 MIBC

Through univariate and multivariate Cox regression analyses, this study identified the number of intravesical tumors, tumor size, histological grade, absolute neutrophil count, and red blood cell count as independent risk factors for intravesical recurrence in patients with stage T2 MIBC following their first TURBT procedure. These factors collectively influence the risk of postoperative intravesical recurrence from two dimensions—tumor-specific characteristics and host inflammation and nutritional status—with each factor having distinct mechanisms of action and clinical significance. Tumor number, tumor size, and histological grade are all core tumor-specific characteristics. They are all positively correlated with the risk of postoperative intravesical recurrence in T2-stage patients and serve as strong predictors of intravesical recurrence, consistent with the findings of previous studies on bladder cancer prognosis [36,37]. The predictive value of tumor number was the most significant (HR = 3.59); multiple tumors imply multicentric origin, which facilitates the formation of micrometastatic foci and makes complete surgical resection difficult [21]. Pathological grade (HR = 2.34) remains an important predictor; high-grade tumors exhibit greater cellular atypia and stronger proliferative and invasive capabilities, making them more prone to surgical residual disease and micrometastases [38]. Tumor size ≥3 cm (HR = 3.13), as a comprehensive indicator of aggressiveness, provides an important reference for assessing tumor malignancy [39,40]; for every 1-unit increase in the absolute neutrophil count, the risk of intravesical recurrence increases by 48%, validating the “tumor-associated inflammation” theory, whereby neutrophils promote tumor progression and suppress antitumor immunity by secreting inflammatory factors [41]. It is worth noting that the red blood cell count (HR = 1.87), as a newly identified predictive factor, is associated with an increased risk of intravesical recurrence when elevated. The predictive mechanism of the red blood cell count remains unclear but may be related to a chronic inflammatory state or changes in the tumor microenvironment. This finding should be considered exploratory and

requires further validation in an independent cohort [42-44]. As a routine component of a complete blood count, the red blood cell count is easy to measure and inexpensive; its predictive value can provide primary care hospitals with a simple tool for assessing the risk of intravesical recurrence.

4.3 The Value of Building Predictive Models and Their Advantages in Clinical Applications

The column-line chart prediction model developed in this study was validated using time-dependent ROC curves, the C-index, calibration curves, and DCA analysis. It demonstrated good discriminatory power, calibration, and clinical utility in both the training and validation sets. The C-index for the training set reached 0.807 (95% CI: 0.74–0.85), while the C-index for the validation set was 0.72 (95% CI: 0.61–0.82), indicating that the model possesses good predictive ability and stability. It should be noted that the validation cohort was derived from the same institution, the same time period, and the same underlying dataset, representing internal random split validation rather than external validation. Before the model can be considered clinically applicable, external validation must be conducted at an independent institution. Compared with traditional evaluation methods, this model offers the following advantages: comprehensive coverage (integrating tumor characteristics and host factors), high practicality (all indicators are routine clinical tests), ease of use (visualization via line charts), and high clinical net benefit (DCA indicates positive net benefit across a wide range of thresholds) [45]. This model can accurately identify high-risk patients to guide aggressive intervention strategies, while avoiding overtreatment of low-risk patients and optimizing doctor-patient communication. It is important to emphasize that this model is intended for stage T2 MIBC patients who are unsuitable for or refuse radical cystectomy due to advanced age or severe comorbidities. For patients suitable for radical surgery, the model's predictions can serve as an adjunct to decision-making but cannot replace the assessment of indications for radical treatment.

4.4 The Reference Value of Clinical Characteristics of NMIBC in Assessing Intravesical Recurrence of MIBC

Although a systematic comparison of NMIBC and MIBC does not directly contribute to the development or validation of the T2 intravesical recurrence model, it provides a contextual framework for understanding the host status and risk assessment in MIBC patients, offering clinical insights regarding immune function monitoring, nutritional status assessment, coagulation function evaluation, and the management of comorbidities.

4.5 The Core Reasons for Differences in Model Performance Across Different Time Points

The differences in model performance at 12, 24, and 36 months are essentially the result of the combined effects of tumor biological characteristics, host status, and clinical follow-up confounders. Short-term (12-month) intravesical recurrence is primarily determined by the intrinsic malignancy of the tumor and preoperative host status; the core indicators show a strong and stable association with the risk of intravesical recurrence, and the model performs best during this period; At the intermediate-term (24 months) mark, factors such as treatment response and the occurrence of complications begin to influence the outcome, disrupting the simple association between preoperative indicators and the risk of intravesical recurrence, resulting in a slight decline in model performance; at the long-term (36 months) mark, the accumulation of confounding factors—such as loss to follow-up and adjustments to treatment regimens—significantly weakens the predictive value of preoperative baseline indicators. Combined with the reduced incidence of long-term intravesical recurrence events, this leads to a significant decline in model performance. In clinical practice, predictive results should be interpreted reasonably in conjunction with specific follow-up time points: at 1 year post-surgery, risk stratification can be performed directly based on the model; at 2 years post-surgery, predictive conclusions should be adjusted based on dynamic data; and at 3 years or more post-surgery, the model should be used in conjunction with other assessment tools.

4.6 Limitations of the Study

This study has the following limitations, which should be carefully considered when interpreting the results: First, the single-center, retrospective design inevitably

involves selection bias and information bias; the generalizability of the model requires validation through multicenter, prospective studies; Second, the small sample size of the validation set (n = 72) resulted in wide AUC confidence intervals (e.g., AUC at 12 months: 0.72, 95% CI 0.60–0.82); the generalizability of the model requires further confirmation through multicenter, prospective external validation studies; Third, the follow-up period was limited, with a median follow-up of 41 months; some patients did not reach 36 months, which may affect the stability of long-term predictions; Fourth, molecular biomarkers (such as PD-L1, FGFR3, ctDNA, etc.) and radiomic features were not included. While these novel indicators may further improve predictive accuracy, this model is based on routine clinical indicators, making it easier to implement in primary care settings; Fifth, although all patients received intravesical chemotherapy, only two drugs—camptothecin and epirubicin—were included. Furthermore, univariate analysis showed no significant association between drug type and intravesical recurrence. However, due to the limited sample size, an in-depth analysis of instillation frequency and treatment duration could not be conducted; the potential impact of different instillation regimens on intravesical recurrence requires further investigation. All of the above limitations need to be addressed in future studies.

4.7 Future Research Directions

Future research could be conducted in the following areas: First, conduct multicenter prospective cohort studies to expand the sample size and validate the model's long-term performance; second, incorporate new biomarkers—such as those from molecular biology and imaging—to construct more accurate combined predictive models; third, combine artificial intelligence and machine learning to explore nonlinear relationships among biomarkers and develop intelligent predictive tools; fourth, conducting interventional studies to verify whether model-based risk stratification strategies can reduce the rate of intravesical recurrence in high-risk patients; fifth, conducting in-depth exploration of the biological mechanisms underlying the differences between NMIBC and MIBC to identify key targets for muscle-invasive cancer.

5. Conclusion

This study systematically compared NMIBC and MIBC and found significant differences in general clinical characteristics, tumor characteristics, and immune, nutritional, and coagulation functions. Analysis of patients with stage T2 MIBC indicated that tumor number, tumor size, histological grade, absolute neutrophil count, and red blood cell count are independent risk factors for intravesical recurrence following the first TURBT procedure. The line graph predictive model constructed based on the above factors demonstrated good discriminatory power, calibration, and clinical utility in both the training set and the internal validation set. It can effectively quantify the risk of postoperative intravesical recurrence in patients with stage T2 MIBC, providing a practical tool for clinical risk stratification. Future multicenter prospective studies are needed to further validate the model's performance.

6. Acknowledgments

Neng Zhang and Wei Cui contributed to the study conception and design.Conggui Liu and Yongpan Zhu interpreted the data and wrote the first draft of the manuscript. YuanJian Liao, MingShun Zuo, Te Xu, XinQi Yang collected data and performed statistical analysis. Conggui Liu and Yongpan Zhu interpreted the data and revised the manuscript. All authors have read and approved the final manuscript.

7. Funding Statement

This research received no external funding.

8. Clinical Trial Registration Number

Not applicable (this study did not involve a clinical trial).

9. Ethics statement

This study was approved by the Clinical Research Ethics Committee of the Affiliated Hospital of Zunyi Medical University（KLLY-2025-054）, and all research and data collection protocols were in accordance with the Declaration of Helsinki. Waiver of

informed consent was approved by the Clinical Research Ethics Committee of the Affiliated Hospital of Zunyi Medical University. Due to the retrospective observational nature of this study, which only collected existing clinical data without additional interventions, the requirement for informed consent was waived.

10. Consent for publication

Not applicable.

11. Disclosure statement

The authors declare that they have no competing interests.

12. Data availability statement

The data are available upon request from the corresponding author.

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