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# Predicting recurrence of nonmuscle-invasive bladder cancer (Ta-T1)

## A study based on 477 patients

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**Abstract**

The aim of this study was to determine clinical recrudescent risk factors of 477 patients with newly discovered nonmuscle-invasive bladder cancer (NMIBC) (Ta-T1) in our hospital, and based on these factors, to establish a recurrence risk prediction model of each NMIBC patient.

This study included 477 patients with newly discovered NMIBC (Ta-T1) from January 2012 to December 2016; all patients were treated surgically by transurethral resection of bladder tumor (TURBT). The outcomes of patients were with or without recurrence within 2 years. The nomograms were based on Cox regression analyses, and the calibration curves were founded to evaluate the agreements of the predicted probability with the actual observed probability.

Of the 477 patients with NMIBC, 392 were males (82.2%) and 85 were females (17.8%), with median age 64 years. Recurrence was identified in 327 cases (68.6%). The results showed that old age, female sex, smoking history, large size of tumor, multifocal tumors, high grade, and high stage are risk factors for NMIBC recurrence, whereas no significant association was seen between tumor location and recurrence in our study. Based on the results of Cox regression analyses, several independent risk factors, including smoking history, tumor size, multifocal, immediate infusion therapy, T stage, and tumor grade, were used to establish a nomogram to calculate the recurrence probability of each NMIBC patient, and the calibration curve displayed that this nomogram had a great value of prediction.

Old age, female sex, smoking history, large size of tumor, multifocal tumors, high grade, and high stage are risk factors for NMIBC recurrence, whereas immediate infusion therapy is a protective factor. And a nomogram was established as a prediction model to calculate the recurrence probability of NMIBC patients.

**Abbreviations:** CIS = concomitant tumors in situ, MIBC = muscle-invasive bladder cancer, NMIBC = nonmuscle-invasive bladder cancer, TURBT = transurethral resection of bladder tumor.

**Keywords:** bladder cancer, non-muscle-invasive, predicting, recurrence

## 1. Introduction

Bladder cancer is the fifth most common malignancy in men and 12th most common malignancy in women worldwide. An estimated 429,000 new cases were diagnosed with bladder cancer in 2012, with 165,000 deaths per annum in the world.[1,2] Among these patients, >70% of them are diagnosed with nonmuscle-invasive bladder cancer (NMIBC).[3] In the past decades, despite the progress in diagnostic techniques and the improvement in surgical and nonsurgical therapies, bladder cancer has a high recurrence rate risk (ranging from 50% to 90% of cases) and the prognosis of muscle-invasive bladder cancer (MIBC) has remained poor.[1]

Several adverse prognostic features have been associated with a high risk of progression, such as old age, cigarette smoking, hydronephrosis, multiple tumors, submucosal invasion, size (≥3 cm), high-grade, concomitant tumors in situ, (CIS).[4–9] Based on these prognostic factors, risk classification models are expected to improve the predictive accuracy of identifying high-risk patients. Among these models for prediction of the risk of NMIBC recurrence and progression, 2 risk models are widely known: the EORTC risk tables and the CUETO scoring model.[9–11]

Although various studies and risk classification models have been done to identify NMIBC recurrence and progression, studies on prognostic factors of NMIBC have a number of limitations. The aim of this study was to determine the recrudescent risk factors of 477 patients with NMIBC (Ta-T1) in our hospital, and to study the role of these factors, including tumor size, tumor grade, T stage, multifocal, smoking history, and immediate perfusion therapy. In addition, on the basis of our Cox regression analyses, a nomogram was constructed to calculate the probability of each NMIBC (Ta-T1) patient recurrence directly.

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## 2. Materials and methods

### 2.1. Study patients

This study collected 477 patients with newly discovered NMIBC (Ta-T1) at the Department of Urology, Zhongnan Hospital of Wuhan University from January 2012 to December 2016. Currently, the 1973 and the 2004 WHO classification coexist. Several studies have compared the 2 classification methods, indicating that that WHO1973 grade cannot be replaced by the WHO2004 classification in NMIBC guidelines.[12–14] In this study, 1973 classification standard (grade1, 2, 3) was used as the grading system of bladder cancer. All patients had undergone transurethral resection of bladder tumor (TURBT). The T stage and tumor grade of each patient were assessed according to the diagnostic criteria of "Chinese diagnosis and treatment of urological diseases Guide"; the patient follow-up protocol was performed with surveillance cystoscopy at 3-month intervals for the initial 2 years. And the immediate perfusion therapy was defined as bladder perfusion chemotherapy within 24 hours after surgery; the perfusion drugs included epirubicin, pirarubicin, hydroxycamptothecin, and gemcitabine. In addition, the clinical information was acquired by retrospective review of all patient medical records, and all methods used for analysis in this study were carried out in accordance with the approved regulations of the Department of Biological Repositories at Zhongnan Hospital of Wuhan University.

### 2.2. Inclusion criteria

Patients were enrolled in this study if they met all the following criteria: presence of primary NMIBC (Ta-T1); without any a previous history of TURBT or bladder perfusion chemotherapy; patients who underwent TURBT; had a complete and detailed clinical, pathological, follow-up data record.

### 2.3. Exclusion criteria

Patients meeting any of the following criteria were excluded: metastatic /secondary bladder cancer; patients with Tis stage; patients who did not undergo surgery; any incomplete clinical, pathological, or follow-up data.

### 2.4. Outcomes and study design

All subjects were diagnosed with bladder cancer for the first time. The outcomes were with or without recurrence within 2 years. The recurrence was defined with surveillance cystoscopy. All patients were divided into 2 groups (recurrence negative group and recurrence positive group) according to whether recurrence.

### 2.5. Statistical analysis

Continuous variables were depicted as averages, ranges and medians. Age was compared by 2-sample $t$ test. $\chi^2$ test was performed for sex, smoking history, multifocal, tumor grade, and immediate perfusion therapy. Mann-Whitney test was used for tumor location, tumor size, and T stage. Cox univariate and multivariate survival analyses were used to estimate the independent factors of recurrence rate. Nomograms were generated based on Cox regression analyses. The calibration curves were found to evaluate the agreements of the nomogram-predicted probability with the actual observed probability. SPSS 16.0 was used to perform all statistical analyses (SPSS Inc, Chicago, IL). Nomograms and calibration curves were generated with R version 3.5.0 and $P$ value $<.05$ was considered significant.

## 3. Results

### 3.1. Patient characteristics

Of the 477 patients with NMIBC, as shown in Table 1, 392 were males (82.2%) and 85 were females (17.8%), with median age 64 years. Smoking history was found in 287 patients (60.2%). Of all the tumors, 178 (37.3%) were located in vesical trigone, 212 (44.4%) were located in side wall, 55 (11.5%) were located in anterior and posterior wall, and 32 (6.7%) at other locations. Multifocal tumors (≥3) were seen in 365 patients (76.5%). Tumor size (centimeters) was divided into 3 groups: <1 cm (193, 40.5%), 1 to 3 cm (148, 31.0%), and ≥3 cm (136, 28.5%). Tumor grade and T stage were as follows: 318 tumors (66.7%) were G1, 106 (22.2%) G2, 53 (11.1%) G3, whereas 359 tumors (75.3%) were Ta, 118 (24.7%) T1. What is more, immediate perfusion therapy was applied in 417 patients (87.4%).

Of these 477 patients, recurrence was identified in 327 cases (68.6%). The 2-sample $t$ test results showed that the age of the patients was significantly different between these 2 groups ($P=.028$), and the average age of recurrence negative group is $63.6 \pm 11.3$ years, whereas recurrence-positive group is $65.0 \pm 10.3$ years, displaying that old age is a risk factor of recurrence. The $\chi^2$ test results showed that NMIBC recurrence was associated with sex ($P=.017$), smoking history ($P=.030$), multifocal ($P=.009$), and immediate perfusion therapy ($P=.003$). In addition, the Mann-Whitney test results indicated that the tumor size ($P=.020$), tumor grade ($P<.001$), and T stage ($P=.002$) were significant influencing factors of recurrence, whereas no significant association was seen between tumor location and recurrence ($P=.874$) in our study.

### 3.2. Cox univariate and multivariate analyses

To assess the recrudescent value of these factors for NMIBC, Cox univariate and multivariate analyses were applied (Table 2). The univariate survival analysis showed that smoking history, tumor size, multifocal, tumor grade, T stage, and immediate infusion therapy were factors significantly affecting NMIBC recurrence. And in these factors, smoking history (hazard ratio [HR]: 1.547; 95% confidence interval [CI]: 1.230–1.826; $P=.037$), large size of tumor (HR: 2.364; 95% CI: 1.393–4.414; $P=.008$), multifocal tumors (HR: 2.305; 95% CI: 1.499–4.051; $P=.011$), high grade (HR: 3.114; 95% CI: 1.976–6.194; $P<.001$), and high stage (HR: 3.776; 95% CI: 2.162–5.703; $P=.003$) are adverse factors of NMIBC recurrence, whereas immediate infusion therapy (HR: 0.069; 95% CI: 0.030–0.091; $P<.001$) is a protective factor of recurrence.

In agreement with univariate analysis results, multivariate analysis also indicated that smoking history (HR: 1.124; 95% CI: 1.102–1.674; $P=.044$), large size of tumor (HR: 2.627; 95% CI: 1.510–4.085; $P=.018$), multifocal tumors (HR: 2.048; 95% CI: 1.661–4.276; $P=.010$), high grade (HR: 3.253; 95% CI: 2.215–6.488; $P<.001$), and high stage (HR: 3.132; 95% CI: 2.002–5.614; $P=.002$) were independent adverse factors for NMIBC recurrence, and immediate infusion therapy (HR: 0.059; 95% CI: 0.024–0.087; $P<.001$) is an independent protective factor.

**Table 1**

**Clinical characteristics of bladder cancer patients.**

| Variables | All patients (n = 477) | Recurrence negative (n = 327) | Recurrence positive (n = 150) | P |
|---|---|---|---|---|
| Sex, n (%) | | | | .017 |
| Male | 392 (82.2) | 278 (85.0) | 114 (76.0) | |
| Female | 85 (17.8) | 49 (15.0) | 36 (24.0) | |
| Age, y, n (%) | | | | .028 |
| Average/median | 64.3 ± 11.0/64 | 63.6 ± 11.3/63 | 65.0 ± 10.3/66 | |
| Range | 17–92 | 19–90 | 17–92 | |
| <60 | 191 (40.0) | 134 (41.0) | 57 (38.0) | |
| 60–69 | 118 (24.7) | 95 (29.1) | 23 (15.3) | |
| 70–79 | 99 (20.8) | 57 (17.4) | 42 (28.0) | |
| ≥80 | 69 (14.5) | 41 (12.5) | 28 (18.7) | |
| Smoking history, n (%) | | | | .030 |
| No | 190 (39.8) | 141 (43.1) | 49 (32.7) | |
| Yes | 287 (60.2) | 186 (56.9) | 101 (67.3) | |
| Tumor location, n (%) | | | | .874 |
| Vesical trigone | 178 (37.3) | 127 (38.8) | 51 (34.0) | |
| Sidewall | 212 (44.4) | 144 (44.0) | 68 (45.3) | |
| Anterior and posterior wall | 55 (11.5) | 34 (10.4) | 21 (14.0) | |
| Others | 32 (6.7) | 22 (6.7) | 10 (6.7) | |
| Tumor size, cm, n (%) | | | | .020 |
| <1 | 193 (40.5) | 141 (43.1) | 52 (34.7) | |
| 1–3 | 148 (31.0) | 114 (34.9) | 34 (22.7) | |
| ≥3 | 136 (28.5) | 72 (22.0) | 64 (42.7) | |
| Multifocal, n (%) | | | | .009 |
| No | 112 (23.5) | 88 (26.9) | 24 (16.0) | |
| Yes | 365 (76.5) | 239 (73.1) | 126 (84.0) | |
| Tumor grade, n (%) | | | | <.001 |
| $G_1$ | 318 (66.7) | 235 (71.9) | 83 (55.3) | |
| $G_2$ | 106 (22.2) | 77 (23.5) | 29 (19.3) | |
| $G_3$ | 53 (11.1) | 15 (4.6) | 38 (25.3) | |
| T stage, n (%) | | | | .002 |
| $T_a$ | 359 (75.3) | 262 (80.1) | 97 (64.7) | |
| $T_1$ | 118 (24.7) | 65 (19.9) | 53 (35.3) | |
| Immediate perfusion therapy, n (%) | | | | .003 |
| No | 60 (12.6) | 31 (9.5) | 29 (19.3) | |
| Yes | 417 (87.4) | 296 (90.5) | 121 (80.7) | |

### *3.3. Construction of nomogram to predict recrudescent probability*

Based on our – regression analyses, Figure 1 provides a nomogram to calculate the recurrence probability of each NMIBC patient; according to the information of each patient (tumor size, smoking history, multifocal, immediate infusion therapy, T stage, and tumor grade), recurrence probability can be calculated directly. For example, for a patient with a 3.0-cm size, T1 stage, G2 grade and single NMIBC tumor, having smoking history, and have been performed with immediate infusion therapy, his total points are 81, with an approximated 2-year recurrence probability of 28%. Furthermore, the calibration curve (Fig. 2) displayed good agreement of the predicted probability with the real probability for NMIBC recurrence, which indicated that this nomogram had a great value of prediction.

**Table 2**

**Cox regression analyses for bladder cancer recurrence.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variables | HR | 95% CI | P | HR | 95% CI | P |
| Sex (male/female) | 0.911 | 0.753–1.009 | .072 | — | — | — |
| Age, y | 1.124 | 0.945–1.349 | .121 | — | — | — |
| Smoking history (yes/no) | 1.547 | 1.230–1.826 | .037 | 1.124 | 1.102–1.674 | .044 |
| Tumor location (vesical trigone/others) | 0.975 | 0.962–1.023 | .918 | — | — | — |
| Tumor size, cm | 2.364 | 1.393–4.414 | .008 | 2.627 | 1.510–4.085 | .018 |
| Multifocal (yes/no) | 2.305 | 1.499–4.051 | .011 | 2.048 | 1.661–4.276 | .010 |
| Tumor Grade (G3 vs G1-G2) | 3.114 | 1.976–6.194 | <.001 | 3.253 | 2.215–6.488 | <.001 |
| T stage (T1 vs Ta) | 3.776 | 2.162–5.703 | .003 | 3.132 | 2.002–5.614 | .002 |
| Immediate infusion therapy (yes/no) | 0.069 | 0.030–0.091 | <.001 | 0.059 | 0.024–0.087 | <.001 |

CI = confidence interval, HR = hazard ratio.

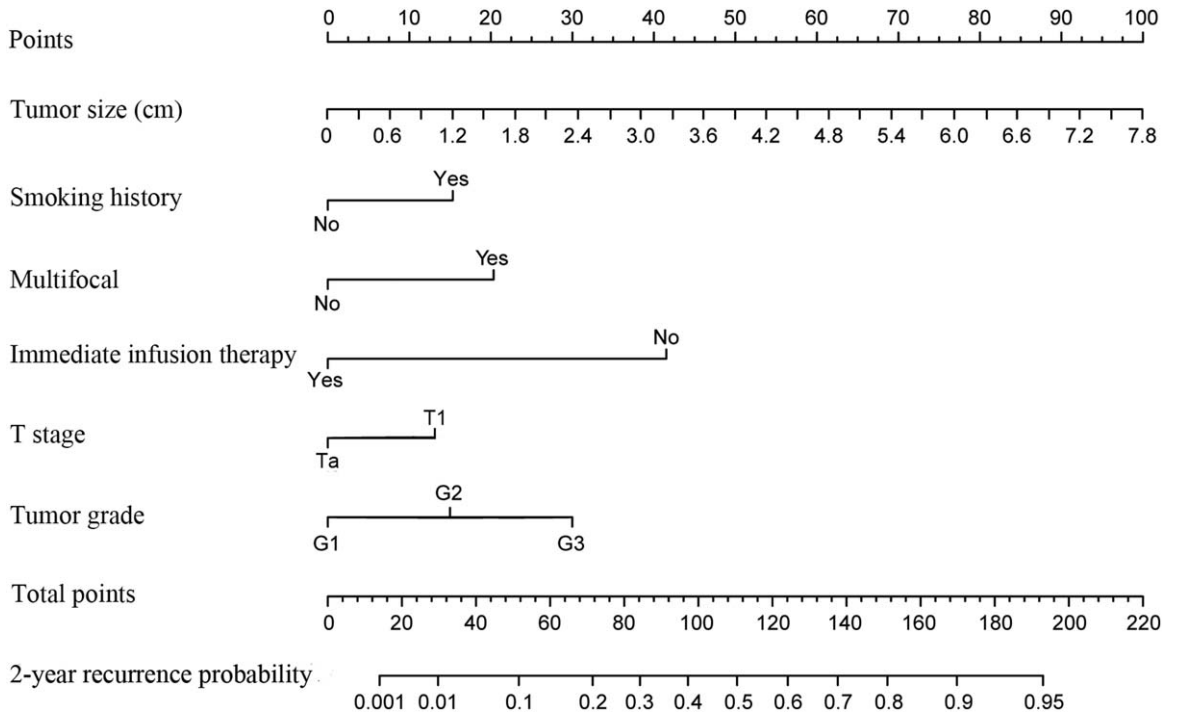


**Figure 1.** The nomogram for recurrence prediction of nonmuscle-invasive bladder cancer patients according to smoking history, tumor size, multifocal, immediate infusion therapy, T stage, and tumor grade. To estimate the risk of recurrence, the points for each variable were calculated by drawing a straight line from a patient's variable value to the axis labeled "Points." The score sum is converted to a probability in the lowest axis.

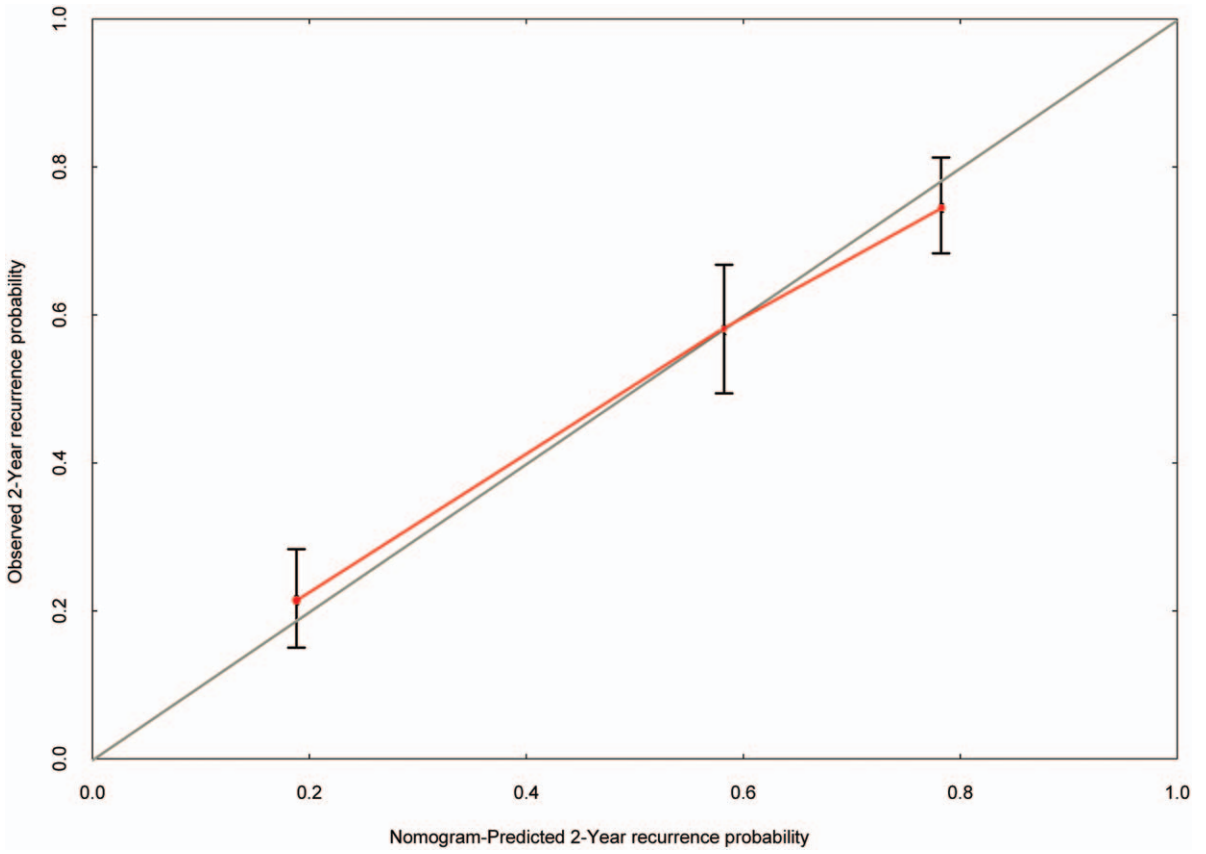


**Figure 2.** The calibration curve developed for recurrence among 477 nonmuscle-invasive bladder cancer (Ta-T1) patients. The nomogram-predicted probability is plotted on the *x* axis, and the actual probability is plotted on the *y* axis.

## 4. Discussion

In China, it is predicted that there were about 80,000 newly diagnosed bladder cancer cases in 2015, with 33,000 deaths per year.[15] In the newly diagnosed cases, most of them are diagnosed with NMIBC,[1] given the very high recurrence rate, recurrence prediction is particularly important in NMIBC. In this study, we evaluated several recrudescent risk factors of NMIBC in 477 patients from our hospital. The incidence of bladder cancer is about 4 times more frequent in men than in women[3]; our date of 477 patients with NMIBC showed that the male-to-female ratio was 4.6:1. Several studies pointed out that the reasons for this sex disparity maybe the lower prevalence of smoking among women and the higher exposure to carcinogens in men.[16,17] Admittedly, tobacco smoking is recognized as the most important risk factor for bladder cancer; smoking is estimated to account for 50% of tumors, and current cigarette smoking triples bladder cancer risk compared to never smoking.[18,19] In our study, smoking history was identified as an independent adverse factor for NMIBC recurrence (HR: 1.124; $P=.044$). Tobacco smoking contains aromatic amines, which were known to cause bladder cancer, and these carcinogens could be renally excreted to produce a carcinogenic effect on the whole urinary system. However, smoking history does not solely explain the difference in risk of bladder cancer between sexes, Shiota et al[20] reported that androgen and androgen receptor signaling might play an important role in bladder cancer progression. Furthermore, despite the higher incidence of male preponderance, it has been reported that female sex is a prognostic factor for worse cancer-specific survival following diagnosis with bladder cancer.[16] Similarly, our results also showed that women had higher recurrence rate (42.4% in female vs 29.1% in male). More research is needed to explore the relationship between this sex disparity and bladder cancer progression and recurrence.

Our Cox regression analyses results displayed that smoking history, tumor size, multifocal, tumor grade, and T stage were important risk factors affecting NMIBC recurrence. In agreement with this conclusion, previous studies have identified these same recurrence factors for NMIBC; an important study by Sylvester et al[10] showed that tumor size, the number of tumors, and the previous recurrence rate were the most important prognostic factors for recurrence. And another recent research also displayed that the number of tumors and degree of invasion were the most important prognostic factors for recurrence of NMIBC.[21] In addition, the poor prognosis and the high recurrence rate of T1 G3 patients has been mentioned in several publications[10,22,23]; as shown in Table 2, our regression Cox analysis results revealed that the recurrence risk of T1 tumors was obviously higher than Ta tumors (HR: 3.132; $P=.002$), and G3 tumors also had a higher risk of recurrence compared with G1-G2 tumors (HR: 3.253; $P<.001$). What is more, immediate perfusion therapy could kill the residual cancer cells after surgery, to reduce implantation and recurrence of bladder cancer. As expected, our results demonstrated that immediate perfusion therapy could reduce recurrence rate of NMIBC significantly (HR: 0.059; $P<.001$).

In our study, the perfusion drugs included epirubicin, pirarubicin, hydroxycamptothecin, and gemcitabine; several studies have demonstrated the therapeutic value of these drugs in bladder cancer recurrence. A study based on 431 patients showed that the recurrence rate after a single epirubicin instillation was decreased by nearly half compared with intravesical instillation of water.[24] Naya et al[25] reported that instillation of pirarubicin could reduce the risk of tumor recurrence in NMIBC patients with intermediate risk. In addition, intravesical administration of gemcitabine has an excellent toxicity profile and promising efficacy in NMIBC patients, which has been reported in several clinical trials.[26–28] There are many types of perfusion drugs for bladder cancer, and further clinical trials are needed to prove the difference efficacy between various drugs, to provide more reference for drug selection.

Next, on top of these factors, we constructed a nomogram to calculate the recurrence probability. Based on the information of each patient, we could calculate the total points, to estimate its 2-year recurrence probability. At present, 3 risk models are well known for the prediction of NMIBC recurrence risk: the EORTC, CUETO, and new EORTC models.[9–11] Based on 2596 patients, the EORTC Genito-Urinary Cancer Group exploited a risk table to predict the probabilities of NMIBC recurrence, and the scoring system is based on the 6 most significant factors (number of tumors, tumor size, prior recurrence rate, tumor grade, T stage, and presence of concomitant CIS). Although the CUETO scoring model contains 7 clinical and pathological factors: sex, age, number of tumors, recurrent tumor, T category, associated Tis, and grade. And our nomogram to predicate 2-year recurrence probability of NMIBC was based on tumor size, smoking history, multifocal, immediate infusion therapy, T stage, and tumor grade. This research was carried out in 477 patients with NMIBC of our hospital, given the effect of racial/ethnic differences and regional disparity in recurrence rate of NMIBC.[29] We think that our prediction nomogram of NMIBC recurrence risk could provide an evidence for clinical decision of NMIBC patients in our hospital.

## 5. Conclusion

Based on 477 patients with NMIBC in our hospital, this study evaluated several recrudescent risk factors of NMIBC, indicating that old age, female sex, smoking history, large size of tumor, multifocal tumors, high grade, and high stage are risk factors for NMIBC recurrence, whereas immediate infusion therapy is a protective factor. What is more, based on the Cox regression analyses results, we established a nomogram as a prediction model to calculate the recurrence probability of NMIBC patients, and the calibration curve displayed that this nomogram had a great value of recrudescent prediction for NMIBC.

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## Author contributions

**Data curation:** Mengxin Lu, Song Chen, Qiang Zhou, Lu Wang, Tianchen Peng.
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**Writing – original draft:** Mengxin Lu.
**Writing – review & editing:** Song Chen.

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