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## Development and validation of a nomogram for predicting prostatic urethral involvement in bladder cancer

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To identify risk factors for prostatic urethral involvement (PUI) in bladder cancer and develop an accurate nomogram prediction model. We retrospectively analyzed 295 male patients with bladder urothelial carcinoma undergoing transurethral prostatic biopsy. Risk factors of PUI in bladder cancer were assessed through univariate and multivariate logistic regression analyses. A nomogram model for predicting clinical outcomes was constructed based on the independent risk factors of PUI. The performance of the model was internally validated by 'leave-one-out' cross-validation (LOOCV) and calibration curve. The decision curve analysis (DCA) was applied to evaluate the clinical utility. Further evaluation of PUI and associated risk factors within the context of non-muscle-invasive bladder cancer (NMIBC) were assessed using the same methods. Multivariate analysis revealed that the tumor multiplicity (OR = 2.44, 95% CI 1.17–5.26, P = 0.019), trigonal/neck tumor location (OR = 7.42, 95% CI 4.00-14.24, P < 0.001), high-grade tumor (OR = 5.17, 95% CI 1.52-21.95, P = 0.014), and recurrent carcinoma (OR = 4.39, 95% CI 2.32-8.63, P < 0.001) were identified as independent risk factors for PUI in bladder cancer (all P<0.05). A final prediction nomogram was established based on these four independent risk factors. After internally validated by LOOCV, the nomogram showed strong discrimination (area under the curve, AUC = 0.8, 95%CI 0.749–0.851) and excellent calibration. DCA further confirmed the model's clinical utility across a wide range of risk thresholds. Subgroup analysis in NMIBC yielded consistent results (AUC = 0.819, 95%CI 0.764–0.874). This nomogram provides a robust tool to stratify PUI risk in bladder cancer, guiding selective prostatic biopsies and personalized management. Integration into clinical workflows may reduce understaging and optimize outcomes. Further external validation is warranted.

Keywords Bladder cancer, Prostate urethral biopsy, Prostatic urethral involvement, Nomogram, Risk stratification

Bladder cancer is one of the most prevalent malignancies globally, particularly among men, who are three to four times more likely than women to develop the disease<sup>1</sup>. In 2020, approximately 573,000 new cases of bladder cancer were diagnosed worldwide, resulting in around 212,000 deaths attributed to the disease<sup>2</sup>. The high mortality of bladder cancer is closely linked to its propensity for frequent recurrence and progression, clinical behaviors driven by aggressive pathological features such as tumor multiplicity, high histological grade, and anatomical invasion patterns<sup>3,4</sup>.

Prostatic urethral involvement (PUI) in bladder cancer, although less common than primary bladder urothelial carcinoma (UC), significantly influences patient prognosis. The incidence of PUI ranges from 16 to 39% in cases of non-muscle-invasive bladder cancer (NMIBC) and from 15 to 48% in radical cystectomy (RC) cases<sup>5,6</sup>. Prostate stromal invasion, in comparison to carcinoma in situ (CIS) or subepithelial invasion, is associated with poorer outcomes and a heightened risk of lymph node metastases<sup>7,8</sup>. The likelihood of PUI is

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Previous studies have primarily concentrated on identifying risk factors for PUI and its prognostic implications. For example, Mungan et al. identified tumor multiplicity as a significant risk factor for mucosal PUI in NMIBC, while Shen et al. underscored the prognostic importance of prostate stromal invasion<sup>7,9</sup>. However, these studies often relied on smaller cohorts or lacked comprehensive predictive models. The European Association of Urology (EAU) guidelines recommend prostatic urethral biopsy under specific conditions, but there is no consensus on a standardized predictive tool to identify patients at risk<sup>12</sup>.

Nomogram prediction models have emerged as powerful tools in oncology for individualized risk assessment and treatment planning. These models integrate multiple clinical and pathological variables into a user-friendly graphical interface, enabling clinicians to estimate the probability of specific outcomes for individual patients. By incorporating key risk factors, nomograms can improve early diagnosis, optimize treatment strategies, and ultimately enhance patient outcomes<sup>13,14</sup>.

Our study aims to develop a nomogram-based predictive model incorporating multiple risk factors, including tumor multiplicity, trigonal/neck location, high-grade tumor, and recurrent carcinoma. This model not only enhances early diagnosis but also provides a quantitative assessment of PUI risk, offering a more personalized approach to patient management. By integrating these factors into a single predictive tool, our study advances beyond previous research, providing clinicians with a robust foundation for making informed treatment decisions.

### Materials and methods

#### Study population

A total of 295 male patients who underwent prostate urethral biopsy for primary bladder urothelial carcinoma between January 2011 and January 2023 were reviewed from our institution. Clinical data, including age, tumor size, pathological stage, grade, location, number (No.) of tumors, presence of CIS, recurrent carcinoma, and pathological results of prostatic urethral biopsy, were extracted from patient files and digital health databases. All patients included in this study had pathologically confirmed primary bladder urothelial carcinoma via transurethral resection of bladder tumor (TURBT). Exclusion criteria included: (1) prostate urethral biopsy without TURBT (lack of information of bladder tumor); (2) lack of urothelial carcinoma histology in the specimen obtained from TURBT (defining pathological type as urothelial carcinoma in bladder); (3) presence of prostatic urethral primaries (to reduce the case selection bias); (4) positive cases of prostate urethral biopsy were non-urothelial carcinoma (defining pathological type as urothelial carcinoma in prostatic urethral; and (5) cases lacking complete clinicopathological information. Patients were categorized into two groups based on pathological findings from prostatic urethral biopsies: the prostate urethral biopsy (+) group and the prostate urethral biopsy (-) group. This study was approved by the Medical Ethics Committee of the Second Hospital of Tianjin Medical University (ethics approval number: KY2024K207).

#### Variables definition

Tumor size was defined as the largest diameter observed during microscopic analysis of the surgical specimen. Individuals were categorized based on age distribution (<65 years versus  $\geq$ 65 years), tumor size (<3 cm versus  $\geq$ 3 cm), multiplicity(single versus multiple), tumor location (trigone/neck versus other locations), pathological stage (pTa, pT1, and pT2-T4), pathological grade (low grade versus high grade), presence of CIS (yes versus no), and recurrent carcinoma (yes versus no, within 5 years). Multiplicity is defined as multiple tumors in the bladder. The selection of tumor size  $\geq$ 3 cm as a specific cutoff was informed by prior studies consistently associating this threshold with elevated risks of recurrence, progression, and prostatic involvement in bladder cancer, attributed to increased tumor burden and multifocality<sup>15,16</sup>. This criterion aligns with the EAU guidelines, which recommend 3 cm as a key threshold for risk stratification in NMIBC. Similarly, age  $\geq$ 65 years was chosen based on its well-established role as a prognostic factor, correlating with advanced disease stage, comorbidities, and poorer outcomes. In our cohort, the median age was 68 years, and the  $\geq$ 65-year cutoff approximated the upper tertile, ensuring balanced subgroup sizes for robust statistical analysis while reflecting real-world clinical demographics. Prior studies broadly categorized "bladder neck involvement" without anatomical precision. In contrast, this study used strict anatomical boundaries (trigone/neck tumors confirmed cystoscopically and pathologically) to define this variable, minimizing misclassification.

#### Surgical procedure and pathological evaluation

Prostatic urethral biopsies were systematically performed at the 5 and 7 o'clock positions (bladder neck to verumontanum) in all patients, regardless of visible prostatic urethral lesions. Adequate urethral mucosa resection during transurethral resection (TUR) was confirmed to assess PUI. All specimens underwent centralized re-evaluation by a dedicated team of genitourinary pathologists to ensure consistency. Tumor grading and staging were performed according to the following criteria: TNM staging followed the 2010 American Joint Committee on Cancer (AJCC) 7th edition guidelines, where the T category was defined as Ta (non-invasive papillary carcinoma confined to the urothelium), T1 (invasion into the subepithelial connective tissue/lamina propria), or T2–T4 (invasion of the muscularis propria, perivesical fat, or adjacent organs, respectively). Tumor grading adhered to the 2004 World Health Organization (WHO) criteria, with low-grade tumors characterized by preserved papillary/flat architecture, mild nuclear atypia, and rare mitotic figures, and high-grade tumors exhibiting architectural disruption (loss of polarity, disordered growth), marked nuclear pleomorphism, and frequent mitotic activity. Specifically, as a result of extravesical/transmural invasion of a bladder tumor into the prostate, prostatic urethral involvement with UC was classified as pT4a<sup>17</sup>.

#### **Statistical analysis**

Statistical analysis was performed by R language statistical software (version 4.2.1) for data processing and graph rendering. Continuous variables were presented as mean and standard deviation, while qualitative variables were represented by frequencies or percentages. Significance of variables associated with PUI in bladder cancer was assessed using chi-squared test and univariate logistic regression analysis. Following this, a multivariate logistic regression analysis was conducted to identify significant parameters. A prediction nomogram model based on the independent risk factors of PUI was constructed and evaluated using Receiver Operating Characteristic (ROC) curve to compute the area under the curve (AUC) for the model. To evaluate calibration, the locally weighted scatter plot smoothing method was employed to plot observed versus predicted values. 'Leave-one-out' cross-validation (LOOCV) was employed for the purpose of internal validation. The model's AUC was computed using the linear prediction of the logistic function, which was adjusted following internal validation, to visually assess calibration and carry out decision curve analysis (DCA). Furthermore, the presence of PUI and associated risk factors were assessed in NMIBC using the same methods. Significance was established at a P < 0.05. This study's disclosure complies with the TRIPOD standards<sup>18</sup>.

#### Primary outcome

The primary outcome of this study was the presence of prostatic urethral involvement (PUI), defined as histopathologically confirmed urothelial carcinoma in the prostatic urethra or prostate based on postoperative pathological evaluation of transurethral prostatic biopsy specimens.

#### Results

Table 1 outlines the clinicopathological profiles of individuals afflicted with bladder cancer. TUR biopsies were performed on all 295 male patients included in the study. Among them, 127 (43.1%) were diagnosed with PUI, while 168 (56.9%) showed no PUI. Additionally, 39 patients (13.2%) underwent transurethral prostate biopsy before RC. Regarding the pathologic stage and grade of bladder cancer, 20 (6.8%) were diagnosed as pTa low-grade, 6 (2.0%) as pTa high-grade, 22 (7.5%) as pT1 low-grade, 177 (60.0%) as pT1 high-grade, and 70 (23.7%) as pT2-4 high-grade diseases, respectively. Among 127 PUI cases, 18 (14.2%) were staged as pT4 due to extravesical invasion. In NMIBC, only two cases were low-grade pTa. Overall, CIS was detected in the bladder of 58 patients (19.7%), with 16 (5.4%) of whose patients also having PUI by CIS.

		Prostatic urethral biopsy		
Characteristics	n	(+)	(-)	P-value
Age (years, $\bar{x} \pm s$ )		$68.15 \pm 11.03$	68.44±9.53	0.809
<65	93	37 (29.1%)	56 (33.3%)	0.521
≥65	202	90 (70.9%)	112 (66.7%)	
Tumor size (cm)				0.009
<3	175	64 (50.4%)	111 (66.1%)	
≥3	120	63 (49.6%)	57 (33.9%)	
Multiplicity				< 0.001
Single	86	17 (13.4%)	69 (41.1%)	
Multiple	209	110 (86.6%)	99 (58.9%)	
Tumor location				< 0.001
Trigone/neck	153	105 (82.7%)	48 (28.6%)	
others	142	22 (17.3%)	120 (71.4%)	
Stage				< 0.001
рТа	26	2 ( 1.6%)	24 (14.3%)	
pT1	199	88 (69.3%)	111 (66.1%)	
pT2-T4	70	37 (29.1%)	33 (19.6%)	
Grade				< 0.001
Low	44	4 ( 3.1%)	40 (23.8%)	
High	251	123 (96.9%)	128 (76.2%)	
Combined CIS				0.875
Yes	58	26 (20.5%)	32 (19.0%)	
No	237	101 (79.5%)	136 (81.0%)	
recurrent carcinoma				< 0.001
Yes	106	67 (52.8%)	39 (23.2%)	
No	189	60 (47.2%)	129 (76.8%)	

 Table 1. Baseline characteristics of prostate urethral biopsy in patients with bladder cancer. CIS, carcinoma in situ.

For the treatment of patients with PUI, 21 (16.5%) underwent urethrectomy along with RC therapy, 10 (7.9%) received neoadjuvant therapy, and 11 (8.7%) experienced disease progression after bladder preservation therapy, subsequently underwent RC during follow-up. Additionally, all other patients with PUI underwent intravesical Bacillus Calmette-Guérin (BCG) or intravesical chemotherapy therapy following TUR.

Following this, we investigated the relationship between PUI and primary tumor characteristics. As depicted in Table 1, no significant differences in clinicopathological characteristics, including age and PUI combined bladder CIS were observed between patients who with and without PUI (all P>0.05). However, the incidence of PUI was found to be increased with tumor size, multiplicity, tumor location, pathological stage, grade, and recurrent carcinoma in individuals diagnosed with bladder cancer (Table 1). Univariate logistic regression analysis identified the tumor size, multiplicity, location, pathological stage, grade, and recurrent carcinoma as risk factors for PUI in bladder cancer (all P<0.05) (Table 2).

Among these characteristics, age, tumor size, and CIS were found to be not significant risk factors. Nevertheless, multivariate logistic regression analysis identified tumor multiplicity (OR=2.44, 95% CI 1.17–5.26, P=0.019), trigonal/neck tumor location (OR=7.42, 95% CI 4.00–14.24, P<0.001), high-grade tumor (OR=5.17, 95% CI 1.52–21.95, P=0.014), and recurrent carcinoma (OR=4.39, 95% CI 2.32–8.63, P<0.001) as independent risk factors for PUI. (refer to Table 2). Specifically, tumor location (trigone/neck) was found to pose the highest risk for PUI (OR=7.42). Anatomically, the bladder neck and trigone lie in close proximity to the prostatic urethra, facilitating direct tumor extension or implantation<sup>5,20</sup>. Additionally, the rich lymphatic and vascular networks in this region may promote metastatic spread<sup>22</sup>. Previous cohorts have similarly highlighted this anatomical predilection, with trigonal tumors exhibiting a 3–5-fold higher risk of PUI compared to other locations<sup>6,29</sup>.

Following the outcomes of the multivariate logistic regression analysis, a predictive clinical nomogram was constructed (Fig. 1A). Variables include tumor-location, tumor multiplicity, grade, and recurrent carcinoma. The nomogram's AUC reached 0.848 (95%CI 0.806–0.891), with a sensitivity of 0.835 and a specificity of 0.726. After performing internal validation by LOOCV, the AUC was 0.8 (95%CI 0.749–0.851), which reflecting the model's capacity to accurately distinguish between patients with and without PUI (Fig. 1B). The relationship between observed and predicted values, analyzed through a calibration plot before and after leave-one-out cross validation, is depicted in Fig. 1C. The calibration plot, closely aligned with the ideal line, confirming the model's reliability. Moreover, the decision curve (Fig. 1D) demonstrated that the nomogram offers significant clinical utility across a wide range of risk thresholds, indicating that its use would lead to better clinical decision-making compared to alternative strategies.

Additionally, we evaluated the presence of PUI and identified the risk factors for PUI in NMIBC. Utilizing similar methods, a clinical prediction nomogram model was developed. Among the 225 male patients with NMIBC, 90 (40.0%) exhibited PUI, while 135 (60.0%) did not. The incidence of PUI was also found to be increased with tumor size, tumor multiplicity, tumor location, pathological stage, grade, and recurrent carcinoma in individuals diagnosed with NMIBC (Tables 3 and 4).

Multivariate logistic analyses demonstrated that tumor multiplicity, trigonal/neck location, high-grade tumor, and recurrent carcinoma were independent risk factors for PUI in patients with NMIBC (all P<0.05) (Table 4).

	Univariable		Multivariable		
Characteristics	OR (95% CI)	P-value	OR (95% CI)	P-value	
Age (years)					
< 65, ≥ 65	1.21 (0.74-2.01)	0.442		NS	
Tumor size, cm					
< 3, ≥ 3	1.92 (1.20-3.08)	0.007	1.49 (0.78–2.86)	0.227	
Multiplicity					
Single, Multiple	4.51 (2.53-8.40)	< 0.001	2.44 (1.17-5.26)	0.019	
Tumor location	·				
Others, Trigone/neck	11.93 (6.87–21.48)	< 0.001	7.42 (4.00 -14.24)	< 0.001	
Stage	·		•		
рТа		NS		NS	
pT1	9.51 (2.72-60.21)	0.002	2.86 (0.50-24.31)	0.275	
pT2-T4	13.45 (3.62-87.78)	0.001	3.07 (0.48-28.18)	0.269	
Grade					
Low, High	9.61 (3.74-32.71)	< 0.001	5.17 (1.52-21.95)	0.014	
CIS					
Yes, No	1.09 (0.610-1.95)	0.760		NS	
Recurrent carcinoma					
Yes, No	3.69 (2.25-6.13)	< 0.001	4.39 (2.32-8.63)	< 0.001	

**Table 2.** Univariate and multivariate analyses to identify risk factors of PUI with bladder cancer. PUI, prostaticurethral involvement; CIS, carcinoma in situ; OR, odds ratio; CI, Confidence interval; NS, excluded from finalmodel because not statistically significant.

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**Fig. 1.** Construction and verification of the nomogram prediction model. (**A**)The nomogram prediction model for PUI in patients with bladder cancer. (**B**) **ROC curve** demonstrates the model's strong ability to discriminate between patients with and without PUI. The AUC of 0.848 (0.8 after LOOCV) indicates excellent predictive accuracy. **X-axis**: Specificity (False Positive Rate), **Y-axis**: Sensitivity (True Positive Rate), **Curve**: The ROC curve, representing the sensitivity and specificity of the model at different thresholds. LOOCV, leave-one-out cross-validation. (**C**) **Calibration curve** demonstrated that the actual value closely aligns with the prediction model, suggesting good calibration. (**D**) **Decision Curve Analysis (DCA)** evaluates the clinical utility of the nomogram across a range of threshold probabilities. **X-axis**: Threshold Probability, **Y-axis**: Net Benefit. **Nonadherence prediction nomogram**: the net benefit curve of the model. **All**: the net benefit assuming all patients receive TUR biopsy. **None**: the net benefit assuming no patients receive TUR biopsy. **LOOCV**: the net benefit curve of the model after LOOCV. The higher the curve, the greater the clinical net benefit of using the model within that threshold range.

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The same methodology was applied to construct and validate the prediction nomogram model (Fig. 2A). The nomogram achieved an AUC of 0.872 (95%CI 0.828–0.915), with a sensitivity of 0.911 and a specificity of 0.696, after internally validated by LOOCV, the AUC is 0.819 (95%CI 0.764–0.874), significantly outperforming

		Prostatic urethral biopsy		
Characteristics	n	(+)	(–)	P-value
Age (years, $\bar{x} \pm s$ )		$67.73 \pm 10.76$	68.05±8.83	0.808
< 65	72	27 (30.0%)	45 (33.3%)	0.705
≥65	153	63 (70.0%)	90 (66.7%)	
Tumor size (cm)				0.041
< 3	149	52 (57.8%)	97 (71.9%)	
≥3	76	38 (42.2%)	38 (28.1%)	
Multiplicity				< 0.001
Single	67	11 (12.2%)	56 (41.5%)	
multiple	158	79 (87.8%)	79 (58.5%)	
Tumor location				< 0.001
Trigone/neck	175	76 (84.4%)	99 (73.3%)	
others	50	14 (15.6%)	36 (26.7%)	
Stage				0.001
рТа	26	2 ( 2.2%)	24 (17.8%)	
pT1	199	88 (97.8%)	111 (82.2%)	
Grade				< 0.001
Low	43	4 ( 4.4%)	39 (28.9%)	
High	182	86 (95.6%)	96 (71.1%)	
CIS				1.000
Yes	49	20 (22.2%)	29 (21.5%)	
No	176	70 (77.8%)	106 (78.5%)	
recurrent carcinoma				< 0.001
Yes	77	46 (51.1%)	31 (23.0%)	
No	148	44 (48.9%)	104 (77.0%)	

**Table 3**. Baseline characteristics of prostate urethral biopsy in patients with NMIBC. Abbreviations: NMIBC,non-muscle-invasive bladder cancer; CIS, carcinoma in situ.

	Univariable		Multivariable		
Characteristics	OR (95% CI)	P-value	OR (95% CI)	P-value	
Age (years)					
< 65, ≥ 65	1.17 (0.66-2.09)	0.600		NS	
Tumor size, cm					
< 3, ≥ 3	1.87 (1.06-3.28)	0.030	1.33(0.61-2.91)	0.473	
Multiplicity					
Single, Multiple	5.09 (2.57-10.91)	< 0.001	3.30(1.33-8.79)	0.013	
Tumor location					
Others, Trigone/neck	4.93 (7.72-30.63)	< 0.001	9.15(4.38-20.20)	< 0.001	
Stage					
pTa, pT1	9.51 (2.72-60.21)	0.002	3.16(0.50-28.57)	0.251	
Grade	·				
Low, High	8.73 (3.34-30.00)	< 0.001	4.83(1.32-21.99)	0.025	
CIS	·		·		
Yes, No	1.04 (0.543-1.98)	0.895		NS	
Recurrent carcinoma					
Yes, No	3.50 (1.98-6.29)	< 0.001	4.65(2.14-10.64)	< 0.001	

**Table 4.** Univariate and multivariate analyses to identify risk factors of PUI in patients with NMIBC.Abbreviations: PUI, prostatic urethral involvement; CIS, carcinoma in situ; OR, odds ratio; CI, Confidenceinterval; NS, excluded from final model because not statistically significant.

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**Fig. 2.** Construction and verification of the nomogram prediction model for PUI in NMIBC. (**A**)The nomogram prediction model for PUI in patients with NMIBC. (**B**) **ROC curve** demonstrated the model's strong ability to discriminate between patients with and without prostatic urethral involvement (PUI) in NMIBC. LOOCV, leave-one-out cross-validation. (**C**) **Calibration curve** revealed that the actual value closely aligns with the prediction model, suggesting good calibration. (**D**) **Decision Curve Analysis (DCA)** showed that the nomogram offers significant clinical utility across a wide range of risk thresholds. LOOCV, leave-one-out cross-validation.

individual indicators alone (Fig. 2B). Additionally, before and after LOOCV, the calibration curve (Fig. 2C) and decision curve (Fig. 2D) demonstrated that the nomogram is well-calibrated and clinically useful.

In summary, multivariate logistic analyses identified four independent risk factors for PUI in bladder cancer: tumor multiplicity, trigonal/neck location, high-grade tumors, and recurrent carcinoma (all P < 0.05). The nomogram prediction model, evaluated both before and after leave-one-out cross-validation, demonstrated strong performance, as indicated by the ROC Curve (AUC=0.8), which suggests that the nomogram possesses excellent predictive ability. Additionally, the Calibration Curve illustrated a close alignment between predicted and actual probabilities, indicating excellent calibration. Decision Curve Analysis (DCA) further confirmed the model's clinical utility across a wide range of risk thresholds. Consistent findings were observed in the NMIBC subgroup. Thus, the nomogram, based on key independent risk factors, serves as a highly accurate and clinically useful tool for predicting PUI in bladder cancer patients, thereby aiding in early diagnosis and personalized treatment planning.

#### Discussion

Prostatic urethral involvement (PUI) in bladder cancer significantly impacts prognosis, with varying incidence (16–48%) depending on tumor stage and biopsy protocols<sup>6,7,19–21</sup>. Accurate identification of PUI is crucial for precise clinical and pathological classification of individuals with bladder cancer. European Association of Urology (EAU) guidelines recommend conducting a prostatic urethral biopsy under specific conditions<sup>12</sup>.

Furthermore, von Rundstedt FC et al. have shown that the occurrence of PUI in bladder cancer and tumors originating invasively from the prostatic urethra or ducts are highly likely to be detected via TUR biopsy<sup>22</sup>. Due to the high concentration of prostatic ducts in this segment of the prostatic urethra, most urothelial carcinomas of the prostate or prostatic urethra can be detected by transurethral biopsy adjacent to the verumontanum<sup>23</sup>. However, as not all patients experience prostatic involvement, screening for suitable candidates is essential to avoid unnecessary transurethral prostate biopsies.

Various subcategories have been reported for the extent of UC involvement in the prostate, including restricted mucosa, restricted duct/acinus involvement, or invasion into the stroma and extraprostatic regions<sup>24</sup>. Our PUI incidence (43.1%) aligns with studies in high-risk cohorts (35–50%)<sup>5,8,25</sup>, but exceeds rates from low-risk NMIBC populations (6–15%)<sup>9</sup>, likely due to rigorous biopsy protocols and inclusion of recurrent/high-grade tumors. Within our cohort of 127 individuals with PUI, 18 (14.2%) patients who underwent RC were ultimately diagnosed as extravesical/transmural invasion of bladder tumor into the prostate and up staged to pT4a. Consequently, thorough evaluation of the prostate sections or whole-mount step sections after RC may be crucial for accurate staging, irrespective of transurethral biopsy results. A critical dilemma in RC for bladder cancer is determining whether to perform concurrent urethrectomy. Thus, recognizing the presence of UC in the prostatic urethra prior to radical cystectomy can assist in advising patients on the most appropriate form of urinary diversion<sup>10,26</sup>. However, there remains controversy regarding the clinical significance of this biopsy before RC. In our study, RC was performed alongside urethrectomy in 21 patients with PUI. While numerous research findings indicate that intraoperative frozen section examination of the urethral margin at the time of cystectomy offers greater reliability in assessing the necessity for urethrectomy<sup>10,27</sup>, detecting PUI before RC may still be essential.

Our study identified tumor multiplicity, trigonal/neck location, high-grade tumor, and recurrent carcinoma as independent risk factors for PUI. These findings align with previous research and reinforce the importance of identifying patients at high risk<sup>20,28,29</sup>. Notably, tumors located at the trigone/neck exhibited the highest association with PUI (OR=7.42, 95% CI 4.00-14.24, P<0.001), emphasizing the necessity of targeted biopsy in these patients. This is consistent with previous reports indicating a high prevalence of PUI in tumors within this anatomical region<sup>30</sup>.

The developed nomogram, based on four independent risk factors, provides an intuitive and quantitative assessment of the risk of PUI. After being internally validated through LOOCV, the ROC curve demonstrated the model's discriminative ability to distinguish between patients with and without PUI, achieving an excellent AUC of 0.8 (95% CI: 0.749–0.851). At the optimal threshold, the model balanced sensitivity (83.5%) and specificity (72.6%), effectively minimizing both false negatives and unnecessary biopsies (Fig. 1). The Calibration curve further validated the model's reliability, indicating a close alignment between predicted probabilities and observed outcomes. Finally, DCA quantified the model's clinical utility by comparing its net benefit to the 'biopsy-all' or 'biopsy-none' strategies across threshold probabilities (10–90%). Together, these analyses confirm the nomogram's robust discrimination (ROC), accurate risk estimation (Calibration), and practical value (DCA), establishing it as a reliable tool for guiding biopsy decisions and optimizing patient management for bladder cancer in clinical practice.

Previous studies have underscored the prognostic significance of PUI in NMIBC, particularly in high-risk cases where tumor cells may be shielded from intravesical therapy by the prostatic urethra<sup>19,31,32</sup>. Our findings indicate a higher incidence of PUI (40%) in NMIBC than previously reported<sup>8</sup>, supporting the necessity of routine prostatic urethral biopsy in patients with high-risk features. Furthermore, our results highlight that recurrent carcinoma is an independent risk factor for PUI (P < 0.001), possibly due to tumor cell implantation during TURBT or failure of intravesical drugs to make direct contact with the prostatic urothelium. CIS may appear as a plush, somewhat elevated, red patch that may be challenging to distinguish from inflammation<sup>33</sup>. This challenge is further intensified in patients who have a swollen, fragile, and blood-rich prostate. Additionally, CIS in the prostatic urethra has been associated with poor prognosis and disease progression. Shen et al. have documented that survival rates following radical cystectomy are reduced in patients with CIS in the PU relative to those without it<sup>7</sup>. Consequently, the presence of CIS in the prostate may lead to the overshadowing of earlystage bladder cancer (CIS and T1). In our study, only 16 (5.4%) of the patients were reported to have CIS in the PU. This low incidence may be attributed to potential variations among pathologists in recognizing CIS at early stages. While there was no association between CIS in the bladder and PUI, a significant association was observed between increased stage, grade, multiplicity of NMIBC, and the presence of the PUI, which is aligning with the results of a study by Mungan MU et al.<sup>9</sup>. According to Herr and Donat, 39% of individuals diagnosed with high-grade Tis/Ta/T1 bladder cancer experience relapse<sup>34</sup>. Our study reveals that patients with PUI are predominantly found in high-risk NMIBC (high-grade or T1 stage) or locally advanced bladder cancer, with only two cases of PUI observed in pTa low-grade bladder cancer. Therefore, routine prostatic urethral biopsy for individuals diagnosed with bladder cancer, particularly those with low-risk NMIBC, is not warranted. However, for individuals with T1 bladder cancer, the PUI group exhibits lower survival rates pertaining to cancer and overall survival, indicating a poorer prognosis in this subgroup<sup>21</sup>. Hence, given its role in understaging and recurrence, routine prostatic urethral biopsy should be considered in high-risk NMIBC cases, particularly in patients with positive cytology and no visible bladder tumor<sup>12</sup>.

In summary, the identification of tumor multiplicity, trigonal/neck location, high-grade tumors, and recurrent carcinoma as independent risk factors for PUI enhances risk stratification in the management of bladder cancer. By utilizing the nomogram as a triage tool, high-risk patients can be prioritized for biopsy, thereby minimizing unnecessary procedures for low-risk individuals. The proposed nomogram-based risk stratification model optimizes biopsy selection and informs clinical decision-making: patients with a high nomogram score undergo TUR biopsy, while those confirmed as PUI-positive receive aggressive therapy. Conversely, patients with a low nomogram score may defer biopsy and proceed with standard care. This strategy ensures tailored

management approaches that balance diagnostic accuracy with therapeutic precision. For NMIBC patients who are PUI-positive, postoperative intravesical BCG instillation combined with prostatic urethral surveillance is recommended. MIBC patients who are PUI-positive should undergo RC with urethrectomy, supplemented by neoadjuvant or adjuvant therapy as necessary. In complex cases, such as CIS or stromal invasion, multidisciplinary collaboration among pathologists, oncologists, and radiation therapists is essential to refine staging and customize treatment plans. It is important to note that a negative biopsy does not entirely exclude the possibility of PUI, particularly in high-risk patients. The nomogram assists in identifying occult involvement, guiding intraoperative frozen section analysis or prophylactic urethrectomy when clinical suspicion remains. This integrated approach ensures precise risk stratification, therapeutic alignment, and improved long-term outcomes.

Distinguishing noninvasive (pTa) from stromal-invasive (pT4a) prostatic involvement is crucial, as treatment and prognosis differ significantly. Utilizing the AJCC 7th edition TNM staging system, our study confirmed that stromal-invasive (pT4a) cases are associated with high-grade MIBC, necessitating radical cystectomy with urethrectomy and adjuvant therapy. A limitation of the current nomogram is its inability to provide separate risk scores for pTa versus pT4a. Future refinements of the nomogram should integrate advanced markers, such as multiparametric MRI (mpMRI)-based stromal assessment<sup>35</sup> or multi-omics biomarkers, including FGFR3 mutations<sup>36</sup>, to improve predictive accuracy.

This study has several limitations. Firstly, as a retrospective, single-center investigation, it is susceptible to selection bias and may suffer from incomplete data, which could affect the generalizability of the findings. The nomogram prediction model is specifically designed for patients with confirmed bladder urothelial carcinoma and is not intended for use in screening undiagnosed populations or individuals lacking histologically confirmed bladder urothelial carcinoma. Moreover, the absence of external data verification limits the applicability of the results. Additionally, the lack of whole-mount procedures and sequential sectioning in pathological assessments may influence the true incidence and extent of prostatic involvement. Finally, the relatively small sample size may constrain the robustness of the findings. Prospective multicenter validation is essential to confirm our results and refine the predictive model.

#### Conclusions

We developed a validated nomogram incorporating tumor multiplicity, trigonal/neck location, high-grade tumor, and recurrent carcinoma to predict PUI risk in bladder cancer. This tool enhances risk stratification, optimizes biopsy selection, and informs treatment planning. Prospective studies are required to further validate and refine the model for broader clinical application.

#### Data availability

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

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#### Author contributions

Hao Xu and Yu Zhang conceptualized and designed the research and prepared the original manuscript draft.Zhe Zhang and Jian Wang assisted with manuscript writing and revisions.Chong Shen and Zhouliang Wu designed and executed the performance tests, analyzed the computational results, and contributed to the interpretation of these results for the manuscript.Yunkai Qie and Dawei Tian provided essential theoretical insights, contributed to algorithm improvements, and critically revised the manuscript for important intellectual content.Shenglai Liu, Hailong Hu and Changli Wu supervised the project, provided strategic direction , and conducted a thorough review and final approval of the manuscript prior to submission.

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#### **Declarations**

#### **Competing interests**

The authors declare no competing interests.

#### **Ethics statement**

In accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later

amendments, the present study was approved by the Medical Ethics Committee of the Second Hospital of Tianjin Medical University (Office Address: Third floor of the Comprehensive Building, The Second Hospital of Tianjin Medical University, Tianjin, China) (ethics approval number: KY2024K207, date of approval: April 15, 2024). All patients' records were analyzed anonymously in the retrospective study, which did not affect the clinical course of any patient. Due to the retrospective nature of the study, Medical Ethics Committee of the Second Hospital of Tianjin Medical University waived the need of obtaining informed consent.

#### Additional information

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