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Development of a predictive risk score for 1-year intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinoma

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Introduction The study aims to develop and internally validate a novel risk stratification model specifically designed to predict 1-year intravesical recurrence (IVR) following radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC), integrating readily available clinicopathologic parameters.

Material and methods We retrospectively analyzed 87 patients who underwent RNU for UTUC between 2012 and 2024. Patients were stratified according to IVR status at 12 months postoperatively. Univariate and LASSO logistic regression analyses were conducted to identify independent predictors. A simplified risk score was derived from regression coefficients. Model performance was assessed using area under the ROC curve (AUC), calibration plots, and bootstrap validation. Clinical utility was evaluated with decision curve analysis (DCA).

Results One-year IVR occurred in 34 patients (39.1%). Seven independent predictors were identified: tumor multifocality, ureteral tumor location, history of non-muscle-invasive bladder cancer, chronic kidney disease, preoperative ureteroscopy, intravesical bladder cuff excision, and positive surgical margins. The final model showed excellent discriminative performance (AUC = 0.854) and good calibration. Patients were stratified into low (0–2 points), intermediate (3–5), and high-risk (6–9) groups, with IVR rates of 11.1%, 53.7%, and 80.0%, respectively (p for trend <0.001). DCA demonstrated a favorable net benefit across a wide range of thresholds.

Conclusions We present a novel, internally validated scoring system that integrates routine clinicopathologic parameters to predict early IVR following RNU for UTUC. This tool may support urologists in implementing risk-adapted cystoscopic surveillance protocols and identifying candidates for early intravesical therapy. External validation is warranted prior to clinical implementation.

Key Words: upper tract urothelial carcinoma ‹› intravesical recurrence ‹› radical nephroureterectomy ‹› risk stratification

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon malignancy, accounting for approximately 5% of all urothelial tumors, yet it poses a significant clinical challenge due to its aggressive biological behavior and elevated risk of recurrence and metastasis [1]. For patients with localized UTUC, radical nephroureterectomy (RNU) with en bloc excision of the bladder cuff remains the gold standard surgical treatment [2]. One of the most frequent and concerning postoperative complications following RNU is intravesical recurrence (IVR), which occurs in approximately 22% to 47% of patients during follow-up [3].

Multiple perioperative, tumor-related, and procedural factors have been implicated in the pathogenesis of IVR following RNU for UTUC, a complication that substantially impairs long-term oncological control. One of the most consistently reported predictors of IVR is a prior history of non-muscle-invasive bladder cancer (NMIBC), which is believed to represent a field cancerization effect within the entire urothelium and may predispose to multifocal tumor development [4]. Tumor multifocality and anatomical distribution, particularly when both the renal pelvis and ureter are simultaneously involved, have also been associated with increased IVR risk, likely reflecting a broader urothelial transformation and higher exfoliation potential of malignant cells [4].

Moreover, diagnostic ureteroscopy (URS), although widely employed for preoperative evaluation and tumor localization, has been increasingly scrutinized for its potential to promote tumor cell dissemination. A comprehensive meta-analysis demonstrated that URS prior to RNU was independently associated with a significantly higher risk of IVR, possibly due to increased intrarenal pressure, pyelovenous backflow, and direct mechanical disruption of the tumor [5]. This association appears to be further exacerbated when URS is combined with biopsy, as supported by recent institutional evidence indicating a markedly elevated IVR risk in such cases [6].

Collectively, these findings underscore the multifactorial etiology of IVR and highlight the need for individualized surveillance and risk-adapted postoperative management strategies in patients undergoing RNU for UTUC. Despite the identification of various clinical, pathological, and procedural predictors, existing risk stratification tools remain suboptimal in discriminating patients at high risk for early IVR. In the present study, we defined early IVR as recurrence occurring within 12 months after RNU. This cutoff was selected in line with recent literature suggesting that a substantial proportion of IVR events occur during the first postoperative year, and that early recurrence may represent a clinically meaningful subset with distinct biological behavior [7].

In this context, our study aims to develop and internally validate a predictive risk model specifically tailored to estimate the likelihood of 1-year IVR following RNU. By systematically evaluating a comprehensive set of demographics, oncologic, and perioperative variables in a well-characterized cohort, we seek to provide clinicians with a practical and evidence-based tool that can inform personalized follow-up protocols and optimize surveillance intensity in high-risk individuals.

MATERIAL AND METHODS

Study design and setting

This retrospective cohort study was conducted at a single tertiary referral center, the University of Health Sciences Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey. We retrospectively reviewed the medical records of patients who underwent RNU for UTUC between January 2012 and July 2024. All patients were managed according to a standardized postoperative surveillance protocol, which included cystoscopic evaluation at 3-month intervals during the first postoperative year. Patients who received postoperative intravesical chemotherapy (e.g., mitomycin C or pirarubicin) were excluded from the analysis. Follow-up compliance was confirmed through the hospital electronic medical record system and outpatient clinic attendance. To minimize inter-operator variability, all surgeries were performed by a dedicated urologic oncology team experienced in upper tract surgery and bladder cuff excision.

Study population and eligibility criteria

Adult patients (≥18 years) who underwent RNU for pathologically confirmed UTUC with a minimum postoperative follow-up period of 12 months, including routine cystoscopic surveillance within the first postoperative year, were included. Exclusion criteria encompassed prior radical cystectomy due to invasive bladder cancer (BC), ureteroscopic ablation), postoperative intravesical chemotherapy (e.g., epirubicin), secondary malignancies (non-urothelial or metastatic tumors), incomplete clinical or pathological data, and inadequate postoperative follow-up (<12 months) or absence of cystoscopic evaluation within the first postoperative year (Figure-1).

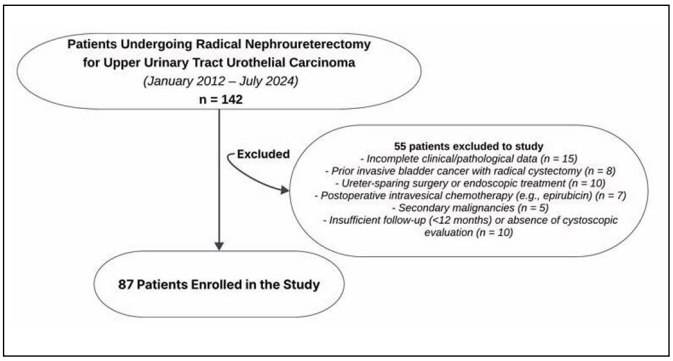

Figure 1. *Flowchart of patient selection and exclusion criteria.*

Data collection

Data including demographic characteristics, clinical variables, and pathological parameters were systematically extracted from patient medical charts, surgical records, and pathology reports. The collected data included patient age, sex, comorbidities (such as CKD), smoking history, prior BC history, preoperative diagnostic URS and cystoscopy results, tumor location (renal pelvis versus ureteral or multifocal), tumor size, tumor focality, surgical margin status, and the surgical technique utilized for bladder cuff excision.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were reported as medians with interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Comparisons between patients with and without 1-year IVR were conducted using the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables.

Variables significantly associated with IVR in univariate analysis were considered for multivariable modeling. Predictor selection was performed using the Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression method. Based on 34 IVR events, the final model included seven predictors, achieving an events-per-variable (EPV) ratio of 4.9. To minimize overfitting and enhance model robustness, we applied LASSO regularization and performed internal validation using 1,000-bootstrap resampling. Model discrimination was assessed via receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) and its 95% confidence interval reported. Calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test and calibration plots.

A simplified point-based risk score was constructed from the LASSO model coefficients, assigning weights according to coefficient magnitude. Patients were subsequently stratified into low-, intermediate-, and high-risk groups based on total risk scores and corresponding observed 1-year IVR rates. The clinical utility of the scoring system was further assessed using decision curve analysis (DCA) to evaluate net benefit across a range of threshold probabilities.

Bioethical standards

The study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital, Clinical Research Ethics Committee (HNEAH-GOAEK/KK/2025-87, Date: July 1, 2025). All participants provided informed consent to participate in the study.

RESULTS

Patient characteristics and univariate analysis

At the 1-year postoperative follow-up, IVR was observed in 34 patients (39.1%), while 53 patients (60.9%) remained recurrence-free. Univariate analysis revealed significant associations between IVR and older age (median 71 vs 67 years, $p = 0.047$), presence of CKD (47.1% vs 18.9%, $p = 0.005$), prior history of BC (50.0% vs 18.9%, $p = 0.002$), and multifocal tumors (38.2% vs 15.1%, $p = 0.014$). Ureteral or multifocal tumor localization was also significantly more common in the IVR group (61.8% vs 35.8%, $p = 0.018$). Additionally, diagnostic URS prior to surgery was associated with a higher IVR incidence (64.7% vs 34.0%, $p = 0.005$). Positive surgical margins (20.6% vs 1.9%, $p = 0.005$) and intravesical bladder cuff excision (52.9% vs 24.5%, $p = 0.030$) were also significantly correlated with recurrence. No statistically significant differences were found for diabetes mellitus, hypertension, sex, smoking history, tumor grade, stage, presence of carcinoma in situ, lymphovascular invasion, or laterality (all $p > 0.05$; Table 1).

LASSO logistic regression and predictor selection

Among 15 candidate variables, LASSO regression identified seven predictors with non-zero coefficients: R1 margin, diagnostic URS, intravesical cuff excision, age ≥70 years, ureteral tumor location, prior history of BC, and CKD. These variables were retained in the final model, while all others were excluded due to coefficients shrunk to zero (Table 2).

Model performance: Discrimination and calibration

The final LASSO model demonstrated strong discriminative performance for predicting 1-year IVR, with an area under the ROC curve (AUC) of 0.854 (Figure 2A). To internally validate the model, we performed bootstrap resampling with 1000 iterations, yielding a mean AUC of 0.856 (95% CI: 0.771–0.928), indicating robust internal validity and low overfitting risk. The Hosmer–Lemeshow goodness-of-fit test indicated no significant deviation between predicted and observed out-

Table 1. *Comparison of demographic, clinical, and pathological variables between patients with and without 1-year IVR after UTUC surgery*

	IVR postop 1-year (n = 34)	Non-IVR postop 1-year (n = 53)	p
Continuous variables (Median [IQR])			
Age (years)	71 (63.75–75)	67 (57.5–73)	**0.047***
Tumour size (cm)	5 (4–7)	4 (3–6.5)	0.148*
Categorical variables (n, %)			
Diabetes mellitus			
Yes	26 (76.5%)	43 (81.1%)	0.362**
No	8 (23.5%)	10 (18.9%)	
Hypertension			
Yes	20 (58.8%)	28 (52.8%)	0.277**
No	14 (41.2%)	25 (47.2%)	
Coronary artery disease			
Yes	14 (41.2%)	15 (28.3%)	0.110**
No	20 (58.8%)	38 (71.7%)	
Chronic kidney disease			
Yes	16 (47.1%)	10 (18.9%)	**0.005****
No	18 (52.9%)	43 (81.1%)	
Sex			
Male	30 (88.2%)	41 (77.4%)	0.201**
Female	4 (11.8%)	12 (22.6%)	
Operation side			
Right	16 (47.1%)	27 (50.9%)	0.724**
Left	18 (52.9%)	26 (49.1%)	
Smoking history			
User	26 (76.5%)	43 (81.1%)	0.600**
Non-user	8 (23.5%)	10 (18.9%)	
Previous bladder cancer history			
Yes	17 (50.0%)	10 (18.9%)	**0.002****
No	17 (50.0%)	43 (81.1%)	
Tumour localisation			
Renal pelvis	13 (38.2%)	34 (64.2%)	**0.018****
Ureter/renal pelvis and ureter	21 (61.8%)	19 (35.8%)	
Tumor focality			
Unifocal	21 (61.8%)	45 (84.9%)	**0.014****
Multifocal	13 (38.2%)	8 (15.1%)	
Preoperative diagnostic URS history			**0.005****
Yes	22 (64.7%)	18 (34.0%)	
No	12 (35.3%)	35 (66.0%)	
Hydronephrosis			
Grade 0/1	7 (20.6%)	19 (35.8%)	0.129**
Grade 2/3	27 (79.4%)	34 (64.2%)	
T subgroup stage			
< T2	19 (55.9%)	30 (56.6%)	0.947**
T2–T4	15 (44.1%)	23 (43.4%)	
Grade			
Low grade	15 (44.1%)	23 (43.4%)	0.947**
High grade	19 (55.9%)	30 (56.6%)	
CIS			
Yes	1 (2.9%)	8 (15.1%)	0.069**
No	33 (97.1%)	45 (84.9%)	
LVI			
Yes	4 (11.8%)	8 (15.1%)	0.660**
No	30 (88.2%)	45 (84.9%)	
Bladder surgical margine			
R0	27 (79.4%)	52 (98.1%)	**0.005****
R1	7 (20.6%)	1 (1.9%)	
Bladder cuff removal technique			
Intravesical	16 (52.9%)	13 (24.5%)	**0.030****
Extravesical	18 (47.1%)	40 (75.5%)	

* Mann-Whitney U test, ** Chi-square
CIS – carcinoma in situ; LVI – lymphovascular invasion; URS – ureteroscopy

Table 2. *Predictors of 1-year intravesical recurrence identified by LASSO logistic regression*

Predictor Variable	Selected by LASSO	β Coefficient	Assigned Score
Bladder surgical margin (R1)	Yes	0.872	2
Preoperative diagnostic URS (Yes)	Yes	0.713	2
Intravesical cuff excision	Yes	0.547	1
Age ≥70 (years)	Yes	0.509	1
Tumor localization (ureter)	Yes	0.500	1
Previous bladder cancer	Yes	0.326	1
Chronic kidney disease	Yes	0.087	1
(Other variables)	No	0	–

URS – ureteroscopy

Table 3. *Distribution of patients and 1-year intravesical recurrence rates according to risk score categories*

Risk group	Score range	n	IVR cases	1-year IVR rate (%)
Low risk	0–2	36	4	11.1
Intermediate	3–5	41	22	53.7
High risk	6–9	10	8	80.0

IVR – intravesical recurrence

comes ($\chi^2 = 5.53$, df = 8, p = 0.700), confirming that the model was well calibrated.

Model calibration was assessed using a calibration curve comparing predicted and observed probabilities across deciles of risk. The curve demonstrated good agreement, with the predicted probabilities closely tracking the actual observed proportions (Figure 2B). This indicates that the model was well-calibrated for predicting 1-year IVR.

Risk score development and grouping

To facilitate practical use in clinical decision-making, a simplified risk score was developed by assigning points based on the magnitude of β coefficients

obtained from the LASSO regression model. Predictor variables with β coefficients ≥0.70 were assigned 2 points, while those with lower but non-zero coefficients received 1 point, yielding a total score ranging from 0 to 9 for each patient.

The cut-off values for stratifying patients into risk groups were empirically determined based on the distribution of total risk scores and the corresponding observed 1-year IVR rates. Patients were classified into three risk categories: low (0–2 points), intermediate (3–5 points), and high (6–9 points). A distinct stepwise increase in IVR was observed across these groups – 11.1% in the low-risk group, 53.7% in the intermediate group, and 80.0% in the high-risk group – underscoring the clinical relevance and discriminative capacity of the scoring system. These intervals also ensured adequate group sizes, reducing class imbalance and improving interpretability. The distribution of patients and their respective 1-year IVR rates across these risk categories is summarized in Table 3.

Based on the assigned scores, patients were stratified into low (0–2 points), intermediate (3–5 points), and high-risk (6–9 points) categories. A stepwise increase in 1-year IVR rates was observed across these groups – 11.1% in the low-risk group, 53.7% in the intermediate-risk group, and 80.0% in the high-risk group – which was statistically significant (p for trend <0.001) (Figure 3A). This trend supports the scoring system's ability to effectively discriminate recurrence risk in clinical settings. The corresponding ROC curve yielded an AUC of 0.833 (95% CI: 0.743–0.906) (Figure 3B), confirming the strong predictive performance of the simplified score. The calibration curve for the simplified score also demonstrated good agreement between predicted probabilities and observed IVR rates (Figure 3C), supporting the model's reliability in estimating recurrence risk across all strata.

To evaluate the clinical utility of the risk score, Decision Curve Analysis (DCA) was performed. As shown in Figure 4, the model provided a higher net benefit across a wide range of threshold probabilities compared to both the "treat all" and "treat none" strategies. This supports the potential value of the risk score in guiding postoperative surveillance and decision-making in patients undergoing surgery for UTUC.

DISCUSSION

UTUC is a relatively rare malignancy, accounting for approximately 5–10% of all urothelial cancers, yet it exhibits aggressive clinical behavior. One of the most frequent and concerning postoperative complications following RNU is IVR, which occurs in approximately 22–47% of patients. The pathogenesis of IVR is thought to involve two main mechanisms: the "seeding" hypothesis, which attributes recurrence to the implantation of exfoliated tumor cells into the bladder, and the "field effect" theory, which suggests a molecularly altered urothelium with a predisposition for multifocal tumor development. This phenomenon represents a major challenge in the long-term oncological control of UTUC patients [8].

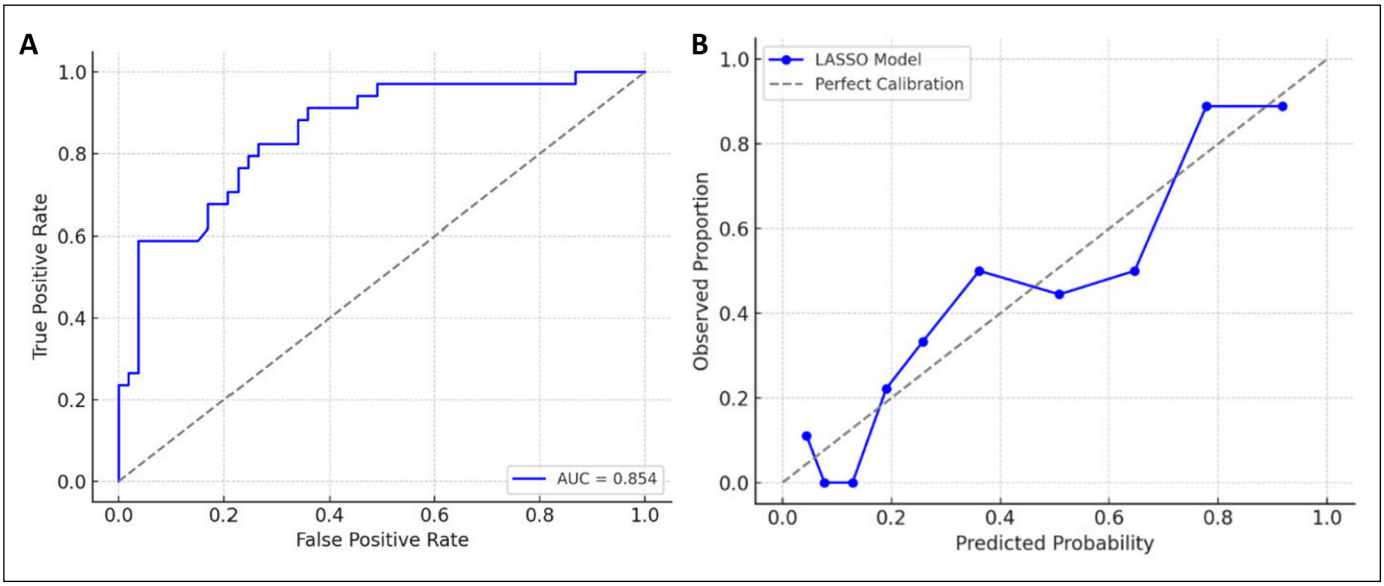

Figure 2. A) *ROC curve for the LASSO logistic regression model predicting 1-year IVR (AUC = 0.854).* **B)** *Calibration curve for the LASSO Logistic Regression Model.*

The relationship between patient age and IVR after RNU for UTUC remains controversial. While the comprehensive meta-analysis by Yuan et al. and the propensity score–matched study by Zhao et al. found no significant association between age and IVR [9, 10], Fradet et al. demonstrated in a large cohort that each additional year of age significantly increased IVR risk [11]. Echoing this finding, our study identified age ≥70 years as an independent predictor of 1-year IVR. This supports the hypothesis that immunosenescence or impaired urothelial regeneration in elderly patients may contribute to early IVR. Unlike previous reports, our analysis specifically focused on early IVR and employed a clear age cutoff, further highlighting the importance of age-adjusted postoperative monitoring.

In terms of preoperative CKD, accumulating evidence suggests a significant association between impaired renal function present at the time of surgery and the subsequent risk of IVR following RNU for UTUC. Seisen et al., in a large-scale meta-analysis, identified preoperative CKD as an independent predictor of IVR, highlighting the potential role of systemic host factors in urothelial field carcinogenesis and tumor implantation [3]. Similarly, Kodama et al. reported a higher incidence of IVR among patients with preoperative CKD, supporting the notion that renal dysfunction may predispose to intraluminal tumor cell reimplantation [12]. In concordance with these findings, our study also demonstrated a significant association between preoperative CKD and early (1-year) IVR.

In terms of prior BC history, accumulating evidence suggests a strong link between previous NMIBC and increased risk of IVR after RNU for UTUC. Milojevic et al. identified prior NMIBC as an independent predictor of IVR, supporting the concept of urothelial field change and multifocal carcinogenesis [13]. Similarly, Veeratterapillay et al. demonstrated that a history of BC remained a significant risk factor for IVR in multivariate analysis, even after adjusting for tumor stage and location [14]. Consistent with these findings, our study also revealed a significant association between prior BC and early (1-year) IVR, highlighting the need for closer postoperative surveillance in this subgroup.

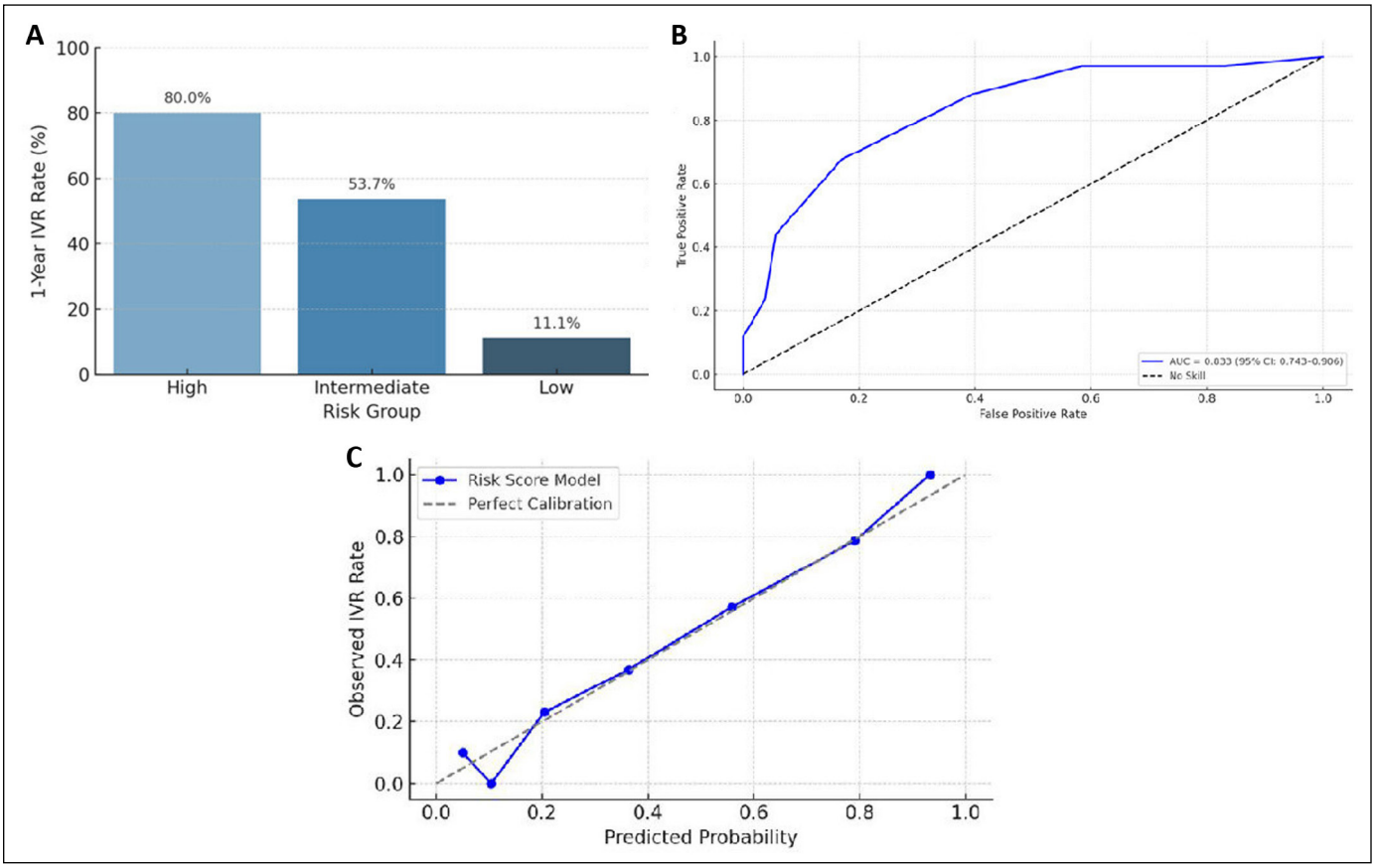

Figure 3. A) *Bar graph illustrating the 1-year IVR rates across the three risk groups defined by the scoring system: low, intermediate, and high.* **B)** *ROC curve for the simplified risk score, demonstrating its performance in predicting 1-year IVR (AUC = 0.833).* **C)** *Calibration plot of the simplified risk score for predicting 1-year IVR.*

The prognostic relevance of tumor location in UTUC remains a subject of debate. Earlier investigations, including those by Favaretto et al. and Liu et al., did not identify a statistically significant association between ureteral location and IVR following RNU [15, 16]. However, more recent large-scale studies have reported contrasting findings. Chen et al., in a multicenter analysis of over 2,000 patients, demonstrated that ureteral tumors were independently associated with increased IVR risk (HR: 1.359, p = 0.001) [17], a result further supported by Lee et al. (HR: 1.476, p = 0.013) [18]. In line with this emerging evidence, our study also identified ureteral involvement as a significant predictor of early (1-year) IVR. These findings may be explained by anatomical proximity to the bladder and the increased likelihood of tumor cell dissemination during urinary flow or surgical manipulation. Collectively, the data suggest that ureteral tumor localization should be considered a high-risk feature for early IVR and may warrant intensified surveillance strategies.

The presence of multifocal tumors has been identified as a significant risk factor for IVR in several studies. Both Lee et al. and Seisen et al. reported that multifocality independently increases the likelihood of IVR following RNU [18, 19]. In alignment with these findings, our study demonstrated a significant association between multifocal tumors and 1-year IVR. This reinforces the notion that multifocality may reflect widespread urothelial field changes, serving as a strong marker for early recurrence.

The prognostic impact of preoperative diagnostic URS in patients undergoing RNU for UTUC remains a subject of ongoing debate. Several studies have reported a significant association between URS and an increased risk of IVR, which is hypothesized to result from mechanical tumor disruption, elevated intrarenal pressure, and pyelovenous or lymphatic backflow during endoscopic manipulation. Tan et al., in a meta-analysis of 11 studies encompassing 4,057 patients, demonstrated that URS prior to RNU was independently associated with a higher risk of IVR [20]. Similarly, İzol et al., in a multicenter retrospective cohort, identified URS as an independent predictor of bladder recurrence, reporting nearly a twofold increase in IVR rates among patients who underwent diagnostic URS compared to those who did not [21]. Consistent with these findings, our study also identified preoperative URS as a significant predictor of early (1-year) IVR, further supporting the hypothesis that diagnostic endoscopic intervention in the upper urinary tract may facilitate downstream tumor cell implantation within the bladder.

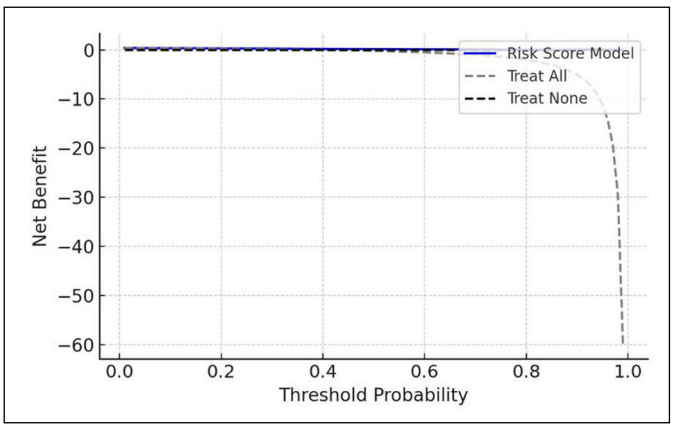

Figure 4. *DCA for the simplified risk score predicting 1-year intravesical recurrence.*

In the context of surgical technique–related risk factors, Katims et al., in a robust multicenter study of patients undergoing exclusively minimally invasive RNU, demonstrated that both positive surgical margins and transurethral bladder cuff excision were independently associated with an increased risk of IVR, even in the absence of prior BC [22]. These findings highlight the oncologic significance of complete tumor excision and optimal distal ureter management in mitigating recurrence risk. In line with these data, our study also identified transurethral cuff excision and positive margin status as independent predictors of early (1-year) IVR. Taken together, these results underscore the critical importance of surgical technique – particularly with regard to bladder cuff management and margin control – in reducing IVR following RNU.

Zhang et al. developed a retrospective model in patients with organ-confined UTUC to predict long-term IVR, identifying tumor stage, size, grade, and localization as independent prognostic factors [23]. In our cohort, tumor localization similarly emerged as a common predictor; however, tumor size and grade were not significant for early recurrence. Instead, perioperative variables such as diagnostic URS, intravesical bladder cuff excision, and positive surgical margins demonstrated strong predictive value. This comparison suggests that IVR is shaped by a multifactorial interplay between intrinsic tumor biology and iatrogenic or surgical factors, with the relative contribution of these determinants varying according to the timing of recurrence.

This study introduces one of the few scoring models specifically designed to predict early (1-year) IVR following RNU for UTUC. By integrating readily available clinicopathologic parameters – including tumor multifocality, ureteral location, prior BC, CKD, diagnostic URS, transurethral bladder cuff

excision, and surgical margin status – we developed an internally validated, risk-based stratification tool. The model may assist clinicians in identifying patients at high risk who could benefit from intensified postoperative surveillance (e.g., 3-monthly cystoscopy) and early initiation of adjuvant intravesical therapies, particularly Bacillus Calmette–Guérin (BCG). Conversely, low-risk patients may be managed with conventional follow-up protocols. This approach promotes personalized management, facilitates appropriate resource utilization, and may help prevent early IVR in patients undergoing surgery for UTUC.

This study has several limitations that should be acknowledged. Its retrospective design and single-center setting may introduce selection bias and limit generalizability. While the sample size was adequate for model development and internal validation, external validation in larger, multicenter cohorts is warranted to confirm the model's predictive accuracy. The lack of standardized postoperative intravesical chemotherapy administration across patients precluded assessment of therapeutic modifiers on IVR. Despite these limitations, the proposed score may serve as a foundation for future prospective studies evaluating the efficacy of risk-adapted adjuvant BCG protocols in preventing IVR after RNU.

CONCLUSIONS

This study presents a novel and internally validated scoring system designed to predict early (1-year) IVR following RNU for UTUC. By incorporating readily available clinicopathologic parameters, the model demonstrated good discriminatory performance and calibration. While the score may assist in identifying patients at elevated risk for early recurrence, its clinical applicability remains exploratory. Pending further external validation, the risk stratification tool may help inform individualized postoperative strategies – such as intensified cystoscopic follow-up or consideration of early intravesical therapy – in high-risk patients.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital, Clinical Research Ethics Committee (HNEAH-GOAEK/KK/2025-87, Date: July 1, 2025). All participants provided informed consent to participate in the study.

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