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# Preoperative multiplex nomogram for prediction of high-risk nonorgan-confined upper-tract urothelial carcinoma

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**Abstract**

**Background:** Accurate risk stratification prior to radical nephroureterectomy remains a challenge with upper-tract urothelial carcinoma (UTUC). Herein, we generated an optimized preoperative tool predicting high-risk nonorgan-confined (NOC)-UTUC.

**Materials and Methods:** Retrospective evaluation of 699 patients undergoing radical nephroureterectomy at 3 academic centers. Multiplex preoperative patient, imaging, endoscopic, and laboratory values were evaluated. Model derivation and validation were based on a split-sample method. Patients were divided randomly into a development (training) cohort (70% of patients) and validation (test) cohort (30% of patients). Univariate and multivariate logistic regression addressed the prediction of NOC disease (pT3/pT4 and/or pN+) based on training cohort. A backward stepdown selection process achieved the most informative nomogram. The ROC analysis identified a cut-off point predicting high-risk disease. The test cohort served as "external" validation to verify the findings based on the training cohort. Bootstrap resampling was conducted for both internal and "external" validation to evaluate the model fitting.

**Results:** Total of 566 patients included for analysis, mean age 69.7 years, 85% Caucasian, 64% male, 62% high grade. NOC-UTUC was found in 184 (32.5%) patients on final pathology. Of 184 patients with NOC-UTUC, an equal number of renal pelvis and ureter only tumors ($n = 74$; 40.2% for each location) were noted; 36 (19.6%) had tumors in both locations. Multivariate model based on development cohort ($n = 396$) demonstrated clinical stage (odds ratio [OR] 14.0, $P < 0.01$), biopsy tumor grade (OR 3.3, $P = 0.01$), tumor architecture (OR 2.65, $P = 0.09$), and Hgb (OR 0.8, $P = 0.02$) level were independently associated with NOC disease. A preoperative nomogram incorporating these 4 variables achieved 82% accuracy, 48% sensitivity, and 95% specificity in predicting NOC-UTUC. The cut-off point for predicting high-risk disease was ≥0.49.

**Conclusions:** We established and validated an accurate tool for the prediction of locally advanced NOC-UTUC. This preoperative nomogram can be used to more optimally select patients for preoperative systemic chemotherapy, and facilitate clinical trial enrollment. 

*Keywords:* Nomogram; Prediction; Nephroureterectomy; Nonorgan confined; Upper-tract urothelial carcinoma

## 1. Introduction

Upper-tract urothelial carcinoma (UTUC) is an uncommon malignancy accounting for only 5−10% of all urothelial carcinomas with an annual estimate of 2 cases diagnosed per 100,000 individuals in the Western hemisphere [1−3]. Surgical resection with radical nephroureterectomy (RNU) and ipsilateral bladder cuff represents the standard treatment for those who have high-volume or high-risk disease, since approximately 60% of UTUC are invasive at presentation, in contrast to 15−20% of bladder urothelial carcinoma [1,4,5]. Although adequate local tumor control can be provided by RNU, a significant

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proportion of patients with adverse features will develop systemic disease progression with resultant mortality [4]. Prior studies have shown that patients with nonorgan-confined (NOC)-UTUC have significantly decreased cancer-specific survival of 41−54% compared to those with organ-confined (OC) disease [4,5].

A major challenge with UTUC remains the accurate clinical risk stratification of patients prior to RNU. Such knowledge has potential multifactorial benefits. First, surgical kidney removal directly contributes to significant loss of renal function precluding effective post-RNU adjuvant therapy [6]. While there is level I evidence to support the use of cisplatin-based neoadjuvant chemotherapy for muscle-invasive bladder cancer [7], the evidence for UTUC has been limited to retrospective and meta-analyses exploring the use of chemotherapy in neoadjuvant and adjuvant settings [8−10]. The largest series thus far showed a 90% 5-year disease-specific survival in patients receiving neoadjuvant chemotherapy compared to 57.6% in a matched historical cohort undergoing initial surgery [10]. Therefore, methods to more accurately predict high-risk disease in the clinical, pre-RNU setting would have a major impact on patient care by allowing better (and more appropriate) patient selection for endoscopic vs. extirpative surgery as well as the optimal timing for integration of perioperative systemic therapy regimens. Finally, with the increased use of immunotherapy for urothelial carcinomas, clinical trial selection and enrollment would be facilitated by preoperative risk stratification.

The European Association of Urology has reported their consensus criteria for high-risk disease including high-grade tumors on both cytology and endoscopic biopsy, presence of hydronephrosis, tumor size >2 cm, multifocal disease, history of bladder cancer treated with prior radical cystectomy, and variant histology [1]. A prior preoperative nomogram incorporated patient and tumor factors [11] but since then various other predictive factors have been reported [12]. To date, diagnostic accuracy of these nomograms has remained promising yet suboptimal to include in clinical practice. Therefore, to further improve UTUC disease prediction using any potentially relevant clinical variable, we developed a multiplex preoperative clinical risk stratification nomogram to predict OC and NOC-UTUC based on patient, tumor, imaging, endoscopic, and laboratory preoperative parameters.

## 2. Materials and Methods

### 2.1. Patients

Three tertiary cancer centers contributed 310, 257, and 132 patients, respectively, undergoing surgical excision with RNU or ureterectomy. Each participating institution obtained institutional review board approval prior to participation with necessary institutional data sharing agreements before study initiation. These 699 patients underwent surgery between April 1993 and October 2016. For the purpose of developing this preoperative nomogram for NOC-UTUC (defined as pT3/pT4 and/or pN+ at surgery), only those patients without prior neoadjuvant chemotherapy, radiation therapy, or clinically node-positive disease were included. The 3 senior urologists from each institution initially agreed on all preoperative variables to analyze based on published data and expert opinion. These included patient variables (age, gender, race, body mass index [BMI], symptoms, Eastern Cooperative Oncology Group performance status, and Charlson comorbidity index); imaging data (maximum tumor size measured on cross-sectional imaging scans, primary tumor location, presence of hydronephrosis, imaging findings of tumor extension, and tumor locality [renal pelvis, ureter, or both]); endoscopic and related data (selective cytology, biopsy tumor grade [low vs. high], clinical stage, tumor architecture [papillary vs. sessile], and multifocality); and laboratory data (neutrophil to lymphocyte ratio [NLR], serum sodium, estimated glomerular filtration rate [eGFR] measured in ml/min/1.73 $m^2$ based on CKD-EPI equation [13], hemoglobin (Hgb), and albumin levels). When performed, lymphadenectomy templates for right-sided renal pelvis and proximal ureter UTUC included hilar, paracaval, and retrocaval lymph nodes, and occasionally interaortocaval nodes. For left-sided UTUC, hilar and paraaortic nodes were included. Surgical specimens were processed according to standard pathologic procedures and these tumors were staged and graded by genitourinary pathologists at each institution [14,15]. Clinical stage incorporated findings from endoscopic biopsy stage and cross-sectional imaging characteristics of infiltrative disease of each patient on the study. Clinical (c) stage classification was according to the American Joint Commission on Cancer criteria: cTx if invasion could not be assessed on biopsy due lack of subepithelial tissue, cTa (noninvasive on biopsy), cTis (carcinoma in situ on biopsy), cT1 (lamina propria invasion on biopsy), cT2 (muscularis invasion on biopsy), and cT3 (infiltrative disease on imaging).

### 2.2. Statistical Analysis and Nomogram Generation

Patient demographics and clinical data were compared between subgroups using Wilcoxon rank sum and Fisher's exact tests for continuous and categorical variables, respectively. Model derivation and validation were based on a split-sample method. Patients were divided randomly into 2 subgroups: a development (training) cohort (70% of eligible patients) used to derive the final model; and a validation (test) cohort (30% of eligible patients) used to validate the final model. The process involved starting with all candidate variables: patient demographics, imaging, endoscopic, biopsy, and laboratory data. In the development cohort, variables with $P \leq 0.1$ on the univariate analyses were considered in a saturated model. Then a backward stepdown selection process was used to achieve a reduced model with

Table 1a
Patient and imaging characteristics included in the study

| Variables | Study cohort ($n = 566$) (%)[a] | Development cohort ($n = 396$) (%)[a] | Validation cohort ($n = 170$) (%)[a] | *P* Value |
|---|---|---|---|---|
| *Demographics* | | | | |
| Age, years (SD) | 69.7 (10.7) | 69.7 (10.8) | 69.6 (10.6) | 0.99 |
| Gender | | | | 0.29 |
| Male | 362 (64) | 259 (65.4) | 103 (60.6) | |
| Female | 204 (36) | 137 (34.6) | 67 (39.4) | |
| Race | | | | 0.24 |
| Caucasian | 462 (85.4) | 325 (86.7) | 137 (82.5) | |
| Non-Caucasian | 79 (14.6) | 50 (13.3) | 29 (17.5) | |
| BMI, kg/m$^2$ (SD) | 28.7 (6.4) | 28.9 (6.3) | 28.7 (6.5) | 0.70 |
| Symptoms | | | | |
| None | 151 (30.4) | 106 (29.9) | 45 (31.7) | 0.75 |
| Local (gross hematuria/flank pain) | 345 (69.6) | 248 (70.1) | 97 (68.3) | |
| None | 479 (96.6) | 344 (97.2) | 135 (95.1) | 0.28 |
| Systemic | 17 (3.4) | 10 (2.8) | 7 (4.9) | |
| ECOG performance status | | | | 0.26 |
| 0–1 | 459 (87.3) | 317 (86.1) | 142 (89.9) | |
| 2–3 | 67 (12.7) | 51 (13.9) | 16 (10.1) | |
| CCI | | | | 0.27 |
| 0, 1, 2, 3 | 151 (33.9) | 102 (32.3) | 49 (37.7) | |
| >3 | 295 (66.1) | 214 (67.7) | 81 (62.3) | |
| Year of surgery | | | | 0.01 |
| ≤1999 | 57 (10.1) | 31 (7.8) | 26 (15.3) | |
| 2000–2009 | 245 (43.3) | 168 (42.4) | 77 (45.3) | |
| ≥2010 | 264 (46.6) | 197 (49.7) | 67 (39.4) | |
| *Imaging* | | | | |
| Tumor size, cm (SD) | 3.63 (2.4) | 3.6 (2.5) | 3.6 (2.3) | 0.70 |
| Hydronephrosis[b] | | | | 0.40 |
| None/mild | 352 (68.3) | 245 (67.1) | 107 (71.3) | |
| Moderate/severe | 163 (31.7) | 120 (32.9) | 43 (28.7) | |
| Tumor location | | | | 0.28 |
| Renal pelvis/calyces | 259 (46.5) | 174 (44.7) | 85 (50.6) | |
| Ureter | 247 (44.3) | 181 (46.5) | 66 (39.3) | |
| Both | 51 (9.2) | 34 (8.7) | 17 (10.1) | |
| Tumor focality[c] | | | | 0.40 |
| Unifocal | 336 (75.5) | 241 (76.8) | 95 (72.5) | |
| Multifocal | 109 (24.5) | 73 (23.2) | 36 (27.5) | |
| Infiltrative component[d] | | | | 0.13 |
| Absent | 370 (88.9) | 261 (90.6%) | 109 (85.2%) | |
| Present | 46 (11.1) | 27 (9.4%) | 19 (14.8%) | |

BMI = body mass index; CCI = Charlson comorbidity index; ECOG = Eastern Cooperative Oncology Group.
[a] Values represent percentages except where noted.
[b] Data were available for 515 patients.
[c] Data were available for 445 patients.
[d] Data were available for 416 patients.

least number of pertinent clinicopathologic variables remaining with $P \leq 0.1$ that would result in the most informative nomogram identifying pT-stage/pN-stage [16]. The multivariate logistic regression model coefficients were used to construct the nomogram. The Hosmer-Lemeshow test was conducted to check the goodness of fit for the final model (higher *P* value indicates a good fit). The discrimination and calibration of the nomogram were evaluated by the receiver operating characteristic (ROC) curve (AUC or *c*-index) and calibration plot, respectively, using bootstrap resampling (repetition = 1,000). ROC curve analyses were used to identify the threshold value of predictive probability for grouping patients into high- or low-risk groups for NOC disease where the identified cut-off point was utilized to maximize the accuracy (efficiency) of the nomogram [17]. In addition, the test cohort ($n = 170$ patients) was used to "externally" validate the final model. For each patient, we calculated the predictive probability using the parameter estimates from the final model developed utilizing training cohort. Applying the cutting threshold of high risk, the patients were categorized into high- or low-risk group, and the subsequent estimates such as sensitivity, specificity, and *c*-index (accuracy) were computed. One thousand bootstrap samples based on the validation cohort were created

Table 1b
Laboratory and endoscopic data for patients included in the study

| Variables | Study cohort ($n = 566$) (%)[a] | Development cohort ($n = 396$) (%)[a] | Validation cohort ($n = 170$) (%)[a] | *P* Value |
|---|---|---|---|---|
| *Laboratory* (SD) | | | | |
| N:L ratio | 3.9 (3.88) | 4.1 (3.97) | 3.6 (3.69) | 0.31 |
| Serum Na, mEq/L | 139.9 (3.32) | 139.7 (3.31) | 140.6 (3.28) | 0.02 |
| eGFR, ml/min/1.73 $m^2$ | 60.6 (22.4) | 60.8 (22.9) | 60.2 (21.26) | 0.88 |
| Hgb, g/dl | 12.8 (1.76) | 12.7 (1.8) | 12.7 (1.66) | 0.18 |
| Albumin, g/dl | 4.1 (0.42) | 4.1 (0.45) | 4.1 (0.35) | 0.58 |
| *Endoscopic* | | | | |
| Clinical stage[b] | | | | 0.15 |
| cTx, cTa, cTis | 290 (79) | 211 (81.2) | 79 (73.8) | |
| cT1-cT2 | 31 (8.4) | 22 (8.5) | 9 (8.4) | |
| cT3 | 46 (12.5) | 27 (10.4) | 19 (17.8) | |
| Biopsy tumor grade[c] | | | | 0.90 |
| Low | 140 (38.5) | 101 (38.1) | 39 (39.4) | |
| High | 224 (61.5) | 164 (61.9) | 60 (60.6) | |
| Tumor architecture[d] | | | | 0.52 |
| Papillary | 433 (89.3) | 303 (88.6) | 130 (90.9) | |
| Sessile | 52 (10.7) | 39 (11.4) | 13 (9.1) | |
| Tumor location | | | | |
| Renal pelvis/calyces | 230 (43.6) | 159 (42.6) | 71 (45.8) | 0.72 |
| Ureter | 256 (48.5) | 185 (49.6) | 71 (45.8) | |
| Both | 42 (8) | 29 (7.8) | 13 (8.4) | |
| Tumor focality | | | | |
| Unifocal | 336 (75.5) | 241 (76.8%) | 95 (72.5%) | 0.40 |
| Multifocal | 109 (24.5) | 73 (23.2%) | 36 (27.5%) | |

N:L = neutrophil: lymphocyte, Na = sodium; eGFR = estimated glomerular filtration rate; Hgb = hemoglobin.
[a] Values represent percentages except where noted.
[b] Data were available for 367 patients.
[c] Data were available for 364 patients.
[d] Data were available for 485 patients.

and were used to formulate the confidence intervals (CIs) of the estimates. All tests were 2-sided. The computations were carried out using SAS version 9.3 and R version 3.3.3 statistical software.

## 3. Results

A total of 566 patients were considered in the design of this preoperative nomogram (development cohort, $n = 396$) and (validation cohort, $n = 170$) after exclusion of ineligible patients (=133). Patient demographics, endoscopic, imaging, and laboratory data were well balanced between the 2 cohorts with exception of year of surgery and serum sodium level as summarized in Tables 1a and b. This confirmed the prognostic comparability between the 2 cohorts. In summary, the mean patient age at surgery was 69.7 years (range, 38–94), majority were male (64%), Caucasian (85%), presented with gross hematuria and/or flank pain (69.6%) and had good Eastern Cooperative Oncology Group performance status ≤1 (87%). NOC-UTUC was found in 184 (32.5%) patients on final pathology: pT3 Nx/N0/N1/N2 = 69/63/22/5, pT4 Nx/N0/N1/N2 = 7/5/5/1, and pT1-2 N1-2 = 7. Of 184 patients with NOC-UTUC, 74 (40.2%) had tumors equally originating from renal pelvis and ureter, whereas 36 (19.6%) had tumors in both locations.

Template node dissection was performed in 51% (287/563) patients.

In univariate analysis (Table 2), age, year of surgery, preoperative hydronephrosis, infiltrative component on imaging, clinical stage, biopsy tumor grade, tumor architecture, log transformed NLR, eGFR, and Hgb levels were significantly associated with NOC-UTUC. Systemic symptoms, tumor size on imaging, NLR, and serum sodium did not reach statistical significant on univariate analysis but were considered potentially important, thus were entered into the initial final multivariate model since they had *P* value <0.1.

Table 3 shows multivariate logistic regression analysis. After applying a backward stepdown selection process, clinical stage (cT1-cT2 vs. cT3), biopsy tumor grade (high vs. low), tumor architecture (sessile vs. papillary), and lower Hgb levels were independently associated with NOC-UTUC. These predictors were used to generate the novel nomogram, Fig. 1A. The Hosmer-Lemeshow test indicated goodness-of-fit ($P = 0.48$). This nomogram had a discriminative accuracy of 82% by *c*-index with 48% sensitivity, and 95% specificity in predicting NOC-UTUC.

Table 2
Univariate logistic regression analysis predicting NOC-UTUC (pT3-pT4 and/or pN+) at surgery based on development cohort ($n = 396$)

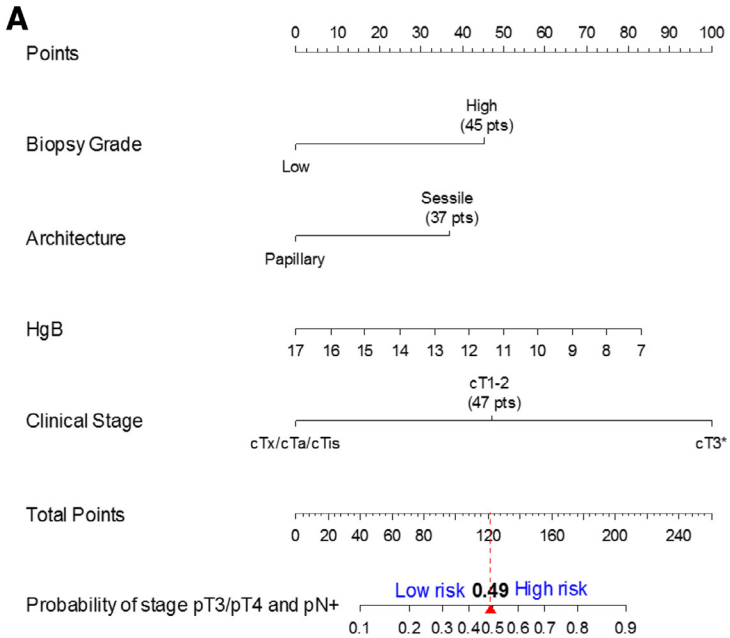
| Variables | OR | 95% CI | *P* Value[a] | Overall *P* Value |
|---|---|---|---|---|
| Age, years | 1.03 | (1.01−1.05) | **0.01** | |
| Gender (male vs. female) | 0.92 | (0.60−1.43) | 0.71 | |
| Race (Caucasians vs. non-Caucasians) | 0.82 | (0.43−1.56) | 0.54 | |
| BMI, kg/m$^2$ | 1.00 | (0.96−1.03) | 0.81 | |
| Symptoms | | | | |
| Local (present vs. none) | 1.35 | (0.83−2.22) | 0.23 | |
| Systemic (presents vs. none) | 3.02 | (0.84−10.93) | **0.09** | |
| ECOG performance status (2, 3 vs. 0, 1) | 1.28 | (0.70−2.36) | 0.42 | |
| CCI (>3 vs. 0, 1, 2, 3) | 1.11 | (0.67−1.82) | 0.70 | |
| Year of surgery | | | | **0.02** |
| ≤1999 vs. ≥2010 | 2.69 | (1.24−5.80) | **0.01** | |
| 2000−2009 vs. ≥2010 | 1.47 | (0.95−2.29) | **0.09** | |
| Tumor size on imaging, cm | 1.10 | (1.00−1.21) | **0.05** | |
| Hydronephrosis | | | | |
| Moderate/severe vs. none/mild | 1.67 | (1.05−2.64) | **0.03** | |
| Tumor location on imaging | | | | 0.43 |
| Renal pelvis vs. multifocal | 1.71 | (0.73−4.01) | 0.33 | |
| Ureter vs. multifocal | 1.73 | (0.74−4.05) | 0.29 | |
| Tumor focality on imaging | | | | |
| Multifocal vs. unifocal | 1.20 | (0.69−2.08) | 0.51 | |
| Infiltrative component on imaging | | | | |
| Present vs. absent | 15.69 | (5.24−46.97) | **< 0.01** | |
| Selective cytology | | | | |
| Suspicious/positive vs. negative/atypical | 1.07 | (0.50−2.32) | 0.86 | |
| Clinical stage | | | | **<0.01** |
| cTx, cTa, cTis vs. cT1-cT2 | 2.42 | (0.97−6.00) | **0.06** | |
| cTx, cTa, cTis vs. cT3 | 20.06 | (6.61−60.89) | **<0.01** | |
| Biopsy tumor grade (high vs. low) | 7.06 | (3.33−14.98) | **<0.01** | |
| Tumor architecture (sessile vs. papillary) | 5.06 | (2.51−10.22) | **<0.01** | |
| Tumor focality on endoscopy | | | | |
| Mutltifocal vs. unifocal | 1.20 | (0.69−2.08) | 0.51 | |
| N:L ratio | 1.08 | (1.00−1.16) | **0.05** | |
| Log transformed N:L ratio | 1.70 | (1.07−2.70) | **0.02** | |
| Serum Na, mEq/L | 0.94 | (0.87−1.01) | **0.08** | |
| eGFR, ml/min/1.73 m$^2$ | 0.98 | (0.97−0.99) | **<0.01** | |
| Hgb, g/dl | 0.83 | (0.73−0.94) | **<0.01** | |
| Albumin, g/dl | 0.95 | (0.51−1.76) | 0.86 | |

BMI = body mass index; CCI = Charlson comorbidity index; ECOG = Eastern cooperative oncology group; eGFR = estimated glomerular filtration rate; Hgb = hemoglobin; Na = sodium; NOC = nonorgan confined; N:L = neutrophil: lymphocyte; UTUC = upper-tract urothelial carcinoma; vs = versus.
[a] *P* values in bold (≤0.1) represent variables that were entered into multivariate model.

Table 3
Multivariate model for preoperative risk prediction of NOC-UTUC (pT3-pT4 and/or pN+) at surgery based on development cohort ($n = 396$)

| Effect | Point estimate of odds ratio (OR) | 95% Wald confidence interval of OR | *P* Value |
|---|---|---|---|
| Clinical stage cT1-cT2 | 3.47 | (1.23−9.83) | **0.02** |
| Clinical stage cT3 | 14.0 | (4.33−45.30) | **<0.01** |
| Biopsy tumor grade (high vs. low) | 3.30 | (1.44−7.57) | **0.01** |
| Tumor architecture (sessile vs. papillary) | 2.65 | (0.86−8.15) | **0.09** |
| Hgb, g/dl | 0.80 | (0.66−0.97) | **0.02** |
| Hosmer and Lemeshow Goodness of fit test: $P = 0.48$ | | | |
| *c*-index = 0.82 | | | |

Hgb = hemoglobin; NOC = nonorgan confined; UTUC = upper-tract urothelial carcinoma; vs = versus.




* Peripelvic fat, parenchymal invasion (renal tumor) or periureteral fat invasion (ureteral tumor) or other infiltrative component on imaging

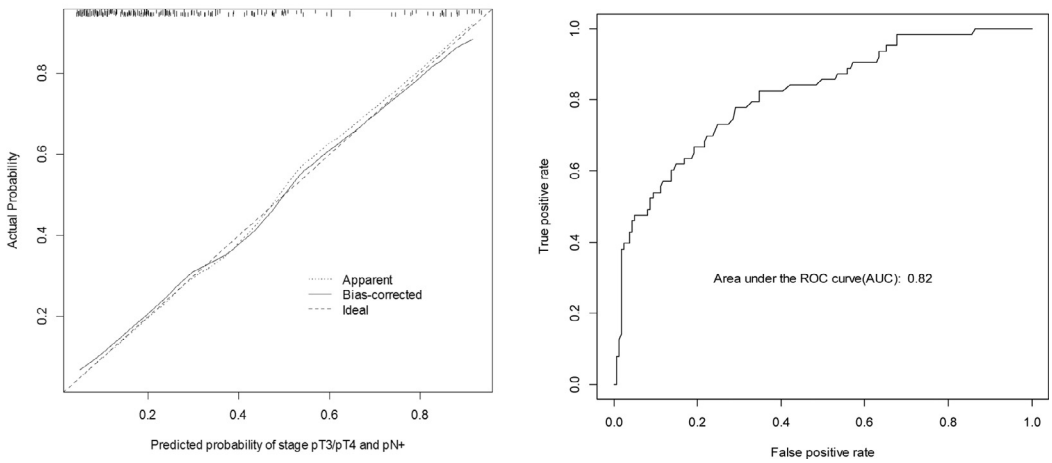



Fig. 1. Multiplex preoperative novel nomogram (A), and calibration plot (B, top panel) and receiver operating characteristics curve (B, lower panel), for prediction of nonorgan-confined (pT3-pT4 and/or pN+) upper-tract urothelial carcinoma (UTUC) at surgery based on development cohort ($n = 396$). Calibration plot illustrates essentially ideal predictions. Instructions: Locate the patient's biopsy tumor grade on the biopsy grade axis. Draw a line straight upward to the point axis to establish how many points toward the probability of nonorgan-confined (NOC) disease the patient gets for that particular tumor grade. Repeat the process for each of the other variables. Calculate total points for each of the predictors. Pinpoint the final score on the total point axis. Draw a line straight down to determine the patient's predicted probability of having NOC-UTUC. The cut-off point for predicting high-risk disease is 49 which corresponds to 122 points on the nomogram. As examples using this nomogram, a patient with a low grade (0), papillary tumor (0), Hgb level of 14 g/dl (25), and cTa (0) receives a total of 25 points, corresponding with a <1% risk of NOC-UTUC. Conversely, a low grade (0), sessile tumor (37), Hgb 11 g/dl (50), and cT1 (47) receives 134 points and has a roughly 55% of NOC-UTUC and would be considered high risk. A patient with a high grade (45), papillary tumor (0), Hgb of 14.5 g/dl (20), and cTx or cTa (0) receives 65 points and would be considered low risk with <20% risk of NOC disease. A patient with a high grade (45), sessile tumor (37), Hgb of 11 g/dl (50), and cT1 (47) receives 179 points corresponding to high-risk disease with approximately 80% risk of NOC disease.

Furthermore, the calibration plot of the nomogram exhibited performance characteristics that were virtually ideal (designated by the 45° line; Fig. 1B). The ROC analysis revealed a cut-off point ≥0.49 (corresponding to 122 points on the nomogram) which predicted high-risk, NOC disease. In order to "externally" validate the final model, we utilized the test cohort ($n = 170$) to evaluate the findings. For each patient ($n = 170$), we calculated the predictive probability

using the parameter estimates from the final model developed under training cohort. Applying the cutting threshold of high risk, the patients were categorized into high- or low-risk group, and the subsequent estimates such as, sensitivity, specificity, and *c*-index (accuracy) were computed. With 1,000 bootstrap resampling for the test cohort, applying the final model (nomogram) with the identified cutting threshold, we achieved an accuracy, sensitivity, and specificity of 77% (95% CI: 0.68, 0.86), 43% (95% CI: 0.25, 0.64), and 89% (95% CI: 0.81, 0.96), respectively. The results were consistent with the findings under the training cohort. Additionally, of the pNx patients, 9 patients had nodal relapse with or without other metastases, and of these, 5 had isolated nodal recurrence at a median interval of 10 months (only 1 had isolated nodal recurrence within 6 months). Sensitivity analysis after excluding all 9 patients showed no difference in the integrity of the nomogram.

## 4. Discussion

Accurate risk stratification is crucial to appropriately individualize treatments for patients with any cancer. While there has been continued improvement in endoscopic technology and biopsy instruments, tumor staging of UTUC lesion is notoriously challenging given the current limitation of imaging studies [18], challenges of anatomy, and ureteroscopic biopsy size limitations [19]. Collectively, these challenges underscore the need to find surrogate stratification tools predicting high-risk disease. Preoperative predictive tools may help in identifying which patients have high-risk disease and therefore can potentially benefit from neoadjuvant chemotherapy [8], since RNU alone is associated with reduced survival in patients with advanced stage (pT3/pT4 or pN+) disease at RNU [4,5]. Post-RNU patients frequently become ineligible for cisplatin adjuvant therapy [6]. An accurate preoperative nomogram should help improve clinical risk stratification, allowing better allocation to preoperative chemotherapy. Evidence is growing for pathologic downstaging and a potential survival advantage with use of neoadjuvant therapy for UTUC based on retrospective study and a few small prospective trials [4,8−10,20]; however, large population-based studies showed underutilization of this approach [21]. A phase 2 open-label, single-arm, GFR-stratified trial prospectively evaluating the benefit of neoadjuvant chemotherapy for UTUC recently reported its positive results, showing 14% complete response (ypT0N0) and downstaging to ypT1 or less in the majority of patients [22]. Beyond use of systemic chemotherapy, improved risk stratification could further guide selection for endoscopic vs. extirpative therapy, lymphadenectomy, and potential enrollment in clinical trials for UTUC. While results of a randomized prospective trial of adjuvant therapy were recently been presented, showing benefit compared to surveillance for those with adequate renal function, the data have not shown which proportion of patients were precluded from adjuvant therapy secondary to kidney function or other postoperative limitations (https://meetinglibrary.asco.org/record/157680/abstract, accessed June 28, 2018).

In this large multicenter collaboration study, we generated a prediction tool for high-risk disease at surgery based on multiple readily existing preoperative clinicopathologic parameters. This nomogram not only offers an accurate prediction of 82% for NOC diseases with false positive rate 5% and false negative rate of 52%, but also provides a convenient cut-off point ≥0.49 as predictive probability (corresponding to 122 points on the nomogram) for high-risk disease. Based on critiques, we also evaluated maximizing sensitivity, to 0.87, which lowered the cut-off point to 0.13 (50 points). However, the resulting lower specificity of 0.45 effectively translates to a potential of over half the patients unnecessarily receiving chemotherapy (false positives), which we do not think will be clinically useful. Generalizability is another highly important aspect since it was developed based on multi-institutional dataset originating from both urban and rural populations in the United States. Discrimination indicates nomogram probability to correctly predict a poorer outcome for the patient out of randomly selected patients using either area under the curve for binary data or *c*-index for censored data. On the other hand, discrimination requires complementary calibration that quantifies the accuracy of prediction for individual patients. The present nomogram has met both of these requirements. Furthermore, designating a cut-off point ≥0.49 predicting NOC-UTUC on a continuous scale is another objective feature of this nomogram that will provide useful guidance for providers and counseling of patients. The simplicity of this predictive tool ensures that urologists and medical oncologists are capable of using it in a busy clinical practice.

Several models have been described in the preoperative setting to predict various endpoints for improved patient outcomes at surgery. Margulis et al. proposed a preoperative multivariable prognostic model for the prediction of NOC-UTUC, using clinicopathologic criteria for 659 patients undergoing RNU [11]. Tumor grade, architecture, and tumor location were independently associated with NOC-UTUC, with accuracy of 76.6%. In contrast, Favaretto et al. combined imaging and ureteroscopic findings for 274 patients to develop a multivariable model to predict ≥pT2, pN+ at RNU [23]. In their model, local invasion on preoperative imaging and ureteroscopic high-grade tumors (assessed by biopsy or wash/brush cytology) were significantly associated with NOC-UTUC. Their multivariable model had an accuracy of 71% of predicting NOC-UTUC. Similar models have been proposed from collaborative work albeit with persistent limitations regarding available data across all endpoints in UTUC cohorts [24]. The nomogram presented in the current study has the highest accuracy of all these. It is likely that even better accuracy may not be possible without newer, possibly genomic, data.

Prior studies have demonstrated preoperative anemia to be an independent predictor of UTUC recurrence and

cancer-specific mortality as well as being significantly associated with advanced stage, high grade, and lymph node metastasis at RNU [25,26]. A recent study revealed patients with UTUC with preoperative cancer-related anemia to have worse renal function and higher pathologic stage [27]. It is noteworthy to mention that CKD is not uncommon in patients with UTUC [28] and prior reports demonstrated high rates of urothelial carcinoma in uremic patients [29]. However, Hgb achieved better prediction.

The current study has several limitations including retrospective nature and lack of central pathology review. Furthermore, lymphadenectomy was performed in half of patients in the study which represents a potential for understaging. Sensitivity analysis after exclusion of all pNx patients who had nodal relapse did not affect the performance of the nomogram, but due to the retrospective nature of the study, we cannot be certain of the potential for bias. In spite of the internal validation using the training cohort and external validation with the test cohort, exclusion of patients with incomplete data might introduce selection bias. This nomogram may not be applicable to non-Western areas with endemic rates of UTUC. An additional external cohort validating the performance of the nomogram may be necessary. The present study provides a simple, impactful predictive tool that could be integrated into the decision-making and clinical trial process.

## 5. Conclusions

We developed and validated an accurate tool for the prediction of NOC-UTUC. This preoperative multiplex nomogram can be used for patient counseling, selecting patients for preoperative systemic chemotherapy, or enrollment into clinical trials.

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## Conflict of Interest

Dr. Matin serves as consultant for Taris Biomedical, QED Therapeutics, and Urogen Corp.

Dr. Raman serves as consultant for Pacific Edge, Ltd.

Rest of the authors have nothing to disclose.

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