EUROPEAN UROLOGY ONCOLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Development and Validation of a Multivariable Nomogram Predictive of Post-Nephroureterectomy Renal Function

Patrick J. Hensley[a,b,†], *Craig Labbate*[a,†], *Andrew Zganjar*[c], *Jeffrey Howard*[d], *Heather Huelster*[e,f], *Trey Durdin*[g], *Jonathan Pham*[h], *Lianchun Xiao*[i], *Maximilian Pallauf*[j,k], *Kara Lombardo*[j], *Ilya Glezerman*[l], *Nirmish Singla*[j], *Jay D. Raman*[h], *Jonathan Coleman*[g], *Philippe E. Spiess*[e], *Vitaly Margulis*[d], *Aaron M. Potretzke*[c], *Surena F. Matin*[a,*]

[a] *Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [b] *Markey Cancer Center, University of Kentucky College of Medicine, Lexington, KY, USA;* [c] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [d] *Department of Urology, The University of Texas Southwestern, Dallas, TX, USA;* [e] *Department of Urology, Moffitt Cancer Center, Tampa, FL, USA;* [f] *Department of Urology, Indiana University Health, Indianapolis, IN, USA;* [g] *Department of Urology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [h] *Department of Urology, Penn State Health, Hershey, PA, USA;* [i] *Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [j] *James Buchanan Brady Urological Institute, Johns Hopkins University, Baltimore, MD, USA;* [k] *Department of Urology, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria;* [l] *Department of Nephrology, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Article info

Article history:
Received 22 September 2023
Received in Revised form
8 December 2023
Accepted 4 January 2024

Associate Editor:
Jeremy Teoh

Keywords:
Estimated glomerular filtration rate
Upper tract urothelial carcinoma
Radical nephroureterectomy
Renal function
Neoadjuvant chemotherapy
Adjuvant chemotherapy

Abstract

Background and objective: The timing of perioperative nephrotoxic chemotherapy for upper tract urothelial carcinoma (UTUC) remains controversial and strongly depends on predicted platinum eligibility after radical nephroureterectomy (RNU). The study objective was to develop and validate a multivariable nomogram to predict estimated glomerular filtration rate (eGFR) following RNU.

Methods: This was a multi-institutional retrospective study of patients with UTUC treated with RNU from 2000 to 2020 at seven high-volume referral centers. Use of adjuvant chemotherapy was risk-stratified. Patients were retrospectively randomly allocated 2:1 to discovery and validation cohorts. Discovery data were used to identify independent factors associated with GFR at 1–3 mo after RNU on linear regression, and backward selection was applied for model construction. Accuracy was defined as the percentage of predicted eGFR results within 30% of the corresponding observed eGFR.

Key findings and limitations: We included 1100 patients, of whom 733 were in the discovery and 367 were in the validation cohort. Multivariable predictors of postoperative eGFR decline included advanced age (odds ratio [OR] −0.18, 95% confidence interval [CI] −0.28 to −0.08), diabetes (OR −2.38, 95% CI −4.64 to −0.11), and hypertension (OR −2.24, 95% CI −4.16 to −0.32). Factors associated with favorable postoperative eGFR included larger tumor size (OR 10.57, 95% CI 7.4–13.74 for tumors >5 cm vs ≤2 cm) and preoperative eGFR (OR 0.44, 95% CI 0.39–0.49). A composite nomogram predicted postoperative eGFR with good accuracy in both the discovery (80.5%) and validation (78.6%) cohorts. Limitations include exclusion of patients who received neoadjuvant chemotherapy.

Conclusions: A nomogram that incorporates ubiquitous preoperative clinical variables can predict post-RNU eGFR and was validated with an independent cohort.

† These authors contributed equally to this work.
* Corresponding author. Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. Tel. +1 713 7923250; Fax: +1 713 7944824.
E-mail address: surmatin@mdanderson.org (S.F. Matin).

https://doi.org/10.1016/j.euo.2024.01.005

Patient summary: We developed a tool that uses patient data to predict eligibility for chemotherapy after surgery to remove the kidney and ureter in patients with cancer in the upper urinary tract.

1. Introduction

Upper tract urothelial carcinoma (UTUC) accounts for approximately 5–10% of all urothelial malignancies [1]. The standard treatment for high-grade and bulky low-grade UTUC is radical nephroureterectomy (RNU) with bladder cuff resection [1,2]. Approximately 60% of UTUCs are invasive at presentation, yet they are often understaged by conventional imaging and endoscopic biopsy [3,4]. Efforts dedicated to generating nomograms predicting advanced pathologic stage at RNU have improved our ability to select patients who may receive the highest benefit from preoperative chemotherapy [3].

The timing of perioperative systemic chemotherapy remains controversial. Cisplatin-based regimens are currently used in both neoadjuvant chemotherapy (NAC) and adjuvant chemotherapy (AC) settings, but patient eligibility must be considered in the context of renal function surrounding definitive surgical therapy. NAC provides timely treatment of micrometastatic disease that is clinically understaged with current evaluations, may facilitate surgical resection by downstaging locally advanced disease, and expands the population eligible for systemic therapy because treatment is administered at the time of maximal renal function. Alternatively, AC following RNU reduces the risk of overtreatment by allowing risk-stratified patient selection on the basis of final pathology. It is estimated that 49% of patients are eligible for NAC before RNU, with only 19% eligible for AC after RNU according to an estimated glomerular filtration rate (eGFR) cutoff of 60 ml/min/1.73 m^2 for cisplatin eligibility [5]. Given high rates of medical renal disease in this comorbid patient population, it is prudent to consider the sequencing of systemic nephrotoxic therapy on an individual patient basis. The recent American Urological Association guidelines on UTUC recommend incorporation of renal function estimation as part of treatment planning, specifically recommending cisplatin-based NAC for high-risk patients with estimated post-RNU eGFR of <60 ml/min/1.73 m^2 [2].

While the phase 3 POUT trial supports the use of AC versus observation for high-risk disease, and at least two single-arm prospective phase 2 trials and several retrospective studies support the use of NAC [6–8], AC and NAC approaches have never been directly compared in a prospective trial. The use of preoperative versus postoperative systemic therapy has never been formally compared in a randomized trial, and many experts support a strong rationale for NAC despite the absence of phase 3 data [5]. There is currently limited ability to predict post-RNU eGFR and, in turn, a patient's eligibility for nephrotoxic AC after RNU, and data informing postoperative eGFR estimation are limited to small, retrospective institutional series [5,9–15].

To address this clinical challenge, we developed and validated a predictive nomogram for post-RNU eGFR estimation using contemporary cohorts of patients from high-volume, tertiary referral academic centers to better inform the timing of systemic therapy in relation to RNU and facilitate more insightful patient selection and counseling.

2. Patients and methods

Deidentified data for patients undergoing RNU for UTUC at seven high-volume tertiary care centers in the USA (MD Anderson Cancer Center [MDACC], Mayo Clinic, Moffitt Cancer Center, University of Texas Southwestern Medical Center, Memorial Sloan Kettering Cancer Center, Johns Hopkins University, and Penn State University) between January 1, 2000 and December 1, 2020 were prospectively collected through chart review and included to form the multicenter UTUC Collaborative Network (UCAN) database. Institutional review board approval (RCR05-0521) was obtained at the coordinating center (MDACC) and each contributing center. Patients who received preoperative systemic therapy, those who had previously undergone radical cystectomy, and patients who were initially dialysis-dependent or were rendered anephric were excluded. Patients treated with risk-stratified AC were included in the analysis, and their initial 1–3-mo postoperative documented eGFR was obtained before starting AC.

Renal function was calculated using serum creatinine measurements in the race-neutral 2021 CKD-EPI creatinine formula (https://www.kidney.org/professionals/kdoqi/gfr_calculator). Renal function was captured at baseline (within 6 wk) before RNU and at 1–3 mo (highest GFR if multiple values) and 12 mo after RNU. In addition, the patient's most recent eGFR was collected from their most contemporary follow-up. The primary endpoint modeled was eGFR at 1–3 mo post-RNU, as a continuous variable. To account for missing data at 1–3 mo postoperatively between centers, those with eGFR estimation at 12 mo postoperatively were included if no 1–3-mo data were available and the patients did not receive nephrotoxic adjuvant therapy, given the known stability of eGFR after RNU [16]. Primary tumor size (greatest diameter) was a composite estimate using preoperative endoscopic evaluation and cross-sectional imaging, when applicable, as recorded by the treating physician. Hydronephrosis was evaluated as a binary variable (none/mild vs moderate/severe) using clinician discretion at the time of treatment on the basis of evaluation of available preoperative cross-sectional imaging. The presence/absence of preoperative proteinuria was evaluated using urine dipstick analysis closest to the time of RNU.

Participants were randomly divided in a 2:1 ratio within each institution to generate discovery and validation

Please cite this article as: P.J. Hensley, C. Labbate, A. Zganjar et al., Development and Validation of a Multivariable Nomogram Predictive of Post-Nephroureterectomy Renal Function, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.01.005

cohorts. Continuous variables were summarized using descriptive statistics and compared using the Wilcoxon rank-sum and Kruskal-Wallis tests between the discovery and validation cohorts. Categorical variables were tabulated using the frequency and percentage and were compared using a χ^2 or Fisher's exact test.

Univariable and multivariable linear regression analyses were applied to assess the association between postoperative eGFR and covariates. The following steps were used to identify the covariates that were independently associated with eGFR. First, the discovery cohort was used to identify independent factors that were significantly associated with the postoperative eGFR endpoint. A list of the covariates assessed is provided in the Supplementary material. A full linear regression model that included variables with $p < 0.15$ in the univariable analysis was initially fitted. Backward selection was then applied for model selection until all variables in the model with $p < 0.05$ were included. A nomogram was subsequently generated using the final model with statistically significant variables. Second, this multivariable model generated with the discovery cohort was applied to predict postoperative eGFR in the validation cohort. To analyze the performance of the final model in the validation set, we assessed its accuracy, defined as the percentage of predicted eGFR values within 30% of the corresponding observed eGFR. Pearson coefficients were used to assess the correlation between observed and predicted post-RNU eGFR. Patients with missing data were excluded from analysis of the respective variable. The model was developed and reported using the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist [17].

3. Results

A total of 2280 patients were included in the overall UCAN multicenter cohort, of whom 1100 satisfied the inclusion criteria (Fig. 1). Patients were randomly assigned 2:1 to the discovery (n = 733) or validation (n = 367) cohort.

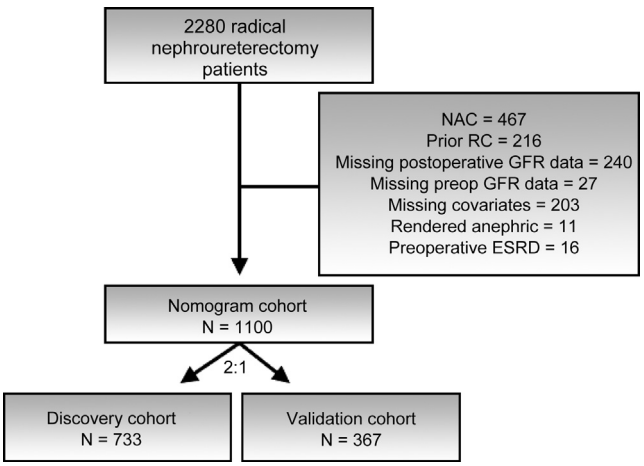

Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) diagram showing patient inclusion in the discovery and validation cohorts. NAC = neoadjuvant chemotherapy; RC = radical cystectomy; GFR = glomerular filtration rate; ESRD = end-stage renal disease.

A comparison of demographic data, comorbidities, and preoperative and postoperative tumor characteristics between the two cohorts is presented in Table 1. There were no

Table 1 – Patient and tumor characteristics overall and in the discovery and validation cohorts

Parameter	Overall (N = 1100)	Discovery (n = 733)	Validation (n = 367)	p value
Median age, yr (IQR)	72 (65–79)	72 (65–79)	72 (65–79)	0.6
Sex, n (%)				
Male	710 (65)	480 (65)	230 (63)	0.38
Female	390 (35)	253 (35)	137 (37)	
Smoking status, n (%)				
Never smoker	358 (33)	229 (31)	129 (35)	0.5
Former smoker	549 (50)	375 (51)	174 (47)	
Current smoker	187 (17)	124 (17)	63 (17)	
Unknown	6 (1)	5 (1)	1 (0)	
Race, n (%)				
White	1027 (93)	686 (94)	341 (93)	0.61
Black	27 (2)	15 (2)	12 (3)	
Other	40 (4)	28 (4)	12 (3)	
Unknown	6 (1)	4 (1)	2 (1)	
Body mass index, n (%)				
<30 kg/m^2	647 (65)	435 (66)	212 (62)	0.3
≥30 kg/m^2	355 (35)	227 (34)	128 (38)	
Diabetes mellitus, n (%)				
No	876 (80)	586 (80)	290 (79)	0.75
Yes	224 (20)	147 (20)	77 (21)	
Hypertension, n (%)				
No	412 (37)	281 (38)	131 (36)	0.43
Yes	684 (62)	450 (61)	234 (64)	
Unknown	4 (0)	2 (0)	2 (1)	
Median CCI (IQR) (N = 1099)	5 (3–6)	5 (3–6)	5 (3–6)	0.67
Proteinuria, n (%)				
No	407 (37)	276 (38)	131 (36)	0.36
Yes	259 (24)	163 (22)	96 (26)	
Unknown	434 (39)	294 (40)	140 (38)	
Biopsy grade, n (%)				
Low	323 (29)	221 (30)	102 (28)	0.68
High	484 (44)	313 (43)	171 (47)	
Unknown	293 (27)	199 (27)	94 (26)	
Biopsy focality, n (%)				
Unifocal	691 (63)	458 (62)	233 (63)	0.98
Multifocal	263 (24)	177 (24)	86 (23)	
Unknown	146 (13)	98 (13)	48 (13)	
Median tumor size, cm (range)	3.0 (0.3–17.0)	2.6 (0.3–17.0)	2.8 (0.3–12.0)	0.68
Tumor size, n (%)				
<2 cm	347 (39)	236 (39)	111 (37)	0.57
2–5 cm	468 (52)	307 (51)	161 (54)	
>5 cm	86 (10)	61 (10)	25 (8)	
Tumor location, n (%)				
Renal pelvis	579 (53)	396 (54)	183 (50)	0.17
Ureter	320 (29)	210 (29)	110 (30)	
Renal pelvis + ureter	155 (14)	92 (13)	63 (17)	
Unknown	46 (4)	35 (5)	11 (3)	
Clinical T stage, n (%)				
cTa	539 (65)	362 (66)	177 (64)	0.40
cTis	21 (3)	13 (2)	8 (3)	
cT1	109 (13)	70 (13)	39 (14)	
cT2	58 (7)	40 (7)	18 (7)	
cT3	92 (11)	57 (10)	35 (13)	
cT4	7 (1)	7 (1)	0 (0)	
Hydronephrosis, n (%)				
None/mild	747 (68)	509 (69)	238 (65)	0.26
Moderate/severe	284 (26)	182 (25)	102 (28)	
Unknown	69 (6)	42 (6)	27 (7)	
Median eGFR, ml/min/1.73 m^2 (IQR)				
Preoperative (N = 1099)	60 (47–77)	60.5 (47–77)	60 (47–77)	0.68
1–3 mo after RNU (N = 970)	44 (36–54)	45 (36–54.3)	43 (36–53)	0.73
12 mo after RNU (N = 731)	45 (36–54)	44 (35–54)	46 (37–54)	0.23

(continued on next page)

Table 1 (continued)

Parameter	Overall (N = 1100)	Discovery (n = 733)	Validation (n = 367)	p value
Most recent measurement (N = 1099)	44 (33–55)	45 (34–55)	44 (33–57)	0.9
Concomitant radical cystectomy, n (%)				
No	1043 (95)	697 (95)	346 (94)	0.82
Yes	53 (5)	33 (5)	20 (5)	
Unknown	4 (0)	3 (0)	1 (0)	
Final tumor grade, n (%)				
Low	298 (27)	195 (27)	103 (28)	0.59
High	770 (70)	519 (71)	251 (68)	
Unknown	32 (3)	19 (3)	13 (4)	
(y)pT stage, n (%)				
pT0	28 (3)	13 (2)	15 (4)	0.51
pTa	359 (33)	238 (32)	121 (33)	
pTis	63 (6)	41 (6)	22 (6)	
pT1	205 (19)	138 (19)	67 (18)	
pT2	112 (10)	79 (11)	33 (9)	
pT3	282 (26)	191 (26)	91 (25)	
pT4	48 (4)	31 (4)	17 (5)	
Unknown	3 (<1)	2 (<1)	1 (<1)	
(y)pN stage, n (%)				
pN0	425	275 (38)	150 (41)	0.55
pN1–3	96	66 (9)	30 (8)	
pNx/unknown	579	392 (53)	187 (51)	
Adjuvant chemotherapy, n (%)				
Any	112 (10)	77 (11)	35 (10)	0.62
Cisplatin-based	52 (5)	33 (5)	19 (5)	0.61

CCI = Charlson comorbidity index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; RNU = radical nephroureterectomy.

significant differences between the discovery and validation cohorts.

The median preoperative eGFR for the entire cohort was 60 ml/min/1.73 m^2 (interquartile range [IQR] 47–77). Following RNU, median eGFR was 44 ml/min/1.73 m^2 (IQR 36–54) at 1–3 mo, 45 ml/min/1.73 m^2 (IQR 36–54) at 12 mo, and 44 ml/min/1.73 m^2 (IQR 33–55) at the most recent follow-up, indicating that initial RNU-induced renal insufficiency stabilized around 1–3 mo postoperatively (Fig. 2).

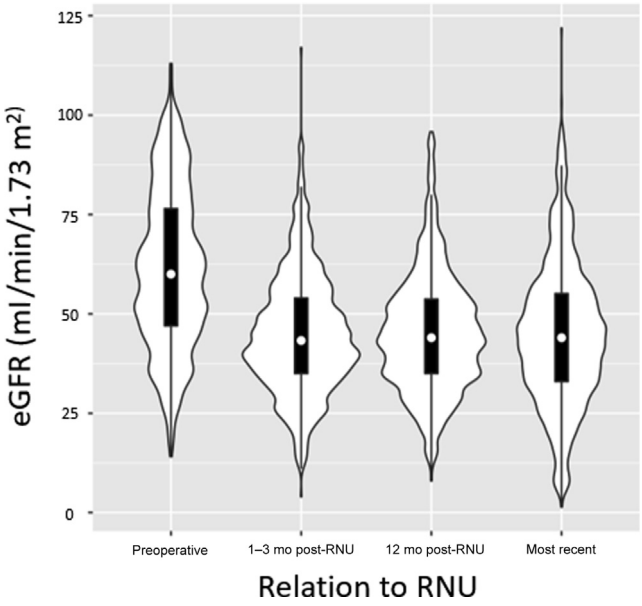

Fig. 2 – Violin plot of estimated glomerular filtration rate (eGFR) in relation to radical nephroureterectomy (RNU). CI = confidence interval.

Univariable and multivariable predictors of the composite postoperative eGFR are listed in Supplementary Tables 1 and 2, respectively. Significant multivariable predictors of postoperative eGFR decline included age (odds ratio [OR] −0.18, 95% confidence interval [CI] −0.28 to −0.08), diabetes mellitus (OR −2.38, 95% CI −4.64 to −0.11), and hypertension (OR −2.24, 95% CI −4.16 to −0.32). Factors associated with a lower degree of surgically induced renal insufficiency postoperatively includes larger tumor size (OR 10.57, 95% CI 7.4–13.74 for size >5 cm; OR 2.43, 95% CI 0.52 to 4.34 for size 2–5 cm vs ≤2 cm), and preoperative eGFR (OR 0.44, 95% CI 0.39–0.49).

These significant multivariable factors were used to generate a nomogram to predict postoperative eGFR following RNU (Fig. 3). The nomogram was used to directly compare the observed versus predicted eGFR values for each individual patient (Fig. 4). The nomogram predicted postoperative eGFR with good accuracy in both the discovery (R = 0.68, 95% CI 0.63–0.72; 80.5% accuracy) and validation (R = 0.66, 95% CI 0.59–0.72; 78.6% accuracy) cohorts.

4. Discussion

There is currently limited ability to predict post-RNU eGFR and, in turn, a patient's eligibility for nephrotoxic chemotherapy after RNU. Using a large multi-institutional cohort of 1100 patients who underwent RNU for whom longitudinal GFR data were available, we generated a predictive nomogram for post-RNU eGFR estimation using preoperative clinical variables, and validated the findings in an independent cohort. Multivariable predictors of postoperative eGFR decline included advanced age, hypertension, and diabetes mellitus, while predictors of favorable postoperative eGFR included larger tumor size and high preoperative eGFR at baseline. This nomogram represents a useful clinical tool for patient counseling and patient selection for perioperative chemotherapy, and efforts to make it available as an interactive online resource after publication are ongoing.

Studies with information on postoperative eGFR are limited to small, retrospective institutional series with notable limitations [5,9–15]. The majority were performed in East Asian populations, which limits generalization of the findings to Middle Eastern, European, and American patients [18]. In addition, the referent postoperative eGFR endpoint and eGFR cutoffs for platinum eligibility vary considerably between studies. A previous continuous-variable nomogram developed by Fang et al. [9] used clinical and pathological factors to predict post-RNU eGFR at postoperative day 7. While studies suggest that the post-RNU eGFR decline ranges from 18% to 32%, there is evidence of considerable postoperative GFR fluctuation in the short term that makes this nomogram less clinically applicable [10,14,16,19]. We evaluated a more clinically relevant postoperative eGFR estimate (1–3 mo post-RNU) that can inform decisions on eligibility for AC [5,13].

Our analysis did not reveal the "protective" effect of preoperative hydronephrosis on postoperative renal function reported for previous studies [9,15]. We grouped the absence of hydronephrosis and mild hydronephrosis for

Please cite this article as: P.J. Hensley, C. Labbate, A. Zganjar et al., Development and Validation of a Multivariable Nomogram Predictive of Post-Nephroureterectomy Renal Function, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.01.005

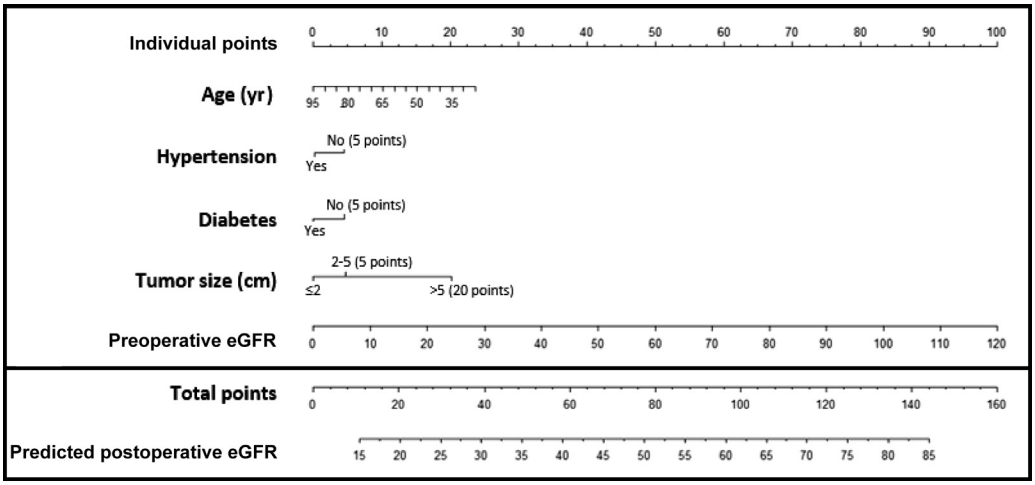

Fig. 3 – Nomogram for predicting the estimated glomerular filtration rate (eGFR) at 1–3 mo after radical nephroureterectomy.

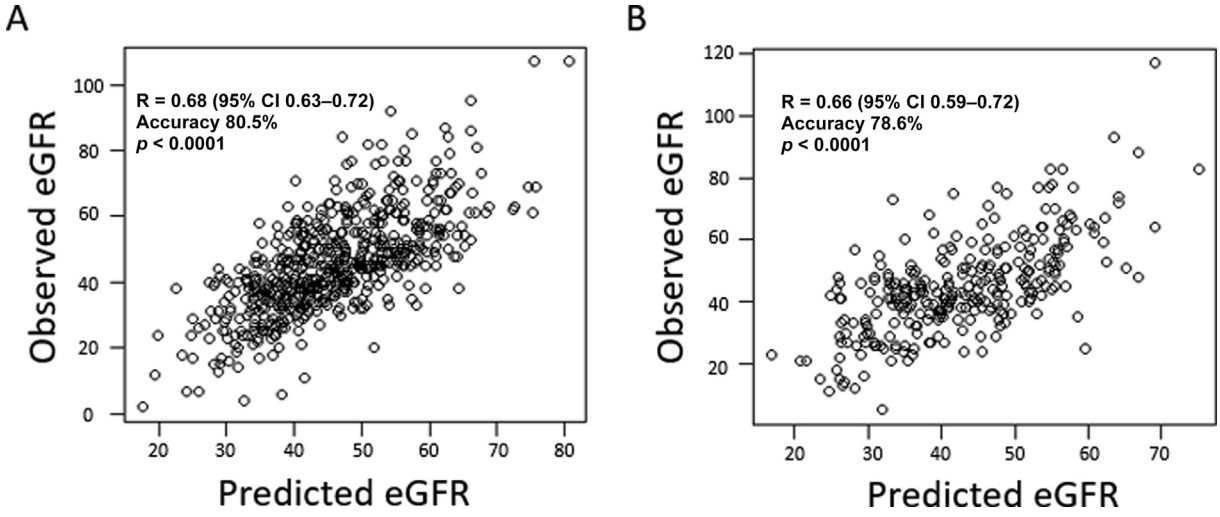

Fig. 4 – Observed versus predicted estimated glomerular filtration rate (eGFR) at 1–3 mo after radical nephroureterectomy in (A) the discovery cohort (*n* = 733) and (B) the validation cohort (*n* = 367).

our cohort, which may have underestimated the effect of anatomically mild hydronephrosis. In addition, while proteinuria is a well-established risk factor for progression of medical renal disease [20], preoperative proteinuria was not a significant predictor of postoperative eGFR in this RNU cohort during short-term (1–3 mo) follow-up.

Several studies have found correlation between preoperative imaging findings and post-RNU eGFR estimates, including the degree of hydronephrosis on positron emission tomography/computed tomography (CT) [21], split function according to nuclear medicine renography versus renal cortical enhancement on contrast-enhanced CT [22], contralateral renal length [11], and contralateral renal cortical volume [12]. Split renal function according to CT volumetric analysis has become a promising tool in predicting eGFR after nephrectomy for renal cell carcinoma, and improves the estimation of postoperative eGFR more than a previously validated multivariable model based on risk factors [23]. A recent systematic review of models for predicting renal function after partial or radical nephrectomy for renal masses categorized predictive variables into patient-, kidney, and tumor-related factors [24]. While each of the variables included in our nomogram (age, hypertension, diabetes, tumor size, and preoperative renal function) is a previously validated independent predictor of eGFR after renal mass surgery, inherent differences in patient demographics, commonly associated medical comorbidities, urinary obstruction, and use of perioperative nephrotoxic systemic therapy may confound efforts to compare eGFR estimates between RNU and radical nephrectomy cohorts. Future predictive models could be strengthened by use of a combination of radiomics data and clinical variables, but such data were available for only 10% of the patients in our cohort and hence were not considered for the model. The association between larger tumor size and better post-RNU eGFR in our cohort is likely to reflect worse differential function of the ipsilateral kidney because of cortical invasion or obstruction, and this association requires further investigation.

The strengths of our nomogram include its development and a priori validation in the largest cohort of patients undergoing RNU for UTUC with perioperative eGFR data.

Please cite this article as: P.J. Hensley, C. Labbate, A. Zganjar et al., Development and Validation of a Multivariable Nomogram Predictive of Post-Nephroureterectomy Renal Function, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.01.005

The cohort represents a clinically relevant, homogeneous patient population unexposed to NAC to limit potential confounding. The nomogram can serve as an optimal tool to help inform patient candidacy for adjuvant cisplatin-based chemotherapy. To date, clinical trials have focused exclusively on randomized intervention in either the neoadjuvant or the adjuvant disease setting, with no head-to-head comparisons between these systemic therapy approaches. Our model can serve as a useful resource for stratifying patients for perioperative chemotherapy on the basis of predicted post-RNU platinum eligibility, which will allow design of a more holistic study approach using stratification based on baseline and predicted post-RNU eGFR.

Our study has some inherent limitations. While patients who underwent neoadjuvant therapy or prior radical cystectomy were excluded in an effort to homogenize the cohort for predicting post-RNU adjuvant therapy eligibility, this limits the generalizability of the predictive model. The final clinical predictors included in the model were primarily objective parameters (age, hypertension, diabetes, and preoperative eGFR), but we recognize that tumor size estimation via preoperative endoscopic evaluation or cross-sectional imaging can be subjective. Hydronephrosis was evaluated as a binary variable (none/mild vs moderate/severe) although obstructive uropathy is a clinical spectrum, and lack of granular data regarding preoperative ureteral stenting or nephrostomy tube placement limits the clinical relevance of this data point. In such cases, however, the GFR before diversion can also help in informing prediction of post-RNU GFR. Lastly, a large number of patients with missing clinical data, including eGFR measurements and results for other covariates, were excluded from the analysis, which may represent a confounder.

5. Conclusions

A multivariable nomogram comprising patient age, the presence of diabetes or hypertension, tumor size, and preoperative eGFR can predict postoperative renal function after RNU for UTUC. This nomogram, which uses easily accessible clinical information, should be incorporated into perioperative counseling before RNU and has the potential to inform clinical decision-making regarding sequencing of systemic therapy in UTUC.

Author contributions: Surena F. Matin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hensley, Glezerman, Singla, Raman, Coleman, Spiess, Margulis, Potretzke, Matin.
Acquisition of data: Hensley, Labbate, Zganjar, Howard, Huelster, Durdin, Pham Xiao, Pallauf, Lombardo.
Analysis and interpretation of data: Hensley, Labbate, Xiao, Matin.
Drafting of the manuscript: Hensley, Labbate, Matin.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Xiao.
Obtaining funding: Hensley, Matin.
Administrative, technical, or material support: Singla, Raman, Coleman, Spiess, Margulis, Potretzke, Matin.
Supervision: Singla, Raman, Coleman, Spiess, Margulis, Potretzke, Matin.
Other: None.

Financial disclosures: Surena F. Matin certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Maximilian Pallauf has received speaker honoraria from Astellas Pharma and Janssen Pharmaceuticals, and a travel grant from Ipsen Pharma. Ilya Glezerman's spouse is employed by and owns stock in Pfizer Inc. Jay D. Raman has financial relationships with American Kidney Stone Management, United Medical Systems, Urogen Pharma, Pacific Edge Biotechnologies, and Steba Biotech. Philippe E. Spiess is Vice Chair of the National Comprehensive Cancer Network guideline panels for bladder cancer and penile cancer. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: This work was supported by a Urology Care Foundation Research Scholars Award to Patrick J. Hensley (IRG 85-001-25); Cancer Center Support Grant P30CA016672; the Monteleone Family Foundation for Research in Kidney and Bladder Cancers and the Eleanor and Scott Petty fund for upper tract urothelial carcinoma research (Surena F. Matin); the Paracelsus Medical University Research and Innovation Fund (Maximilian Pallauf; 2022-FIRE-004-Pallauf); and MSK Core Grant P30 CA008748 (Ilya Glezerman). The funding bodies played no direct role in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.01.005.

References

[1] Rouprêt M, Seisen T, Birtle AJ, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2023 update. Eur Urol 2023;84:49–64. https://doi.org/10.1016/j.eururo.2023.03.013.
[2] Coleman JA, Clark PE, Bixler BR, et al. Diagnosis and management of non-metastatic upper tract urothelial carcinoma: AUA/SUO guideline. J Urol 2023;209:1071–81. https://doi.org/10.1097/JU.0000000000003480.
[3] Petros FG, Qiao W, Singla N, et al. Preoperative multiplex nomogram for prediction of high-risk nonorgan-confined upper-tract urothelial carcinoma. Urol Oncol 2019;37:292.e1–e9. https://doi.org/10.1016/j.urolonc.2018.12.002.
[4] Margulis V, Shariat SF, Matin SF, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer 2009;115:1224–33. https://doi.org/10.1002/cncr.24135.
[5] Kaag MG, O'Malley RL, O'Malley P, et al. Changes in renal function following nephroureterectomy may affect the use of perioperative chemotherapy. Eur Urol 2010;58:581–7. https://doi.org/10.1016/j.eururo.2010.06.029.
[6] Margulis V, Puligandla M, Trabulsi EJ, et al. Phase II trial of neoadjuvant systemic chemotherapy followed by extirpative surgery in patients with high grade upper tract urothelial carcinoma. J Urol 2020;203:690–8. https://doi.org/10.1097/JU.0000000000000644.
[7] Coleman JA, Yip W, Wong NC, et al. Multicenter phase II clinical trial of gemcitabine and cisplatin as neoadjuvant chemotherapy for patients with high-grade upper tract urothelial carcinoma. J Clin Oncol 2023;41:1618–25. https://doi.org/10.1200/JCO.22.00763.

[8] Porten S, Siefker-Radtke AO, Xiao L, et al. Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. Cancer 2014;120:1794–9. https://doi.org/10.1002/cncr.28655.

[9] Fang D, Zhang Q, Li X, et al. Nomogram predicting renal insufficiency after nephroureterectomy for upper tract urothelial carcinoma in the Chinese population: exclusion of ineligible candidates for adjuvant chemotherapy. Biomed Res Int 2014;2014:529186. https://doi.org/10.1155/2014/529186.

[10] Rodríguez Faba O, Palou J, Breda A, et al. Predictive factors for impaired renal function following nephroureterectomy in upper urinary tract urothelial cell carcinoma. Urol Int 2014;92:169–73. https://doi.org/10.1159/000353652.

[11] Shao IH, Lin YH, Hou CP, et al. Risk factors associated with ineligibility of adjuvant cisplatin-based chemotherapy after nephroureterectomy. Drug Des Dev Ther 2014;8:1985–90. https://doi.org/10.2147/DDDT.S72197.

[12] Song W, Sung HH, Han DH, et al. The effect of contralateral kidney volume on renal function after radical nephroureterectomy: implications for eligibility for neoadjuvant chemotherapy for upper tract urothelial cancer. Urol Oncol 2017;35:114.e1–e7. https://doi.org/10.1016/j.urolonc.2016.10.022.

[13] Kaag M, Trost L, Thompson RH, et al. Preoperative predictors of renal function decline after radical nephroureterectomy for upper tract urothelial carcinoma. BJU Int 2014;114:674–9. https://doi.org/10.1111/bju.12597.

[14] Xylinas E, Rink M, Margulis V, et al. Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. BJU Int 2013;112:453–61. https://doi.org/10.1111/j.1464-410X.2012.11649.x.

[15] Singla N, Hutchinson R, Haddad A, Sagalowsky A, Lotan Y, Margulis V. Preoperative hydronephrosis is associated with less decline in renal function after radical nephroureterectomy for upper tract urothelial carcinoma. Can J Urol 2016;23:8334–41.

[16] Labbate CV, Hensley PJ, Miest TS, et al. Longitudinal GFR trends after neoadjuvant chemotherapy prior to nephroureterectomy for upper tract urothelial carcinoma. Urol Oncol 2022;40:454.e17–e23. https://doi.org/10.1016/j.urolonc.2022.06.014.

[17] Heus P, Damen JAA, Pajouheshnia R, et al. Uniformity in measuring adherence to reporting guidelines: the example of TRIPOD for assessing completeness of reporting of prediction model studies. BMJ Open 2019;9:e025611.

[18] Rule AD, Teo BW. GFR estimation in Japan and China: what accounts for the difference? Am J Kidney Dis 2009;53:932–5. https://doi.org/10.1053/j.ajkd.2009.02.011.

[19] Lee BH, Zabor EC, Tennenbaum D, et al. Renal function recovery after radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol 2018;36:257–63. https://doi.org/10.1007/s00345-017-2139-9.

[20] Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease study. Ann Intern Med 1995;123:754–62. https://doi.org/10.7326/0003-4819-123-10-199511150-00003.

[21] Asai S, Fukumoto T, Watanabe R, et al. New classification of hydronephrosis on 18F-FDG-PET/CT predicts post-operative renal function and muscle-invasive disease in patients with upper urinary tract urothelial carcinoma. Jpn J Clin Oncol 2018;48:1022–7. https://doi.org/10.1093/jjco/hyy135.

[22] Waseda Y, Saito K, Ishikawa Y, et al. Predictive ability of renal cortex enhancement in dynamic computed tomography for residual renal function after nephroureterectomy: comparison with ^{99m}Tc-diethylenetriaminopentacetic acid renography and validation study. Int J Urol 2019;26:266–72. https://doi.org/10.1111/iju.13855.

[23] Rathi N, Palacios DA, Abramczyk E, et al. Predicting GFR after radical nephrectomy: the importance of split renal function. World J Urol 2022;40:1011–8. https://doi.org/10.1007/s00345-021-03918-9.

[24] Pecoraro A, Campi R, Bertolo R, et al. Estimating postoperative renal function after surgery for nonmetastatic renal masses: a systematic review of available prediction models. Eur Urol Oncol 2023;6:137–47. https://doi.org/10.1016/j.euo.2022.11.007.

Please cite this article as: P.J. Hensley, C. Labbate, A. Zganjar et al., Development and Validation of a Multivariable Nomogram Predictive of Post-Nephroureterectomy Renal Function, Eur Urol Oncol (2024), https://doi.org/10.1016/j.euo.2024.01.005