2-3-2021

A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group)

Zhenjie Wu

Qi Chen

Hooman Djaladat

Andrea Minervini

Robert G. Uzzo

See next page for additional authors

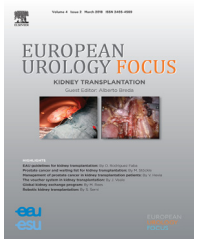
Recommended Citation

Wu Z, Chen Q, Djaladat H, Minervini A, Uzzo RG, Sundaram CP, Rha KH, Gonzalgo ML, Mehrazin R, Mazzone E, Marcus J, Danno A, Porter J, Asghar A, Ghali F, Guruli G, Douglawi A, Cacciamani G, Ghoreifi A, Simone G, Margulis V, Ferro M, Tellini R, Mari A, Srivastava A, Steward J, Al-Qathani A, Al-Mujalhem A, Bhattu AS, Mottrie A, Abdollah F, Eun DD, Derweesh I, Veccia A, Autorino R, and Wang L. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus 2021.

Authors

Zhenjie Wu, Qi Chen, Hooman Djaladat, Andrea Minervini, Robert G. Uzzo, Chandru P. Sundaram, Koon H. Rha, Mark L. Gonzalgo, Reza Mehrazin, Elio Mazzone, Marcus Jamil, Alyssa Danno, James Porter, Aeen Asghar, Fady Ghali, Georgi Guruli, Antoin Douglawi, Giovanni Cacciamani, Alireza Ghoreifi, Giuseppe Simone, Vitaly Margulis, Matteo Ferro, Riccardo Tellini, Andrea Mari, Abhishek Srivastava, James Steward, Ali Al-Qathani, Ahmad Al-Mujalhem, Amit Satish Bhattu, Alexander Mottrie, Firas Abdollah, Daniel D. Eun, Ithaar Derweesh, Alessandro Veccia, Riccardo Autorino, and Linhui Wang

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Urothelial Cancer

A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group)

Zhenjie Wu [a,†], *Qi Chen* [b,†], *Hooman Djaladat* [c], *Andrea Minervini* [d], *Robert G. Uzzo* [e], *Chandru P. Sundaram* [f], *Koon H. Rha* [g], *Mark L. Gonzalgo* [h], *Reza Mehrazin* [i], *Elio Mazzone* [j], *Jamil Marcus* [k], *Alyssa Danno* [k], *James Porter* [l], *Aeen Asghar* [m], *Fady Ghali* [n], *Georgi Guruli* [o], *Antoin Douglawi* [c], *Giovanni Cacciamani* [c], *Alireza Ghoreifi* [c], *Giuseppe Simone* [p], *Vitaly Margulis* [q], *Matteo Ferro* [r], *Riccardo Tellini* [d], *Andrea Mari* [d], *Abhishek Srivastava* [e], *James Steward* [f], *Ali Al-Qathani* [g], *Ahmad Al-Mujalhem* [g], *Amit Satish Bhattu* [h], *Alexander Mottrie* [j], *Firas Abdollah* [k], *Daniel D. Eun* [m], *Ithaar Derweesh* [n], *Alessandro Veccia* [o], *Riccardo Autorino* [o], *Linhui Wang* [a,*]

[a] *Department of Urology, Changzheng Hospital, Naval Medical University, Shanghai, China;* [b] *Department of Health Statistics, Naval Medical University, Shanghai, China;* [c] *Institute of Urology & Catherine and Joseph Aresty Department of Urology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA;* [d] *Department of Experimental and Clinical Medicine, University of Florence - Unit of Oncologic Minimally-Invasive Urology and Andrology, Careggi Hospital, Florence, Italy;* [e] *Division of Urologic Oncology, Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA;* [f] *Indiana University School of Medicine, Indianapolis, IN, USA;* [g] *Department of Urology, Urological Science Institute, Yonsei University College of Medicine, Seoul, Republic of Korea;* [h] *Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA;* [i] *Icahn School of Medicine at Mount Sinai, Department of Urology, New York, NY, USA;* [j] *OLV Hospital, Aalst, Belgium;ORSI Academy, Melle, Belgium;* [k] *Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA;* [l] *Swedish Medical Center, Seattle, WA, USA;* [m] *Department of Urology, Temple University, Philadelphia, PA, USA;* [n] *Department of Urology, UCSD, San Diego, CA, USA;* [o] *Division of Urology, VCU Health, Richmond, VA, USA;* [p] *Department of Urology, Regina Elena National Cancer Institute, Rome, Italy;* [q] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [r] *Division of Urology - European Institute of Oncology, IRCCS*

Article info

Article history:
Accepted January 13, 2021

Associate Editor: Richard Lee

Keywords:
Radical nephroureterectomy
Functional outcome
Upper tract urinary carcinoma
Chemotherapy

Abstract

Background: Postoperative renal function impairment represents a main limitation for delivering adjuvant chemotherapy after radical nephroureterectomy (RNU).
Objective: To create a model predicting renal function decline after minimally invasive RNU.
Design, setting, and participants: A total of 490 patients with nonmetastatic UTUC who underwent minimally invasive RNU were identified from a collaborative database including 17 institutions worldwide (February 2006 to March 2020). Renal function insufficiency for cisplatin-based regimen was defined as estimated glomerular filtration rate (eGFR) $<$50 ml/min/1.73 m^2 at 3 mo after RNU. Patients with baseline eGFR $>$50 ml/min/1.73 m^2 (n = 361) were geographically divided into a training set (n = 226) and an independent external validation set (n = 135) for further analysis.
Outcome measurements and statistical analysis: Using transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines, a nomogram to predict postoperative eGFR $<$50 ml/min/1.73 m^2 was built based on

† These authors contributed equally.
* Corresponding author. Department of Urology, Changzheng Hospital, Naval Medical University, 415 Fengyang Road, Huangpu District, Shanghai 200003, China. Tel. +86 2181886813; Fax: +86 2181886813.
E-mail address: wanglinhui@smmu.edu.cn (L. Wang).

https://doi.org/10.1016/j.euf.2021.01.014

the coefficients of the least absolute shrinkage and selection operation (LASSO) logistic regression. The discrimination, calibration, and clinical use of the nomogram were investigated.

Results and limitations: The model that incorporated age, body mass index, preoperative eGFR, and hydroureteronephrosis was developed with an area under the curve of 0.771, which was confirmed to be 0.773 in the external validation set. The calibration curve demonstrated good agreement. Besides, the model was converted into a risk score with a cutoff value of 0.583, and the difference between the low- and high-risk groups both in overall death risk (hazard ratio [HR]: 4.59, $p < 0.001$) and cancer-specific death risk (HR: 5.19, $p < 0.001$) was statistically significant. The limitation mainly lies in its retrospective design.

Conclusions: A nomogram incorporating immediately available clinical variables can accurately predict renal insufficiency for cisplatin-based adjuvant chemotherapy after minimally invasive RNU and may serve as a tool facilitating patient selection.

Patient summary: We have developed a model for the prediction of renal function loss after radical nephroureterectomy to facilitate patient selection for perioperative chemotherapy.

1. Introduction

The value of adjuvant platinum-based chemotherapy for patients undergoing radical nephroureterectomy (RNU) with curative intent has recently been described with level I evidence, while a subgroup analysis showed that cisplatin-treated patients benefited significantly but carboplatin-treated patients did not [1,2]. Moreover, cisplatin use is found to be an independent favorable prognostic factor, and this benefit is independent of baseline characteristics or comorbidities [3].

The main limitation of using adjuvant chemotherapy remains the limited ability to deliver cisplatin-based regimen following RNU, given that the surgical procedure is likely to impact renal function, which is the most common reason of cisplatin-based treatment ineligibility [3–5]. Therefore, tools predicting renal functional decline would facilitate perioperative management planning and help in the selection of those patients who could benefit the most from neoadjuvant chemotherapy. Although there are reported clinical factors associated with worse renal functional outcomes [6,7], to the best of our knowledge, there are no existing validated nomograms for predicting renal function insufficiency for cisplatin-based adjuvant chemotherapy after RNU.

The aim of the present study was to develop and validate a model for the prediction of significant renal function reduction in a global multi-institutional dataset (ROBotic surgery for Upper tract Urothelial cancer Study—ROBUUST project), thereby allowing the identification of patients likely to be ineligible for cisplatin-based adjuvant chemotherapy after minimally invasive radical nephroureterectomy, and investigate its significance in prognostic risk stratification.

2. Patients and methods

2.1. Study population and variables

ROBUUST is a multinational, multicenter project including 17 institutions worldwide. A dataset of patients who underwent single-stage minimally invasive (robotic or laparoscopic) RNU for upper tract urothelial carcinoma (UTUC) was created. Institutional review board approval or exempt was obtained at each center. The study design for this project was not unblinded until the completion of data collection. The purpose-built ROBUUST database including cases of minimally invasive RNU performed at participating centers from February 2006 to March 2020 was queried with the following exclusion criteria: (1) preoperative metastatic diseases, (2) anatomically single kidney, and (3) missing data in predictors.

The following variables of interest were included for analysis:

1 Demographics, smoking history, American Society of Anesthesiologists (ASA) score, hypertension, diabetes, presence of hematuria, history of bladder cancer, preoperative serum creatinine (SCr) recorded most recent to the surgery of RNU (estimated glomerular filtration rate [eGFR] calculated by the Chronic Kidney Disease Epidemiology Collaboration formula [8]), tumor characteristics, and perioperative data
2 Functional data, including SCr and eGFR at postoperative day 1, discharge, postoperative 3 and 12 mo, and last follow-up
3 Oncological data, including tumor recurrence, tumor metastasis, cancer-specific mortality, and overall mortality

2.2. Outcome definition

Regarding the timing of postoperative eGFR for analysis, closest to 3 mo after surgery was selected to best approximate the measured SCr that would affect the delivery of adjuvant chemotherapy [1,5]. Although an eGFR of <60 ml/min/1.73 m^2 forms part of the Galsky definition of being cisplatin unfit [9], here we use the most recent criteria of eGFR <50 ml/min/1.73 m^2 according to UTUC-specific perioperative trials (POUT trial, etc.) [1,10].

2.3. Model development, validation, and clinical use analysis

According to the tutorials about clinical prediction models, nonrandom splitting of training and validation sets (eg, by centers) is considered more preferable, as it reduces the similarity of the two sets of patients and, generally, more individuals should be allocated to the training set [11,12]. Besides, geographic external validation is often possible with collaborative studies and is more meaningful than a standard cross-validation [13]. Thus, the sample was geographically separated into a training cohort (data from centers in the USA) and an external validation cohort (data from centers in China, Belgium, Italy, and Korea). The methodology of sample size estimation is provided in the Supplementary material. The least absolute shrinkage and selection operation (LASSO) regression model was used for the selection of variables in

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.01.014

the training set. Model development was performed according to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline [14]. Additional methodology is provided in the Supplementary material.

2.4. Statistical analysis

The LASSO regression model was used with penalty parameter tuning that was conducted by ten-fold cross-validation based on 1 standard error criteria. A restricted cubic spline (RCS) analysis was adopted to assess the nonlinear relationship between the candidate variables and the predicted outcome. The decision curve analysis (DCA) method was used to evaluate the clinical utility of the presented nomogram. Overall death risk and cancer-specific death risk were obtained using the Kaplan-Meier method, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a univariate Cox regression analysis. Statistical analyses were performed using R 3.6.0 software (http://cran.r-project.org). All tests were two sided, with a significance level set at $p < 0.05$.

3. Results

3.1. Baseline patient characteristics

A total of 490 patients were identified; out of them, 129 (26.3%) patients had preoperative eGFR <50 ml/min/1.73 m^2, who were considered initially ineligible for cisplatin-based neoadjuvant or adjuvant chemotherapy. Finally, 361 patients were included for further analysis, with 226 cases in the training set and 135 cases in the validation set (Fig. 1).

Descriptive characteristics for this cohort, the training set (X), and the validation set (Y) are reported in Table 1. The median (interquartile range [IQR]) age at surgery of the whole, training, and validation sets was 70 (62, 77), 72 (63, 78), and 67 (60, 74.5) yr, respectively; 240 (66.5%), 141 (62.4%), and 99 (73.3%) patients were male in the respective sets. Ipsilateral hydroureteronephrosis was found in 162

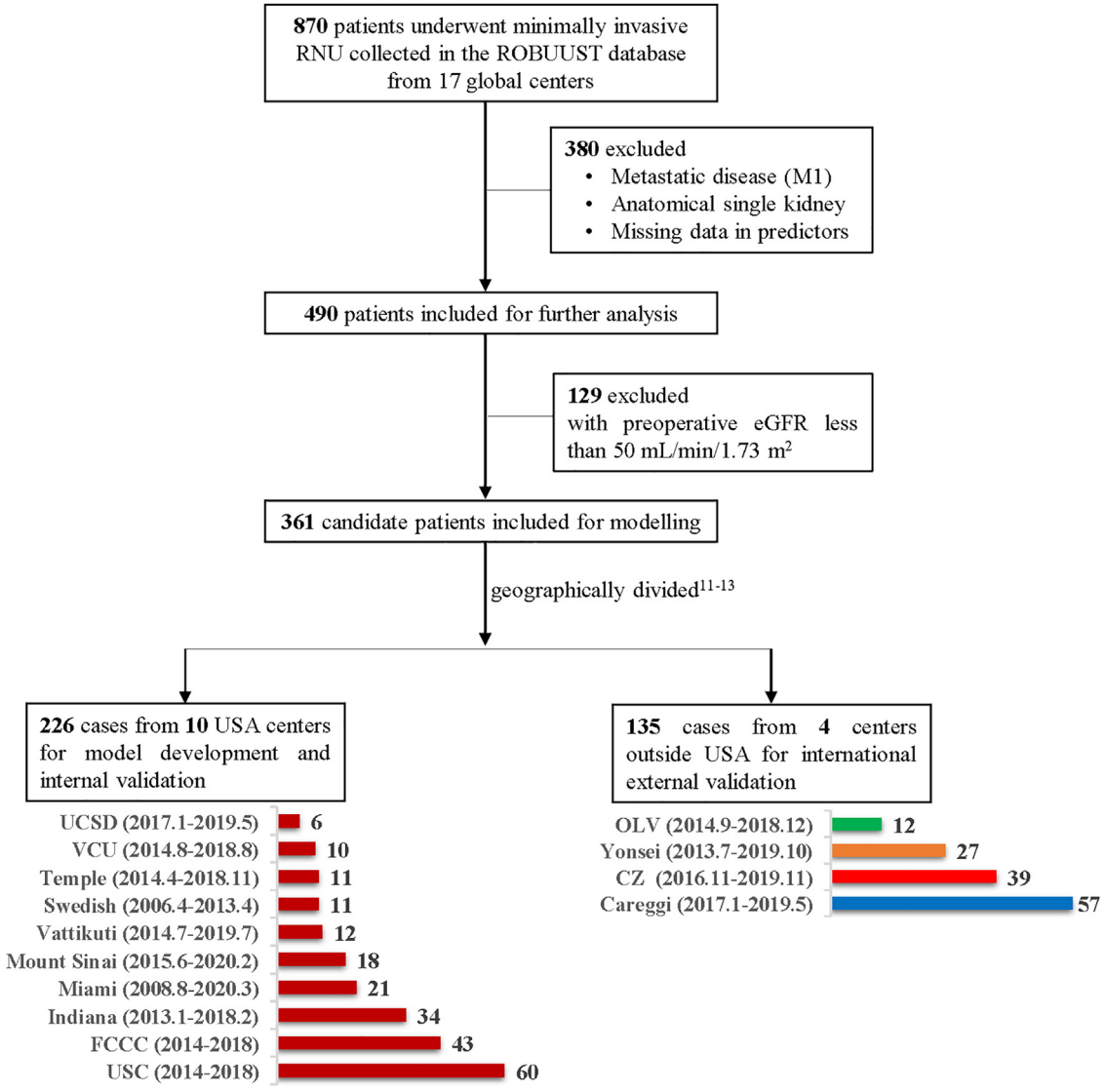


Fig. 1 – Diagram of study cohort selection steps. eGFR = estimated glomerular filtration rate; RNU = radical nephroureterectomy; ROBUUST = ROBotic surgery for Upper tract Urothelial cancer Study.

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.01.014

Table 1 – Descriptive characteristics of the overall cohort, training set, and validation set

Variables	Overall (*n* = 361)	Training set (*n* = 226)	Validation set (*n* = 135)	*p* value [a]
Number of centers	14	10	4	
Age (yr)	70 (62, 77)	72 (63, 78)	67 (60, 74.5)	**0.001**
Race, *n* (%)				<**0.001**
Caucasian	237 (65.7)	168 (74.3)	69 (51.1)	
Black/Hispanic/Asian	117 (32.4)	51 (22.6)	66 (48.9)	
Other	7 (1.9)	7 (3.1)	0 (0)	
Gender, *n* (%)				**0.033**
Male	240 (66.5)	141 (62.4)	99 (73.3)	
Female	121 (33.5)	85 (37.6)	36 (26.7)	
BMI (kg/m^2)	26.2 (24.2, 29)	26.7 (24.4, 30.5)	25.7 (24, 27)	<**0.001**
Smoking history, *n* (%)	196 (54.3)	143 (63.3)	53 (39.3)	<**0.001**
ASA score, *n* (%)				<**0.001**
1–2	172 (47.6)	71 (31.4)	101 (74.8)	
3–4	189 (52.4)	155 (68.6)	34 (25.2)	
Hypertension, *n* (%)	207 (57.3)	130 (57.5)	77 (57)	0.928
Diabetes, *n* (%)	55 (15.2)	33 (14.6)	22 (16.3)	0.665
Presence of gross hematuria, *n* (%)	251 (69.5)	164 (72.6)	87 (64.4)	0.105
History of bladder cancer, *n* (%)	66 (18.3)	53 (23.5)	13 (9.6)	**0.001**
Baseline eGFR (ml/min/1.73 m^2)	72.3 (60.6, 85.5)	69.7 (60.1, 83.2)	75.7 (63, 88.3)	**0.007**
Baseline eGFR category [b], *n* (%)				**0.040**
1 (eGFR ≥90)	60 (16.6)	31 (13.7)	29 (21.5)	
2 (60 ≤ eGFR < 90)	220 (61)	139 (61.5)	81 (60)	
3a (eGFR <60)	81 (22.4)	56 (24.8)	25 (18.5)	
Tumor laterality, *n* (%)				0.674
Right	187 (51.8)	119 (52.7)	68 (50.4)	
Left	174 (48.2)	107 (47.3)	67 (49.6)	
Tumor size (cm)	3.2 (2.2, 4.5)	3.0 (2.0, 4.1)	4.0 (2.5, 5.1)	<**0.001**
Tumor site, n (%)				<**0.001**
Renal calyx/pelvis	196 (54.3)	141 (62.4)	55 (40.7)	
Ureter	133 (36.8)	66 (29.2)	67 (49.6)	
Both	32 (8.9)	19 (8.4)	13 (9.6)	
Multifocal tumor, *n* (%)	59 (16.3)	40 (17.7)	19 (14.1)	0.367
Hydroureteronephrosis, *n* (%)	162 (44.9)	87 (38.5)	75 (55.6)	**0.002**
cT stage, *n* (%)				<**0.001**
T_{a-1}	239 (66.2)	192 (85)	47 (34.8)	
T_{2-4}	122 (33.8)	34 (15)	88 (65.2)	
cN stage, *n* (%)				0.399
N_0	344 (95.3)	217 (96)	127 (94.1)	
N_{1-2}	17 (4.7)	9 (4)	8 (5.9)	
Robotic approach, *n* (%)	278 (77)	186 (82.3)	92 (68.1)	**0.002**
Bladder cuff management, *n* (%)				0.869
Standard excision	271 (75.1)	169 (74.8)	102 (75.6)	
Other technique [c]	90 (24.9)	57 (25.2)	33 (24.4)	
Tumor grade [d], *n* (%)				0.159
Grade 1	56 (15.5)	40 (17.7)	16 (11.9)	
Grade 2	24 (6.7)	2 (0.9)	22 (16.3)	
Grade 3	270 (74.8)	176 (77.9)	94 (69.6)	
Unknown	11 (3.0)	8 (3.5)	3 (2.2)	
Follow-up duration (mo)	14 (7, 27)	14.3 (4, 29)	14 (9.8, 26)	0.352
Postoperative eGFR (ml/min/1.73 m^2)				
POD 1 (*n* = 310)	53.3 (44.8, 65.5)	49.6 (42.4, 56.9)	60.6 (49.2, 76.1)	<**0.001**
At discharge (*n* = 337)	53.2 (43.5, 66)	51.1 (41.9, 59.4)	60.2 (47.6, 74.8)	<**0.001**
3 mo (*n* = 361)	52.0 (42.5, 64.9)	50.5 (41.9, 60.4)	57.8 (45.2, 70.2)	<**0.001**
3 mo eGFR <50, *n* (%)	158 (43.8)	112 (49.6)	46 (34.1)	**0.004**
12 mo (*n* = 160)	49.9 (41.5, 60.9)	46.9 (39.2, 56)	53.9 (45.1, 65.8)	**0.001**
Last follow-up (*n* = 306)	52.6 (43.2, 65.9)	48.5 (40, 59)	58.7 (47.4, 73.7)	<**0.001**
Tumor recurrence, *n* (%)	107 (29.6)	78 (34.5)	29 (21.5)	**0.009**
Time to recurrence (mo)	6 (3, 10.3)	6 (3, 9.8)	7 (6, 12)	0.135
Tumor metastasis, *n* (%)	41 (11.4)	32 (14.2)	9 (6.7)	0.062
Time to metastasis (mo)	7 (4.5, 16)	6.8 (4, 12.7)	15 (6.8, 22)	0.123
Cancer-specific mortality, *n* (%)	25 (6.9)	22 (9.7)	3 (2.2)	**0.007**
Overall mortality, *n* (%)	36 (10)	31 (13.7)	5 (3.7)	**0.002**

ASA = American Society of Anesthesiologists; BMI = body mass index; eGFR = estimated Glomerular Filtration Rate; POD = postoperative day; RNU = radical nephroureterectomy.
Medians (interquartile range) or frequencies (proportions) are displayed for continuous and categorical variables, respectively.
[a] *p* values compare the training set with the validation set using Mann-Whitney *U* test, chi-square test, or exact Fisher test, depending on whether the variable is continuous or categorical.
[b] According to the Kidney Disease: Improving Global Outcomes guidelines for chronic kidney disease.
[c] Pluck technique (*n* = 0), stripping (*n* = 2), transurethral resection (*n* = 24), intussusception (*n* = 2), Hem-o-Lok closure (*n* = 36), EndoGia/Ligasure (*n* = 1), not removed because of contemporary cystectomy (*n* = 16), and unknown (*n* = 9).
[d] According to the result of post-RNU pathological examination.

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.08.014

(44.9%), 87 (38.5%), and 75 (55.6%) cases of the whole, training, and validation sets, respectively. The median (IQR) baseline eGFRs were, respectively, 72.3 (60.6, 85.5), 69.7 (60.1, 83.2), and 75.7 (63, 88.3) ml/min/1.73 m^2. Overall, 158 (43.8%) patients experienced eGFR reduction to <50 ml/min/1.73 m^2 at 3-mo postoperative follow-up, with 112 (49.6%) and 46 (34.1%) patients for the training and the validation group, respectively. The median follow-up for survivors was 14 (7, 27) mo. Overall, 110 patients were followed up for ≥24 mo. The overall mortality and cancer-specific mortality rates for the whole cohort were 10% and 6.9%, respectively.

3.2. Model development, performance evaluation, and external validation

Four preoperative factors (age, body mass index [BMI], preoperative eGFR, and hydroureteronephrosis) were screened by a LASSO regression as important features for scoring function development in the training set (Supplementary Fig. 1 and 2). An RCS analysis showed a nonlinear association between the variable of age and the outcome ($p < 0.05$), and the risk function demonstrated an inflection point at 70 yr, then age was transformed into a binary variable. A nonlinear association was not detected for the other two continuous factors (both $p > 0.05$; Supplementary Fig. 3).

A model that incorporated the above independent predictors was developed (see the Supplementary material for the formula of risk score calculation) and presented as the nomogram (Fig. 2) with an area under the curve (AUC) of 0.771 (95% CI: 0.711–0.831; Fig. 3A), which was confirmed to be 0.759 via bootstrapping validation. External validation of the nomogram revealed an AUC of 0.773 (95% CI: 0.697–0.850; Fig. 3B).

The calibration plot showed that the predicted probability of postoperative eGFR <50 ml/min/1.73 m^2 had concordance to that of the observed frequency, with most predictions within a mean absolute error of 0.031 in the training set (Fig. 3C) and 0.072 in the external validation set (Fig. 3D). The Hosmer-Lemeshow goodness of fit test revealed $p = 0.16$ (the training set) and 0.263 (the external validation set), indicating nonsignificant miscalibration.

3.3. Clinical usefulness

The DCA for the nomogram is presented in Figure 4A. The DCA indicated that when the threshold probability ranges from 0 to 0.83, the nomogram adds more net benefit than the "treat all" or "treat none" strategies, which means that our nomogram could bring benefits to patients in practice.

Stratification of the high-risk probability for 1000 samples was predicted on the clinical impact curve (Fig. 4B). The predictive high-risk number was close to the actual number of positive cases when the threshold probability was >0.3. At this time, the cost-to-benefit ratio was 2:5. An optimal risk score cutoff value of 0.583 was achieved based on the principle of achieving a maximum Youden index in the training set. The relevant specificity was 0.81 and sensitivity 0.60. The patients were classified into low- and high-risk groups according to the optimal cutoff value. The high-risk group had a greater likelihood of postoperative eGFR <50 ml/min/1.73 m^2 (risk ratio [RR]: 2.618, 95% CI: 1.805–3.798 in the training set and RR: 1.604, 95% CI: 1.035–2.487 in the validation set). Notably, the difference in both overall death risk (HR: 4.59, 95% CI: 2.28–9.23, $p < 0.001$; Fig. 5A) and cancer-specific death risk (HR: 5.19, 95% CI: 2.24–12.04, $p < 0.001$; Fig. 5B) was statistically significant between the two groups for the combined training and validation set. Besides, the significance of difference in death risk between the two groups remained in the subgroup of $pT_{2-4}Nx$ or $TanyN_{1-2}$ patients (overall death risk, HR: 4.58, 95% CI: 2.17–9.65, $p < 0.001$; cancer-specific death risk, HR: 5.79, 95% CI: 2.36–14.25, $p < 0.001$; Fig. 5C and 5 D).

4. Discussion

In this retrospective global, multicenter, development and validation study, we constructed a clinical signature-based

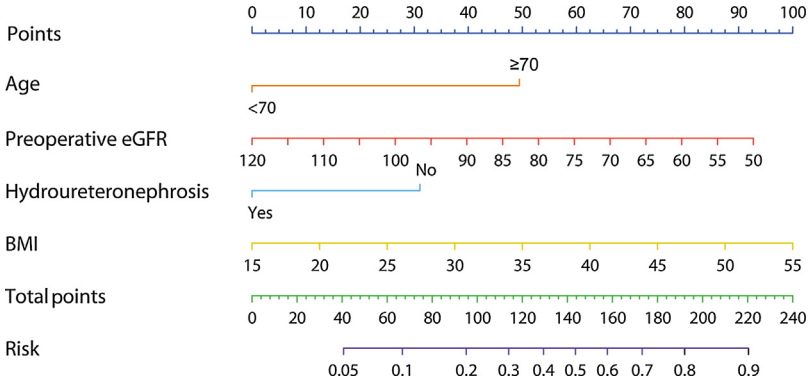


Fig. 2 – Nomogram for the prediction of postoperative eGFR <50 ml/min/1.73 m^2 after RNU based on a multivariable model. Instructions for utilization: locate the patient's preoperative eGFR on the corresponding axis. Draw a line straight downward to the point axis to determine how many points toward the probability of postoperative eGFR <50 ml/min/1.73 m^2 the patient receives for the preoperative eGFR. Repeat the process for each additional predictor. Add the points for each of the variables. Locate the final sum on the total points axis. Draw a line straight up to find the patient's risk probability. BMI = body mass index; eGFR = estimated glomerular filtration rate; RNU = radical nephroureterectomy.

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.01.014

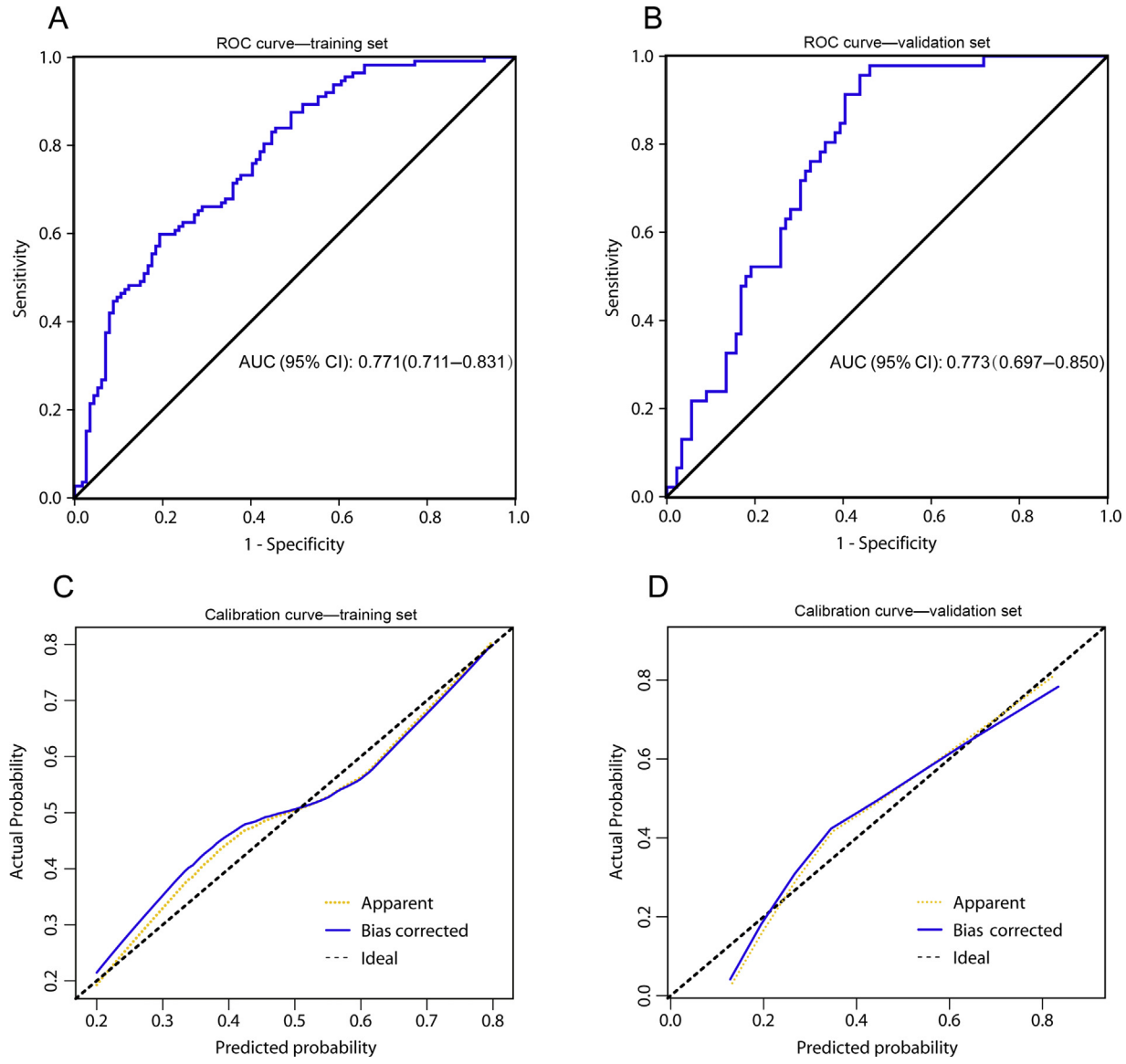


Fig. 3 – ROC curve and calibration plot of the model. (A and B) ROC curves predicted probabilities from the nomogram in the training set and the external validation set. (C and D) Calibration curves for the nomogram to predict probability of postoperative eGFR <50 ml/min/1.73 m^2 for the training set and the external validation set. AUC = area under the curve; CI = confidence interval; eGFR = estimated glomerular filtration rate; ROC = receiver operating characteristics.

nomogram for the preoperative individualized prediction of renal function insufficiency for cisplatin-based adjuvant chemotherapy in UTUC patients after RNU. The model successfully stratified patients according to their risk of renal function insufficiency for cisplatin use as well as mortality. Incorporating clinical risk factors into an easy-to-use nomogram facilitates the preoperative individualized risk prediction and optimum timing of perioperative cisplatin-based chemotherapy.

The nomogram AUC of 0.771 (95% CI: 0.711–0.831) in the development cohort confirmed good discrimination ability. However, application of a prediction model is always limited by the type of validation or the lack of external validation [15,16]. In this study, to improve the generalizability of the model's performance, we constructed a geographically independent validation set comprising 135 patients from four different institutions in four different non-USA countries. The difference in the distribution of important variables (demographics, predictors, and outcome; Table 1) reveals that the validation set comprises populations that are "plausibly related" to the development cohort. The achieved predictive accuracy of the nomogram in the external validation cohort was comparable with a slight improvement (AUC of 0.773, 95% CI: 0.697–0.850), although the outcome positivity was much lower in the validation cohort (34.1% vs 49.6%), which suggested a robust prediction model sufficiently capturing informative predictive factors. The calibration plot showed good agreement

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.09.014

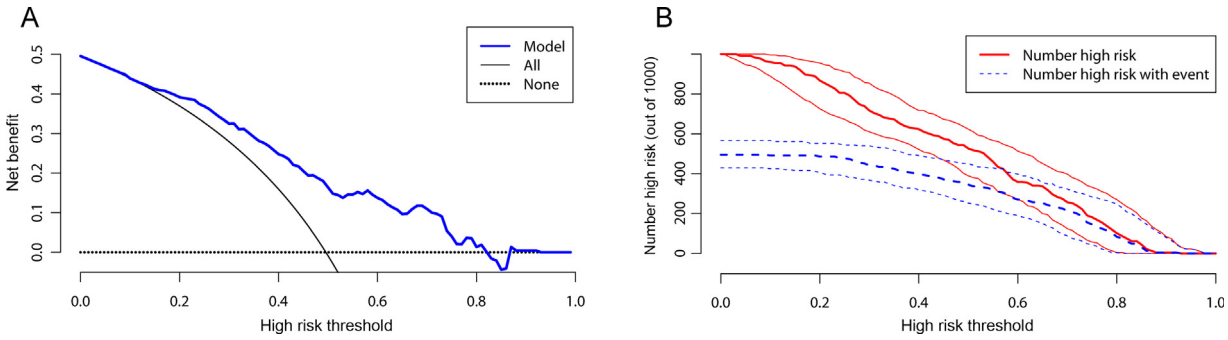


Fig. 4 – Decision curve and clinical impact curve for the predictive nomogram. (A) The net benefits were measured at different threshold probabilities. The blue line represents the predictive nomogram. The solid line represents the assumption that all patients have the study outcomes and intervention. The dotted line represents the assumption that no patients have the study outcomes and no intervention is done. (B) Clinical impact curve to predict the high-risk number for a population size of 1000. The red curve shows the predicted high-risk number at different threshold probabilities and the blue curve represents the actual high-risk patients.

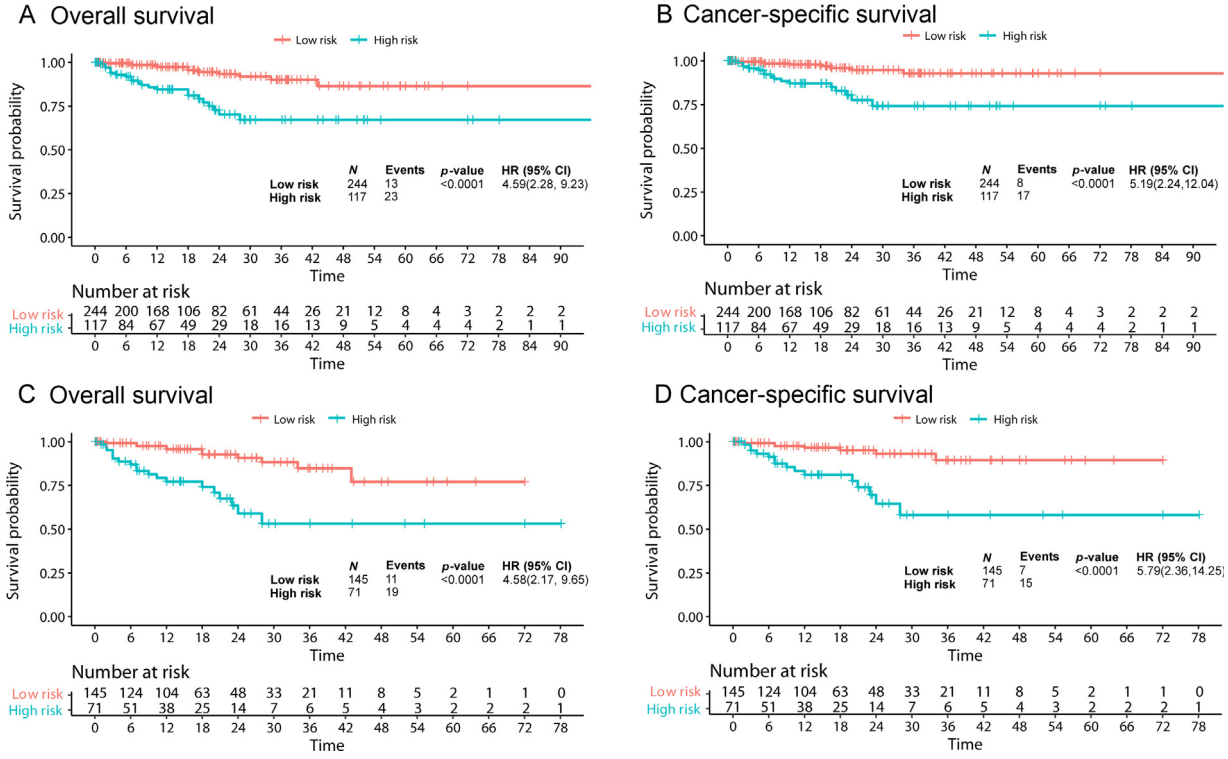


Fig. 5 – Kaplan-Meier estimates with Cox regression analysis for overall and cancer-specific survival in RNU patients with low and high risk for postoperative eGFR <50 ml/min/1.73 m^2. (A and B) The whole group combined the training set and validation set. (C and D) The subgroup of pT2–4Nx or TanyN1–2 patients. CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; RNU = radical nephroureterectomy.

between predicted probability and observed frequency. Last but not least, robustness of the model was confirmed via a sensitivity analysis.

Many clinical factors are found to be associated with worse renal functional outcomes following RNU [6,17,18], but there is a high risk of overfitting, multicollinearity, and interaction in predictive modeling of these data, characterized by reduced significance of the predictor when applied to an independent dataset [19]. The LASSO penalization for optimal variable selection not only surpasses the method of selecting predictors on the basis of the strength of their univariable association with outcome, but also enables the panel of candidate features to be converted into a combined signature [20,21]. In the present study, we have applied this method successfully and identified four clinical items: age at surgery, BMI, preoperative eGFR, and hydroureteronephrosis of the operated kidney. Additionally, linearity may not always hold between the relationship of a continuous independent variable and the dependent variable. To address this issue, an RCS analysis was adopted [22], which has recently been used to study the relationship between survival/outcome and treatment in patients with cancer [23,24]. In this study, it uncovered nonlinearity of the relationship between patient age and the predicted

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.01.014

outcome with an inflection point at 70 yr (if incorporated as a continuous variable, the AUC decreased to 0.736; data not shown), a threshold in concordance to others despite their relatively arbitrary classification [5,6,17].

Contrary to what is reported in previous studies [6,17,25], our results demonstrated that BMI was an independent risk factor for renal function decline after RNU. Although the relationship between obesity and CKD progression is complex, its negative effect has been revealed from large prospective series [26,27]. Not surprisingly, preoperative renal function status is predominant for postoperative functional preservation. Actually, split renal function of the operated kidney by nuclear renal scans could be more accurate to reflect the function loss, but it is not routinely obtained before the surgery of RNU. Nevertheless, some alternative factors related to the split renal function such as tumor size, multifocality, ureteral location, and hydronephrosis are more practical to use in our clinical practice. Owing to the overlapping effect between these variables, the results derived from common multivariable regression analysis in previous studies are not consistent [6,17,18,25]. In our study, only the hydroureteronephrosis was demonstrated to be a predictive factor after adjusting for others with improved methodology. Finally, the model shows additional value in prognostic evaluation. A Cox regression analysis indicated that the risk cutoff score based on our model was a significant predictive factor distinct from the pathological traits. In this regard, should these patients be considered for neoadjuvant chemotherapy, it will be important to maximize preoperative renal function via ureteral stents or percutaneous drainage when indicated.

The clinical usefulness of the nomogram was also evaluated to facilitate decision-making on further intervention. When categorized patients into low- and high-risk groups on the basis of the cutoff values derived from the nomogram; the high-risk group had a significantly greater probability of having a predicted outcome in both the training and the independent validation group. Furthermore, the present model showed better net benefit at a threshold probability of $\leq$83%. At this time, we still lack confidence to avoid overtreatment versus risk of disease progression, and there is recommendation to provide neoadjuvant cisplatin-based multidrug regimens, given the high likelihood (43.8%, as shown in Table 1) of being unable to offer cisplatin-based therapy in adjuvant setting, similar to previous reports [5,7,25,28]. Therefore, the prediction tool may be especially helpful for treatment selection in favorable surgical candidates classified at a lower risk for cisplatin ineligibility to skip neoadjuvant chemotherapy, and, on the contrary hand, for treatment selection of those who are at a high risk of renal insufficiency postoperatively and would probably benefit from neoadjuvant chemotherapy.

The main limitation of the present study lies in its retrospective nature despite the data collected in a structured form. It is still subject to selection and recall biases, and some unmeasured data (ie, split renal function) that were not retrospectively retrievable. Missing data on predictors led to cases being excluded and to a further decrease in the power of our study. Moreover, we have to acknowledge that postoperative renal function is a time-sensitive outcome and eGFR fluctuations are common in the immediate postoperative period (within 1 mo). Nevertheless, the proper eGFR (median 3 mo, IQR 1.8–3 mo) was selected in this study to demonstrate cisplatin eligibility in the adjuvant setting if the patient indeed required systemic therapy. Finally, the follow-up duration was relatively short for survival analysis. Prospective randomized clinical trials with a large sample size are needed to acquire high-level evidence for clinical application in the future.

5. Conclusions

A nomogram incorporating immediately available clinical variables can accurately predict renal insufficiency for cisplatin-based adjuvant chemotherapy after minimally invasive RNU and may serve as a tool optimizing patient selection.

***Author contributions*:** Linhui Wang 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: Wu, Autorino.
Acquisition of data: Wu, Djaladat, Minervini, Uzzo, Sundaram, Rha, Gonzalgo, Mehrazin, Mazzone, Marcus, Danno, Porter, Asghar, Ghali, Guruli, Douglawi, Cacciamani, Ghoreifi, Simone, Margulis, Ferro, Tellini, Mari, Srivastava, Steward, Al-Qathani, Al-Mujalhem, Bhattu, Mottrie, Abdollah, Eun, Derweesh, Veccia, Autorino.
Analysis and interpretation of data: Wu, Autorino.
Drafting of the manuscript: Wu.
Critical revision of the manuscript for important intellectual content: Autorino, Veccia, Djaladat, Mari, Margulis.
Statistical analysis: Wu, Chen.
Obtaining funding: Wu, Wang, Chen.
Administrative, technical, or material support: None.
Supervision: Wang, Autorino.
Other: None.

Financial disclosures: Linhui Wang 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: None.

***Funding/Support and role of the sponsor*:** This work was supported by National Natural Science Foundation of China (82072825 and 81874093 to Zhenjie Wu, 81730073 and 81872074 to Linhui Wang); Program of Shanghai Hospital New Star (YYXX-WZJ to Zhenjie Wu); Program of Shanghai Hospital Development Center (SHDC12018108 to Linhui Wang); Special Clinical Research in Health Industry in Shanghai (20184Y0054 to Qi Chen); and Shanghai Sail Program (19YF1459200 to Qi Chen).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2021.01.014.

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.01.014

References

[1] Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet 2020;395:1268–77.

[2] Leow JJ, Chong YL, Chang SL, Valderrama BP, Powles T, Bellmunt J. Neoadjuvant and adjuvant chemotherapy for upper tract urothelial carcinoma: a 2020 systematic review and meta-analysis, and future perspectives on systemic therapy. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2020.07.003.

[3] Bamias A, Tzannis K, Harshman LC, et al. Impact of contemporary patterns of chemotherapy utilization on survival in patients with advanced cancer of the urinary tract: a Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Ann Oncol 2018;29:361–9.

[4] Rouprêt M, Babjuk M, Burger M, et al. EAU guidelines on upper urinary tract urothelial carcinoma 2020. European Association of Urology guidelines 2020 edition. Arnhem, The Netherlands: European Association of Urology Guidelines Office; 2020.

[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.

[6] 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.

[7] 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.

[8] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

[9] Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432–8.

[10] 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.

[11] Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925–31.

[12] Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ 2009;338:b605.

[13] Steyerberg EW. Clinical prediction modelsChapter 17: Validation of prediction models. New York, NY: Springer; 2009.

[14] Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1–73.

[15] Correa AF, Jegede O, Haas NB, et al. Predicting renal cancer recurrence: defining limitations of existing prognostic models with prospective trial-based validation. J Clin Oncol 2019;37:2062–71.

[16] Damen JA, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ 2016;353:i2416.

[17] 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.

[18] 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.

[19] Cook JA, Ranstam J. Overfitting. Br J Surg 2016;103:1814.

[20] Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Ser B (Methodol) 1996;58:267–88.

[21] Steyerberg EW, Eijkemans MJ, Harrell Jr FE, Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. Stat Med 2000;19:1059–79.

[22] Marrie RA, Dawson NV, Garland A. Quantile regression and restricted cubic splines are useful for exploring relationships between continuous variables. J Clin Epidemiol 2009;62, 511–7.e1.

[23] Salazar MC, Rosen JE, Wang Z, et al. Association of delayed adjuvant chemotherapy with survival after lung cancer surgery. JAMA Oncol 2017;3:610–9.

[24] Kutikov A, Smaldone MC, Egleston BL, et al. Anatomic features of enhancing renal masses predict malignant and high-grade pathology: a preoperative nomogram using the RENAL nephrometry score. Eur Urol 2011;60:241–8.

[25] 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.

[26] Yun HR, Kim H, Park JT, et al. Obesity, metabolic abnormality, and progression of CKD. Am J Kidney Dis 2018;72:400–10.

[27] Madero M, Katz R, Murphy R, et al. Comparison between different measures of body fat with kidney function decline and incident CKD. Clin J Am Soc Nephrol 2017;12:893–903.

[28] Lane BR, Smith AK, Larson BT, et al. Chronic kidney disease after nephroureterectomy for upper tract urothelial carcinoma and implications for the administration of perioperative chemotherapy. Cancer 2010;116:2967–73.

Please cite this article in press as: Wu Z, et al. A Preoperative Nomogram to Predict Renal Function Insufficiency for Cisplatin-based Adjuvant Chemotherapy Following Minimally Invasive Radical Nephroureterectomy (ROBUUST Collaborative Group). Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.01.014