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Kidney Cancer

A Nomogram to Predict Significant Estimated Glomerular Filtration Rate Reduction After Robotic Partial Nephrectomy

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Abstract

Background: Decreased functional outcome after partial nephrectomy is associated with overall mortality.
Objective: To create a model that predicts ≥25% reduction from baseline estimated glomerular filtration rate (eGFR) in patients undergoing robot-assisted partial nephrectomy (RAPN) and to investigate the role of acute kidney injury (AKI) in this patient population.
Design, setting, and participants: A total of 999 patients were identified from a multi-institutional database. Renal function was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for chronic kidney disease (CKD). AKI was defined as >25% reduction in eGFR from pre-RAPN period to discharge.
Outcome measurements and statistical analysis: A nomogram to predict significant eGFR reduction (≥25% from baseline) in the time-frame between 3 and 15 mo after RAPN was built based on the coefficients of Cox survival function that ultimately included age, sex, Charlson comorbidity index, baseline eGFR, RENAL nephrometry score, AKI in patients with normal baseline renal function, and AKI on CKD. Such landmark analysis was chosen in order to account for eGFR fluctuations occurring within the first 3 mo of RAPN. The proportional hazard assumption was evaluated through the Schönfeld test. Internal validation was performed using the leave-one-out cross validation. Calibration was graphically investigated. The decision curve analysis (DCA) was used to evaluate the net clinical benefit.
Results and limitations: Median (interquartile range [IQR]) age at surgery was 61 yr (51, 68). Overall, 146 patients experienced significant eGFR reduction; median follow-up for survivors was 12.4 mo. The 15-mo probability of significant eGFR reduction was 19%. All variables fitted into the model, including AKI in patients with normal renal function (hazard ratio [HR]: 4.51; 95% confidence interval [CI]: 3.12, 6.60; $p < 0.001$) and AKI on CKD (HR: 4.90; 95% CI: 2.17, 11.1; $p < 0.001$), emerged as predictors of significant eGFR reduction (all $p \leq 0.048$) and were considered to build a nomogram. The internally validated *c* index was 73%. The model demonstrated excellent calibration and a net benefit at the DCA with probabilities ≥4%.

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Conclusions: We developed a nomogram that accurately predicts significant eGFR reduction after RAPN. This model may serve as a tool for early identification of patients at high risk for significant renal function decline after surgery.
Patient summary: We have developed a model for the prediction of renal function loss after partial nephrectomy for renal cancer.

1. Introduction

Partial nephrectomy (PN) is the current standard of care treatment for T1 renal cancer [1,2]. This conservative approach toward renal tumors is associated with a lower incidence of postoperative chronic kidney disease (CKD), cardiovascular events, and death compared with radical nephrectomy in certain subgroups of patients [3,4]. Over time, the rate of PN has been increasing, which is also attributable to stage migration toward more localized disease [5,6]. The majority of contemporary PNs in the USA and Europe are performed robotically, with the open approach utilized on a case-by-case basis due to various anatomic complexities [7,8].

Renal function after PN remains of pivotal importance in the immediate, short, and long terms [9]. In fact, acute kidney injury (AKI), irrespective of its cause, can predispose patients to CKD [10] and postsurgical estimated glomerular filtration rate (eGFR) can affect survival, especially in patients with pre-existing CKD [11–13].

The decline of renal function after PN is poorly understood, and the occurrence of postoperative AKI is generally regarded as a self-limiting condition. However, there is a need for tools that aid in predicting renal functional decline. This would better facilitate patient and doctor functional outcome expectation and postoperative management planning.

Although there are clinical and surgical factors that are associated with worse renal functional outcomes [14], to the best of our knowledge, there are no existing nomograms for predicting renal function decline after PN. Thus, the aim of this study was to develop a model for the prediction of significant eGFR reduction between 3 and 15 mo after robot-assisted partial nephrectomy (RAPN). Additionally, we sought to determine if there was a difference in the occurrence of postoperative AKI between patients with normal renal function and those with pre-existing CKD, and its impact on renal function loss.

2. Patients and methods

2.1. Study population

Data from 1150 patients from a multi-institutional Research Electronic Data Capture (REDCap) database with complete follow-up data were identified. All patients received RAPN between 2008 and 2017 for suspected renal cell carcinoma at five tertiary referral centers. No patient underwent neoadjuvant therapy. All procedures were performed by experienced robotic surgeons. Patients with missing data were excluded from the analysis (Charlson comorbidity index [CCI], $n = 17$ and RENAL nephrometry score, $n = 134$). Overall, 999 patients were considered for further analyses.

2.2. Variables and outcome definition

Estimated GFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula [15]. Renal function was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD. We considered grades 1–2 from these guidelines as normal preoperative kidney function. Patients with grade >2 were considered to have CKD [16]. Postoperative AKI was defined according to the risk/injury/failure/loss/end-stage (RIFLE) criteria (>25% reduction in preoperative baseline eGFR or >1.5-fold increase in preoperative creatinine, both at discharge from hospital) [17]. We adopted this definition since only four patients experienced grade 2 AKI according to the RIFLE criteria. The complexity of RAPN was defined according to the RENAL nephrometry score [18].

The outcome of this study was an eGFR reduction of ≥25% from baseline between 3 and15 mo after RAPN. This eGFR threshold was chosen based on the National Institute for Health and Care Excellence guidelines for CKD [19]. The same guidelines refer to an eGFR decrease of ≥25% within 12 mo in their definitions of CKD progression [19]. As eGFR fluctuations are common in the immediate postoperative period (3 mo), our analysis utilized a landmark-based technique that allowed us to consider the outcome of interest occurring between 3 and 15 mo postoperatively.

In building our model, we investigated the role of pre- and postoperative variables. Regarding the latter, we considered the occurrence of postoperative AKI (no vs yes) overall, and then its occurrence in patients with normal preoperative renal function and in patients with CKD.

2.3. Statistical analysis

First, descriptive statistics were attained: frequencies and proportions were reported for categorical variables, with medians and interquartile ranges (IQRs) reported for continuous variables.

Second, the incidence rate of significant eGFR reduction was estimated nonparametrically using the Kaplan-Meier method. The follow-up for significant eGFR reduction-free patients was estimated using the inverse Kaplan-Meier method.

Third, multivariable semiparametric Cox regression analyses were performed for the outcome of interest. We then relied on the most parsimonious model in terms of the number of significant covariates. After computing Harrell's *c* index and verifying the proportional hazard (PH) assumption, we used the coefficients of the Cox survival function for the development of a nomogram that predicts ≥25% eGFR reduction between 3 and 15 mo after RAPN. The PH assumption was verified by performing the Schönfeld test.

Fourth, internal validation was performed using the leave-one-out cross validation (LOOCV). The prediction of significant eGFR reduction between 3 and 15 mo, obtained from the Cox regression, adjusted after internal validation, was used to compute the *c* index of the model and perform the decision curve analysis (DCA).

Statistical analyses were performed using Stata 14 (StataCorp LP, College Station, TX, USA). All tests were two sided with a significance level set at $p < 0.05$.

2.4. Sensitivity analyses

Characteristics of the excluded patients, due to missing data, were compared with those of the study population. Moreover, since the occurrence of AKI was the only postoperative variable considered in the model, we repeated the multivariable analysis after its exclusion. Again, the DCA was used to graphically evaluate the difference between the two models.

3. Results

3.1. *Baseline patients' characteristics*

Descriptive characteristics for the overall population are listed in Table 1. Median (IQR) age at surgery was 61 (51, 68) yr; 419 (42%) patients were female, while 580 (58%) were male. Median (IQR) ischemia time during RAPN was 15 (11, 20) min; a clampless approach was used in 69 (7%) cases. Median time to discharge was 1 d (IQR 1–2 d) with 95% discharged by postoperative day 3.

There were 817 (82%) patients with normal preoperative kidney function and 182 (18%) patients with CKD. During the hospital stay, postoperative AKI occurred in 195 (20%) patients overall, 172patients with normal preoperative kidney function, and 23 patients with pre-existing CKD.

Overall, 146 patients experienced significant eGFR reduction in the time period between 3 and 15 mo after RAPN (Table 1); 59, 59, 22, and six patients had preoperative GFR stages of 1, 2, 3a, and 3b, respectively. Median follow-up for survivors was 12.4 mo. Overall, 229 patients were followed up for >24 mo. The 15-mo probability of significant eGFR reduction was 19% (95% confidence interval [CI]: 16%, 22%). Figure 1 displays the Kaplan-Meier failure function curve for the overall patient population, according to our landmark method.

Table 1 – Descriptive characteristics of 999 patients who underwent robot-assisted partial nephrectomy

Variable	Overall (n = 999)
Age (yr)	61 (51, 68)
Race, n (%)	
Caucasian	908 (91)
African American	64 (6)
Other	27 (3)
Sex, n (%)	
Female	419 (42)
Male	580 (58)
BMI (kg/m^2)	29 (26, 34)
Hypertension, n (%)	
No	565 (57)
Yes	426 (43)
CCI, n (%)	
0	516 (52)
1	253 (25)
2	153 (15)
3	53 (5)
≥4	24 (3)
Baseline eGFR (ml/min/1.73 m^2)	82 (66, 96)
Baseline GFR category[a], n (%)	
1	358 (36)
2	459 (46)
3a	127 (13)
3b	46 (4)
4	9 (1)
RENAL score	7 (6, 9)
Ischemia time (min)	15 (11, 20)
AKI, n (%)	
No	805 (80)
Yes	195 (20)
Pathological T stage, n (%)	
1a	798 (80)
1b	141 (14)
2a	10 (1)
2b	2 (0.2)
3a	48 (4.8)

AKI = acute kidney injury; BMI = body mass index; CCI = Charlson comorbidity index; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate.
Medians (interquartile range) or frequencies (proportions) are displayed for continuous and categorical variables, respectively.
[a] According to the Kidney Disease: Improving Global Outcomes guidelines for chronic kidney disease.

3.2. *Uni- and multivariable analysis predicting significant eGFR reduction*

The role of age, race, gender, body mass index, hypertension, CCI, RENAL nephrometry score, baseline eGFR, and ischemia time during RAPN was investigated on a multivariable analysis (Supplementary Table 1). Covariates were then excluded according to their statistical significance (Supplementary Table 1). Eventually, we used the most parsimonious model based on the number of covariates and the statistically significant effect of the variables included. Table 2 displays the multivariable Cox regression including age, gender, CCI, RENAL nephrometry score, baseline eGFR, and occurrence of postoperative AKI (model 1).

3.3. *Stratification of AKI for predicting significant eGFR reduction*

To investigate the different effect of AKI in patients with normal renal function versus those with CKD, patients were stratified accordingly (Table 2, model 2). In doing so, the model achieved better discrimination in terms of c index (76% vs 75%). The PH assumption was met by both models as the Schönfeld test demonstrated (p = 0.2).

Coefficients from multivariable model 2 were utilized to build a nomogram for the prediction of significant eGFR

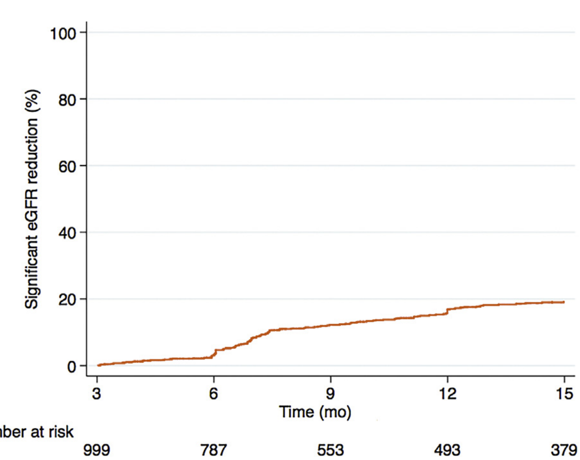

Fig. 1 – Kaplan-Meier failure function estimating the incidence rate of significant eGFR reduction from baseline in the period of time between 3 and 15 mo after surgery. eGFR = estimated glomerular filtration rate.

Table 2 – Multivariable Cox regression analyses predicting significant eGFR reduction between 3 and 15 mo after robot-assisted partial nephrectomy

Covariate	Multivariable analysis Model 1			Multivariable analysis Model 2		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.01	1.00, 1.03	0.049	1.01	1.00, 1.03	0.048
Gender						
Female	1			1		
Male	0.58	0.41, 0.82	0.002	0.58	0.41, 0.82	0.002
CCI						
0	1			1		
1	1.57	1.04, 2.37	0.03	1.57	1.04, 2.37	0.03
2	1.91	1.16, 3.14	0.01	1.91	1.16, 3.14	0.01
3	2.05	1.05, 3.99	0.04	2.06	1.06, 4.00	0.03
≥4	4.33	1.83, 10.3	0.001	4.35	1.84, 10.3	0.001
RENAL score	1.12	1.02, 1.23	0.02	1.12	1.02, 1.23	0.02
Baseline eGFR	1.01	1.00, 1.02	0.01	1.01	1.00, 1.02	0.02
AKI						
No	1					
Yes	4.58	3.20, 6.57	<0.001			
AKI						
No				1		
Yes[a]				4.51	3.12, 6.60	<0.001
AKI on CKD				4.90	2.17, 11.1	<0.001
c index (%)		75			76	
p value from Schönfeld test		0.2			0.2	

AKI = acute kidney injury; CCI = Charlson comorbidity index; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio.
[a] Occurring in patients with normal preoperative renal function.

reduction in the time frame between 3 and 15 mo of surgery (Fig. 2). The *c* index after LOOCV was 73%. The DCA demonstrated the net clinical benefit originating from applying this model with probabilities >4% (Fig. 3).

3.4. *Sensitivity analyses*

Supplementary Table 2 depicts the characteristics of individuals excluded due to incomplete information compared with the characteristics of the study population. No significant statistical difference was observed between medians or among frequencies across the two groups.

Since AKI status after RAPN was the only postoperative covariate included in the model, we ran our model again excluding such variable, to evaluate a purely preoperative model. Supplementary Table 3 displays the details of the Cox regression analysis. The predicted probability of significant eGFR reduction between 3 and 15 mo after RAPN was evaluated against the probability derived from model 2 using the DCA (Fig. 3). The DCA showed that both models confer clinical benefits with probabilities >4%. However, it also demonstrated that the model including postoperative AKI performs better than the purely clinical one.

4. Discussion

CKD was first recognized in the 19th century, while the acute cessation of renal function (eg, AKI) was recognized during World War II in patients with crash injuries [10]. Classically, CKD and AKI have been considered as separate entities, but they are largely interconnected. In fact, each one represents a risk factor for the other [10,20].

Concerning the long-term implications of AKI and CKD, it has been demonstrated that the increasing RIFLE grade of AKI and the KDIGO stage of CKD are associated with morbidity and mortality increase [10,17,20,21]. Thus, identification of patients who are at a high risk of developing renal function deterioration remains important.

In our study, we sought to develop a model for the early identification of patients who are at a high risk of developing significant eGFR reduction from their baseline GFR category after PN. We specifically investigated the role of patients, tumor, and immediate postsurgical functional outcome (in terms of AKI) on significant eGFR reduction between 3 and 15 mo after RAPN. We first evaluated the effect of the occurrence of AKI after RAPN alone. Then, we have investigated separately the role of the occurrence of AKI in patients with normal preoperative renal function and the occurrence of AKI on CKD. By doing so, we have found that the latter confers an increased risk of significant eGFR reduction (hazard ratio [HR]: 4.90) compared with the former (HR: 4.51). This stratification also helps achieve higher discriminative power of the model in terms of *c* index. Indeed, our definition of AKI corresponds to grade 1 of the RIFLE criteria. However, this demonstrates that an acute postoperative eGFR reduction (>25% from baseline) confers an increased risk for persistent renal function decline.

Since the AKI occurrence represents the only covariate fitted in the final model (model 2) that is unavailable for

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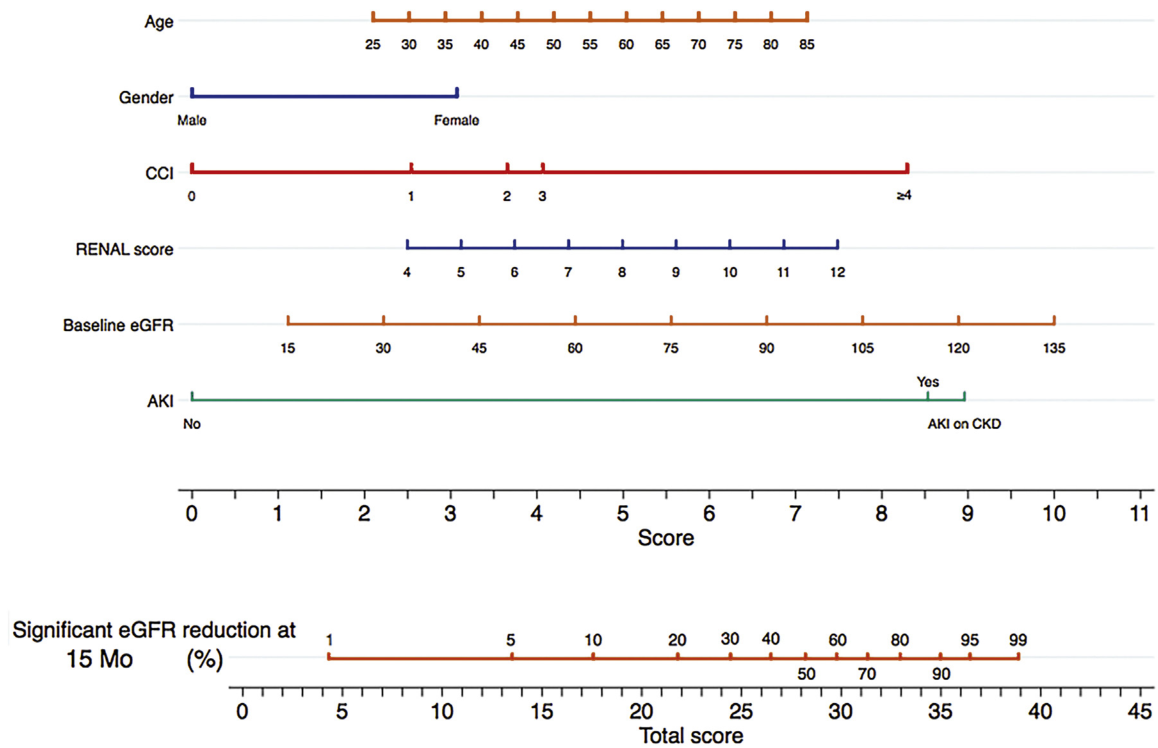

Fig. 2 – Nomogram for the prediction of significant eGFR reduction in the period of time between 3 and 15 mo after surgery, based on multivariable model 2. Instructions: locate the patient's preoperative age on the corresponding axis. Draw a line straight downward to the score axis to determine how many points toward the probability of significant eGFR reduction the patient receives for his/her preoperative age. Repeat the process for each additional variable. Add the points for each of the predictors. Locate the final sum on the total score axis. Draw a line straight up to find the patient's probability of significant eGFR reduction. AKI = acute kidney injury; CCI = Charlson comorbidity index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

preoperative counseling, we have repeated the analysis using preoperative covariates only. The HRs of this model (Supplementary Table 3) do not differ much from those of the model used for building the nomogram. Thus, the probability derived from the nomogram can be used for preoperative counseling, informing the patient that, in the case of the occurrence of AKI, the probability of renal function deterioration will increase.

Since the risk of eGFR reduction reflects reduced overall survival [22,23], a surgeon can counsel the patient

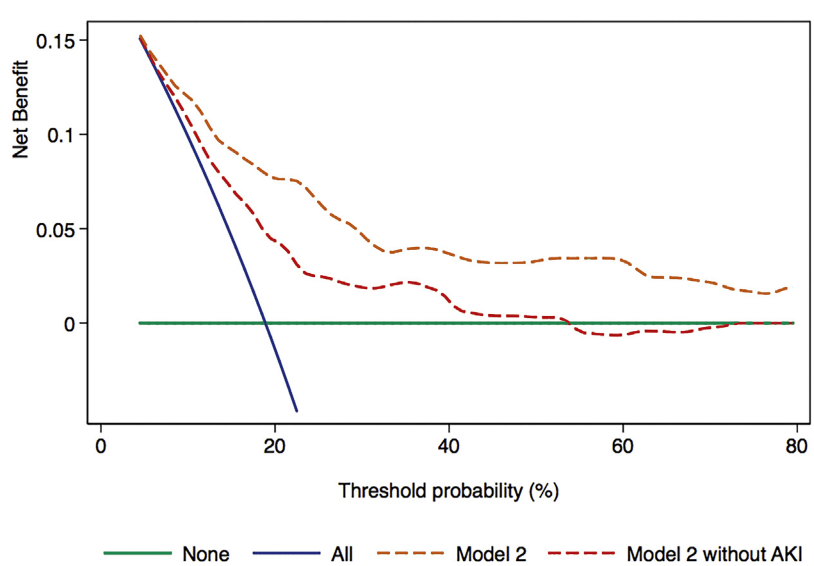

Fig. 3 – Decision curve analyses demonstrating the net benefit associated with the use of the nomogram-derived probability, based on multivariable model 2, for the prediction of significant eGFR reduction. The net benefit originating from the pure clinical model (which does not account for the occurrence of acute kidney injury) is also shown. AKI = acute kidney injury; eGFR = estimated glomerular filtration rate.

regarding this risk and discuss whether the individual might benefit from the operation or not. After surgery, given the occurrence of AKI, a multidisciplinary evaluation should promptly define the follow-up schedule, according to a patient's individual risk. Additionally, when counseling patients, one should mention that adjuvant treatment modalities that might be required after surgery (including VEGF and mTOR inhibitors) list nephrotoxicity among their side effects [24].

Regarding long-term functional outcome after PN, Guillotreau et al. [25] and Kumar et al. [26] have demonstrated that the probability of renal function deterioration is lower in the case of pre-existing CKD. Our findings are in keeping with their results. In fact, from our analysis it has emerged that the higher the preoperative CKD stage, the lesser is the likelihood of experiencing CKD upstage.

Concerning the role of excisional volume loss (EVL) during PN and functional outcome, Dagenais et al. [27] have evaluated the effect of log (EVL) on postoperative eGFR preservation, measured with the MDRD formula in a time range of 3–12 mo postoperatively.

Since the functional outcome after RAPN is a time-dependent outcome, we opted for a time-dependent statistical analysis, namely the semiparametric Cox regression, over the linear regression that Dagenais et al. [27] used. Moreover, since our aim was to provide a model for both preoperative counseling and postoperative evaluation, we did not consider this variable.

To the best of our knowledge, this is the first nomogram for the prediction of eGFR reduction in patients undergoing RAPN. One strong point of our study is the large sample size. Another strong point includes the number of events. Our model demonstrated excellent calibration and improved risk prediction with threshold probabilities of >4%. Moreover, as the DCA demonstrates, a purely preoperative model could be used for patient counseling. Such a model confers a net clinical benefit with probabilities <54%, whereas after this threshold, the analysis does not detect any clinical net benefit. Conversely, relying on the probability obtained from the postoperative model including AKI confers a greater clinical benefit as our DCA shows (Fig. 3). These findings confirm the important role that postoperative AKI plays in predicting eGFR reduction in the relatively short term after RAPN. The postoperative acute decline in renal function has generally been considered as a "self-limiting" condition, but our results provide a different perspective in this regard. Finally, the occurrence of postoperative AKI deserves further attention from the scientific community.

However, the present study is not devoid of limitations. As a multi-institutional study, the procedures were performed by multiple surgeons; however, all surgeons are expert within the field and this does not represent a limitation *sensu stricto*.

Concerning the definition of AKI [17], we have to acknowledge that data on postoperative urine output are lacking in our database and we could potentially have lost some events in terms of postoperative AKI. We are lacking information on the therapy compliance for hypertension and/or whether hypertensive control is optimal or not.

Additionally, we do have to acknowledge that our postoperative covariate, AKI after PN, is a time-dependent outcome and it could be fitted as a time-varying covariate. However, since AKI was evaluated at discharge, there was minimal heterogeneity in terms of when the AKI was evaluated. Indeed, 99% of patients were discharged by postoperative day 5. Thus, we chose to consider it as a categorical covariate, since the time to AKI was extraordinarily low in all patients.

Finally, our model requires external validation and should be validated in open and laparoscopic cohorts as well.

5. Conclusions

We have developed a model that accurately predicts eGFR reduction in the time frame between 3 and 15 mo after surgery in patients undergoing RAPN. Such a model takes into account the occurrence of AKI in patients with CKD and in patients with normal preoperative renal function, where the first confers a higher risk of significant eGFR reduction.

This model may serve as a tool for the identification of patients at high risk for renal function decline after RAPN. It can guide both preoperative counseling and scheduling a tighter follow-up in those who present with a high risk of significant eGFR reduction.

Author contributions: Ketan K. Badani 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: Martini, Badani.
Acquisition of data: Abaza, Eun, Bhandari, Hemal, Porter, Badani.
Analysis and interpretation of data: Martini, Cumarasamy, Badani.
Drafting of the manuscript: Martini, Cumarasamy, Beksac.
Critical revision of the manuscript for important intellectual content: Martini, Cumarasamy, Badani.
Statistical analysis: Martini.
Obtaining funding: None.
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Supervision: Badani.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.08.037.

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