UROLOGIC
ONCOLOGY

Clinical-Kidney cancer

Predicting acute kidney injury after robot-assisted partial nephrectomy: Implications for patient selection and postoperative management

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Abstract

Background: Acute Kidney Injury (AKI) is a common occurrence after partial nephrectomy and is a significant risk factor for chronic kidney disease. We aimed to create a model that predicts postoperative AKI in patients undergoing robot-assisted partial nephrectomy (RAPN).

Methods: We identified 1,190 patients who underwent RAPN between 2008 and 2017 from a multicenter database. AKI was defined as a >25% reduction in eGFR from pre-RAPN to discharge. A nomogram was built based on a binary logistic regression that ultimately included age, sex, BMI, diabetes, baseline eGFR, and RENAL Nephrometry score. Internal validation was performed using the leave-one-out cross validation. Calibration was graphically investigated. The decision curve analysis was used to evaluate the net clinical benefit; a classification tree was used to identify risk categories. The same model was fit adding ischemia time during RAPN.

Results: Median (IQR) age at surgery was 61 (50, 68) years; 505 (42%) patients were female, while 685 (58%) were male. Median (IQR) ischemia time during RAPN was 14 (10, 18) min. postoperative AKI occurred in 274 (23%) patients. All variables fitted in the model emerged as predictors of AKI (all $P \leq 0.005$) and all were considered to build a nomogram. After internal validation, the area under the curve was 73%. The model demonstrated excellent calibration and improved clinical risk prediction at the decision curve analysis. In the low, intermediate, and high-risk groups the postoperative AKI rates were: 10%, 30%, and 48%, respectively. Adding ischemia time to the preoperative model fit the data better (likelihood ratio test: $P < 0.001$) and yielded an incremental area under the curve of 3% (95% confidence interval: 1, 5%)

Conclusion: We developed a nomogram that accurately predicts AKI in patients undergoing RAPN. This model might serve (1) in the preoperative setting: for counsel patients according to their preoperative AKI risk (2) in the immediate postoperative: for identifying patients who would benefit from an early multidisciplinary evaluation, when considering also ischemia time. © 2019 Elsevier Inc. All rights reserved.

Keywords: Acute kidney injury; Partial nephrectomy; Functional outcome; Kidney cancer

1. Introduction

Renal cell carcinoma represents the seventh most common malignancy worldwide, with approximately 65,000 new diagnosed cases in the United States alone [1,2]. Over time, stage migration toward more localized disease has occurred and the rate of conservative approaches, namely nephron sparing surgery (NSS), has increased [3,4]. The majority of contemporary NSS are performed robotically with the open approach utilized on a case by case basis due to various anatomic complexities [2].

Of pivotal importance during PN is the preservation of renal function in both the short and long term. In fact, it has

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been demonstrated that, regardless of the cause, AKI can predispose patients to CKD [5]. Moreover, postsurgical eGFR can affect survival, specifically in patients with pre-existing CKD [6−8]. Thus, the evaluation of renal function within the first days of surgery is crucial [9].

The current stratification of AKI follows the Risk/Injury/Failure/Loss/Endstage (RIFLE) criteria and increasing RIFLE grade of AKI is associated with an increase in morbidity and mortality [10,11].

Few studies have evaluated the predictors of AKI after PN [12−14], In particular, our group has recently investigated the role of the occurrence of AKI after RAPN and demonstrated that the occurrence of AKI after surgery increases the risk of eGFR reduction within 15 months of it [15]. Thus, the aim of this study was to develop a nomogram for the prediction of postoperative AKI in patients undergoing RAPN in order to (1) identify patients at high risk of AKI and discuss other treatment modalities as an alternative to surgery, (2) plan an early multidisciplinary evaluation.

2. Materials and methods

2.1. Study population

Data from 1,190 patients from a multi-institutional Research Electronic Data Capture (REDCap) database were identified. All patients had undergone RAPN between 2008 and 2017 for suspected renal cell carcinoma at 5 tertiary referral centers. No patient had undergone neoadjuvant therapy. All procedures were performed by senior surgeons.

2.2. Variables and outcome definition

Patient's eGFR were calculated according to the CKD-EPI formula [16]. The complexity of RAPN was defined according to the R.E.N.A.L. nephrometry score [17].

According to the RIFLE criteria, the outcome of the present study was represented by the occurrence of AKI, defined as >25% reduction in patient's eGFR from baseline, obtained preoperatively, to discharge. We did not stratify AKI according to AKI grade as only 14 patients experienced >Grade 1 AKI [11].

For the outcome's prediction, we considered preoperative and intraoperative variables including age at RAPN (fitted as a continuous variable), patient's sex (male vs. female), patient's BMI (continuous), hypertension (no vs. yes), diabetes (no vs. yes), preoperative baseline patient's eGFR (continuous), R.E.N.A.L. nephrometry score (continuous), and ischemia time during RAPN (continuous).

2.3. Statistical analysis

First, descriptive statistics were generated, frequencies, and proportions were reported for categorical variables with medians and interquartile ranges (IQR) reported for continuous variables. Differences between medians and frequencies were estimated with the Kruskal-Wallis test and the χ^2 test, respectively.

Second, uni- and multivariable binary logistic regression analyses were performed for the outcome of interest. A nomogram was then built based on the coefficients of the logit function from the most parsimonious model and with the highest number of significant covariates.

The receiver operator curve was graphed to compute the area under the curve (AUC) for the full model. Observed vs. predicted values were plotted to evaluate for calibration by using the locally weighted scatter plot smoothing method.

Third, internal validation was performed using the leave-one-out cross-validation (LOOCV). The linear prediction of the logistic function, adjusted after internal validation, was used to compute the AUC of the model, to graphically assess calibration and to perform the decision curve analysis.

Fourth, in order to provide surgeons with a tool for the discrimination of patients with a high likelihood of developing postoperative AKI, we run a classification tree, considering the nomogram-derived probability after LOOCV as the independent variable, for predicting AKI, the dependent variable.

Finally, since the ischemia time during RAPN is the only covariate unavailable before surgery, the exact same model that was used to build the nomogram was fitted again including ischemia time as a covariate. Given its nature, this second model is nested within the first one. The likelihood ratio test was adopted to evaluate the goodness of fit of the models. The incremental AUC and its associated 95% confidence interval (CI) was computed to evaluate the added value of ischemia time to a pure preoperative predictive model.

Statistical analyses were performed using Stata 14 (StataCorp MP, College Station, TX, USA). All tests were 2-sided with a significance level set at $P < 0.05$.

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 (50, 68) years; 505 (42%) patients were female, while 685 (58%) were male, 681 (57%) patients presented hypertension at surgery. Median (IQR) ischemia time during RAPN was 14 (10, 18) min. Median time to discharge was 1 day (IQR 1−2 Days, range 1−47 Days) with 94.0% discharged by post-operative day 3.

Overall, postoperative AKI occurred in 274 (23%) patients.

Sex, BMI, presence of diabetes, baseline eGFR, tumor size, R.E.N.A.L. nephrometry score and ischemia time during RAPN differed significantly between the group in

Table 1
Descriptive characteristics of 1,190 patients that underwent robot assisted partial nephrectomy

Variable	Overall, $n = 1,190$	No postoperative AKI, $n = 916$ (77%)	Postoperative AKI, $n = 274$ (23%)	*P* value
Age, y	61 (50, 68)	61 (50, 68)	60 (51, 68)	0.9
Sex, *n*				
Female	505 (42)	407 (44)	98 (36)	0.01
Male	685 (58)	509 (56)	176 (64)	
BMI, kg/m^2	29.5 (25.9, 34.6)	29.0 (25.7, 34.0)	31.3 (26.6, 36.4)	<0.001
Hypertension, *n*				
No	509 (43)	403 (44)	106 (39)	0.1
Yes	681 (57)	513 (56)	168 (61)	
Diabetes, *n*				
No	916 (77)	729 (80)	187 (68)	<0.001
Yes	274 (23)	187 (20)	87 (32)	
Baseline eGFR, ml/min	83 (68, 99)	80 (66, 96)	91 (75, 106)	<0.001
Tumor size, cm	3 (2, 4)	3 (2, 4)	3 (2, 5)	<0.001
RENAL score	7 (6, 8)	7 (5, 8)	8 (6, 9)	<0.001
Ischemia time, min	14 (10, 18)	14 (10, 17)	15 (12, 22)	<0.001

AKI = acute kidney injury.

Medians (interquartile range) or frequencies (proportions) are displayed for continuous and categorical variables, respectively.

which AKI occurred postoperatively and the group in which did not (all $P \leq 0.01$). The median age and the frequency of hypertension were not significantly different between the two groups ($P = 0.9$ and 0.1, respectively).

3.2. Uni- and multivariable analysis predicting postoperative AKI

On univariable analyses, sex, BMI, presence of diabetes, baseline eGFR, tumor size, and RENAL nephrometry score emerged as predictors for the outcome of interest (all $P < 0.001$), while age and hypertension did not ($P = 0.8$ and 0.1, respectively) (Table 2). In order to build a preoperative model, all the covariates, including age, and hypertension since clinically relevant, were fitted in the multivariable logistic regression model.

On multivariable analysis, age, sex, BMI, presence of diabetes, baseline eGFR, tumor size, and R.E.N.A.L. nephrometry score were identified as predictors for the outcome of interest, while hypertension did not emerge as a significant predictor (odds ratio: 0.96; 95% CI: 0.69,1.34, $P = 0.8$). Thus, the model was fitted after the exclusion of hypertension and all covariates emerged as significant predictors of AKI (all $P \leq 0.005$) (Table 2).

All predictors were considered for the development of a nomogram (Fig. 1) and the coefficients of the logit function from the multivariable model are displayed in supplementary table 1. The AUC of the nomogram was 74% (95% CI 71, 78%). After performing internal validation, the AUC was 73% (95% CI 70, 76%). The calibration plot, exploring the relationship between observed and predicted values, before and after LOOCV, is depicted in Fig. 2.

Table 2
Uni- and multivariable binary logistic regression analysis predicting postoperative acute kidney injury using preoperative variables

| Covariate	Univariable analyses			Multivariable analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.00	0.99,1.01	0.8	1.02	1.01,1.04	0.001	1.02	1.01,1.04	0.001
Sex									
Female	1	Ref.		1	Ref.		1	Ref.	
Male	1.44	1.09,1.90	0.01	1.66	1.22,2.27	0.001	1.66	1.22,2.25	0.001
BMI	1.04	1.02,1.06	<0.001	1.05	1.03,1.08	<0.001	1.05	1.03,1.08	<0.001
Hypertension									
No	1	Ref.		1	Ref.				
Yes	1.25	0.94,1.64	0.1	0.96	0.69,1.34	0.8			
Diabetes									
No	1	Ref.		1	Ref.		1	Ref.	
Yes	1.81	1.34,2.45	<0.001	1.65	1.16,2.34	0.005	1.63	1.16,2.31	0.005
Baseline eGFR	1.02	1.01,1.02	<0.001	1.03	1.02,1.03	<0.001	1.03	1.02,1.03	<0.001
RENAL score	1.27	1.18,1.37	<0.001	1.28	1.18,1.39	<0.001	1.28	1.18,1.38	<0.001
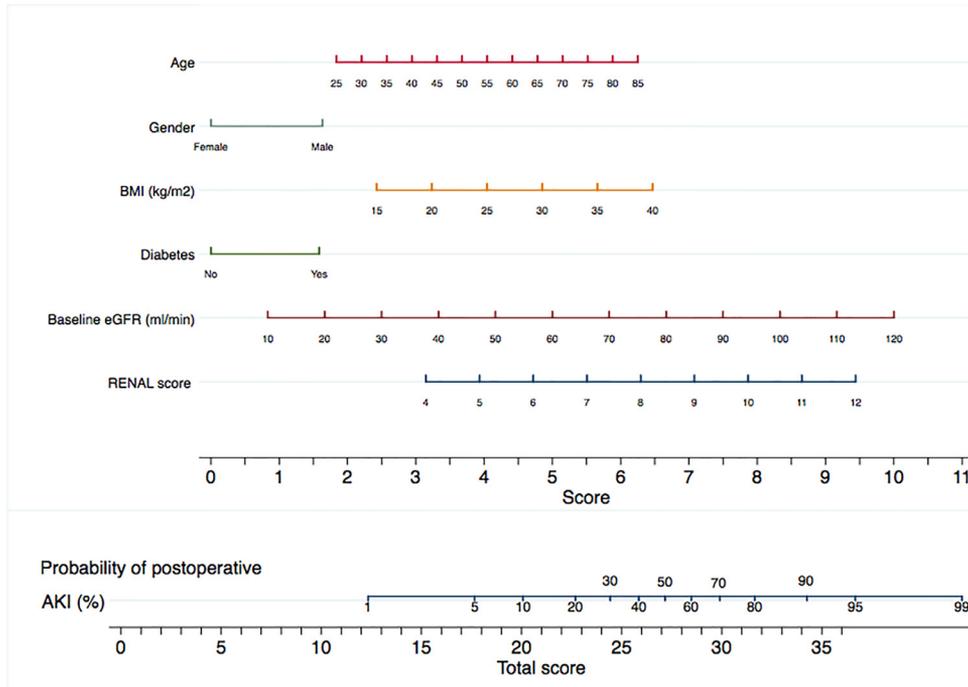
Fig. 1. Nomogram for the prediction of postoperative acute kidney injury (AKI) after robot assisted partial nephrectomy. Instructions: Locate the patient's preoperative age on the corresponding axis. Draw a line straight downward to the score axis to determine how many points toward the probability of AKI the patient receives for his preoperative age. Repeat the process for each additional variable. Sum 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 developing postoperative AKI.

The benefit derived from applying the model in clinical practice, according to the decision curve method, is depicted in Fig. 3. The nomogram-derived probability of AKI demonstrated improved clinical risk prediction with threshold probabilities of AKI >5%. The classification tree identified three risk categories concerning the risk of AKI. We named those categories as low- intermediate- and high-risk for the development of postoperative AKI. Across the three categories the risk for developing AKI was 10% 30% and 48%, respectively, Fig. 4.

3.3. The added value of ischemia time when predicting AKI

On univariable analysis, ischemia time during RAPN emerged as a significant predictor of postoperative AKI (odds ratio: 1.06; 95% CI: 1.05,1.08; $P < 0.001$). This variable was added to the pure preoperative model for predicting postoperative AKI. Table 3 displays the multivariable logistic regression including ischemia time as a covariate. This model achieved an AUC of 76% (95% CI 72, 79%). The incorporation of ischemia time during RAPN into the
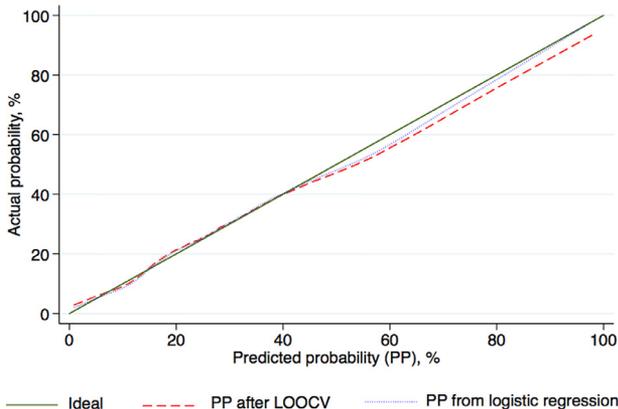

Fig. 2. Calibration plot of observed (actual) vs. predicted probability of acute kidney injury of the nomogram.
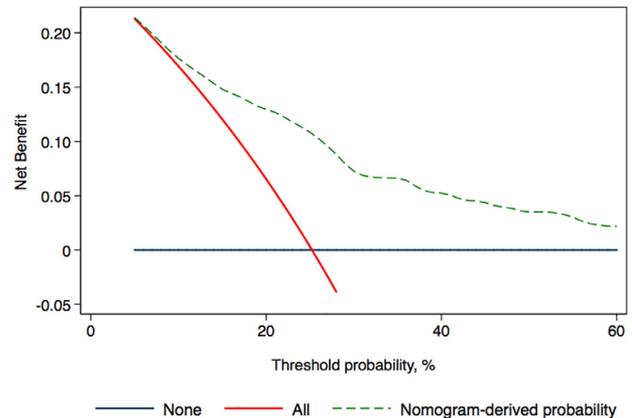

Fig. 3. Decision curve analyses demonstrating the net benefit associated with the use of the nomogram-derived probability for the prediction of postoperative acute kidney injury.
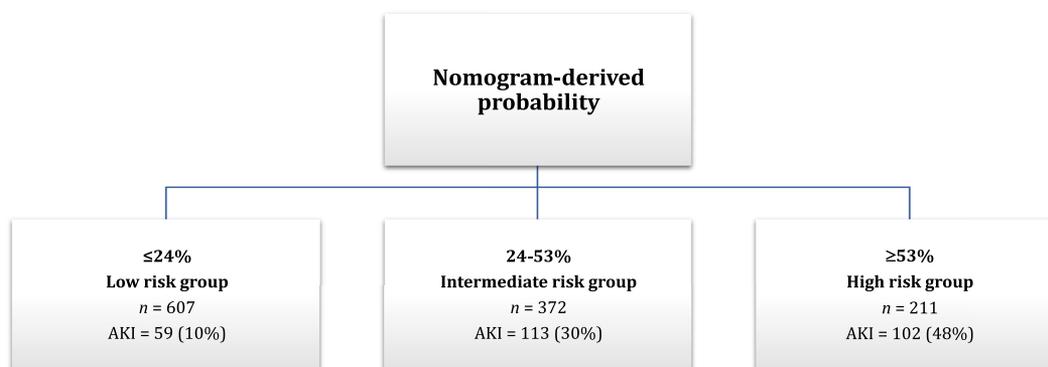
Fig. 4. Classification tree depicting the risk group categories for the occurrence of postoperative acute kidney injury (AKI).

pure preoperative model fit the data better with a likelihood ratio test *P* value < 0.001 and yielded better discrimination in predicting AKI with an incremental AUC of 3% (95% CI: 1, 5%).

4. Discussion

In more recent years, the utilization of NSS has been increasing with PN now regarded as the treatment of choice for small renal masses [2], since radical nephrectomy is associated with unnecessary renal parenchyma loss and ultimately a greater risk for CKD, compared to PN without oncologic compromise [3,12−14]. A worse postoperative renal function is also associated with worse overall survival, irrespective of oncological outcome [18,19]. Moreover, today, different treatments that could be appropriate after surgery, including medications interfering with the pathways of the vascular endothelial growth factor and the mammalian target of rapamycin, list nephrotoxicity among their side effects [20].

The occurrence of postoperative AKI represents a critical outcome. Unfortunately, in the surgical setting this has

generally be regarded as a self-limiting condition and sometimes as a collateral effect of surgery. However, more attention should be given to the occurrence of AKI. In fact, it has been shown that it is associated with major adverse cardiovascular events [4,21], higher risk of new-onset CKD [15,17] and increased healthcare cost [22]. In the latter scenario, our group has recently demonstrated that the occurrence of AKI (both in patients with normal preoperative renal function and in the context of CKD) confers a higher risk of eGFR reduction between 3 and 15 months after surgery. We purposely chose this endpoint in an effort to account for the postoperative recovery process that might occur in the very first 3 months of RAPN [15].

Thus, given the implications of AKI on long-term outcomes, we sought to develop a model for the prediction of AKI after RAPN. We specifically investigated the role of patient, tumor, and surgery-related characteristics in relation to the occurrence of postoperative AKI.

First, we built a pure preoperative model based on patient's and tumor's characteristics. This might serve in the preoperative setting: for counseling patients according to their preoperative AKI risk. In this context other options such as the appropriateness of active surveillance of the renal mass might be discussed. We have then investigated the added role of ischemia time to a pure preoperative model. When considering also ischemia time during RAPN for AKI prediction, the model achieved a better discrimination in terms of AUC. Thus, when considering this variable our model might also serve in the immediate postoperative setting for identifying patients who would benefit from an early multidisciplinary evaluation.

We do acknowledge that the ischemia time represents the only factor that is generally regarded as a modifiable one, however a long ischemia time might be required even in experienced hands. Recent evidences suggest that the use of lactate Ringer's solutions help in the prevention of AKI in comorbid patients with respect to saline solution [23]. Potentially, by adopting our model in clinical practice, novel studies aimed at evaluating the role of different postoperative management strategies and/or potential novel drugs could be implemented.

Table 3
Multivariable binary logistic regression analysis predicting postoperative acute kidney injury including ischemia time during robot-assisted partial nephrectomy

Covariate	Multivariable analysis		
	OR	95% CI	*P* value
Age	1.02	1.01,1.04	0.001
Sex			
Female	1		
Male	1.62	1.18,2.21	0.003
BMI	1.05	1.03,1.08	<0.001
Diabetes			
No	1		
Yes	1.61	1.13,2.29	0.008
Baseline eGFR	1.03	1.02,1.03	<0.001
RENAL score	1.22	1.12,1.32	<0.001
Ischemia time	1.05	1.03,1.07	<0.001

Despite hypertension has been shown to be a risk factor for postoperative AKI [14], in our population, where almost 60% of the patients were affected at surgery, it did not emerge as a significant predictor for the outcome of interest neither on uni- nor on multivariable analysis. This might be attributed to the high rate of hypertension in our cohort that actually represents a contemporary one and/or to the tight blood pressure control through medication. In this context one could speculate that the effect of hypertension, whether well controlled is minimal on postoperative AKI in patients undergoing RAPN.

In our cohort, 23% of the patients experienced AKI, classified as grade 1 of the RIFLE criteria. Over time, the incidence of postoperative AKI in patients undergoing PN has been increasing; [4] while previous studies reported ad incidence rate of 1.8% [4,12], a more recent study by Rayan et al. found that up to 39% of patients experience some degree of postoperative renal dysfunction, in their cohort [14]. Yet, changes in the definition of AKI and/or adopting different AKI classifications may be responsible for this occurrence [4].

In previous studies aimed to assess the ling-term functional outcomes, Guillotreau et al. and Kumar et al. have demonstrated that the likelihood of renal function deterioration after PN is lower in the case of pre-existing CKD [24,25]. Our findings are in line with the results of those authors. In fact, from our analysis it has emerged that the lower the preoperative renal function, the lesser is the likelihood of developing postoperative AKI. It is noteworthy that a functional contralateral kidney can provide functional compensation, especially in the early postoperative period [26]. The status of the contralateral kidney complicates the extrapolation of conclusions regarding renal function loss. However, this is a limitation that is common to each study evaluating a real-word scenario and it is hard to be accounted for.

To the best of our knowledge, this is the first nomogram for the prediction of postoperative AKI in patients undergoing RAPN. The strong points of our study are the large sample size and the number of events, in terms of AKI. Our model demonstrated excellent calibration and improved risk prediction against threshold probabilities of AKI >5%. Yet, the present study is not devoid of limitations, being a multi-institutional study the procedures were performed by different surgeons; however, all surgeons were expert within the field. Concerning renorraphy, all surgeons adopted the same method, that is, double layer suturing with eventual modifications in accordance to the specific case. Additionally, we acknowledge that the functional outcome after PN represents a time-dependent outcome. However, since AKI was evaluated at discharge, there was minimal heterogeneity in terms of when the outcome was evaluated. Indeed, 99% of patients were discharged by postoperative day 5. Thus, we chose to adopt the logistic regression methodology, specifically the binary logistic regression since the time to event was extraordinarily low

in all patients. Finally, our model requires to undergo external validation and to be validated in open and laparoscopic cohorts as well.

5. Conclusions

The prediction of AKI in patients undergoing RAPN is of pivotal importance because this occurrence can bear implications for the development of CKD and overall survival. We developed a nomogram that accurately predicts AKI in patients undergoing RAPN and defined 3 risk categories for preoperative patient stratification. Our model may serve as a tool during patient counseling, whereas, when considering ischemia time, it can aid in the early identification of patients who would potentially benefit from an early multidisciplinary consultation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2019.04.018.

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