Estimating the risk of chronic kidney disease after nephrectomy

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NGO TC, HURLEY MP, THONG AE, JEON SH, LEPPERT JT, CHUNG BI. Estimating the risk of chronic kidney disease after nephrectomy. *Can J Urol* 2013;20(6):7035-7041.

Introduction: *To identify factors associated with the development of chronic kidney disease (CKD) after nephrectomy and to create a clinical model to predict CKD after nephrectomy for kidney cancer for clinical use.*
Materials and methods: *We identified 144 patients who had normal renal function (eGFR > 60) prior to undergoing nephrectomy for kidney cancer. Selected cases occurred between 2007 and 2010 and had at least 30 days follow up. Sixty-six percent (n = 95) underwent radical nephrectomy and 62.5% (n = 90) developed CKD (stage 3 or higher) postoperatively. We used univariable analysis to screen for predictors of CKD and multivariable logistic regression to identify independent predictors of CKD and their corresponding odds ratios. Interaction terms were introduced to test for effect modification. To protect against over-fitting, we used 10-fold cross-validation technique to evaluate model performance in multiple training and testing datasets. Validation against an independent external cohort was also performed.*
Results: *Of the variables associated with CKD in univariable analysis, the only independent predictors in multivariable logistic regression were patient age (OR = 1.27 per 5 years, 95% CI: 1.07-1.51), preoperative glomerular filtration rate (GFR), (OR = 0.70 per 10 mL/min, 95% CI: 0.56-0.89), and receipt of radical nephrectomy (OR = 4.78, 95% CI: 2.08-10.99). There were no significant interaction terms. The resulting model had an area under the curve (AUC) of 0.798. A 10-fold cross-validation slightly attenuated the AUC to 0.774 and external validation yielded an AUC of 0.930, confirming excellent model discrimination.*
Conclusions: *Patient age, preoperative GFR, and receipt of a radical nephrectomy independently predicted the development of CKD in patients undergoing nephrectomy for kidney cancer in a validated predictive model.*

Key Words: renal cell carcinoma, nephrectomy, chronic kidney disease, glomerular filtration rate

Introduction

Although radical nephrectomy (RN) was the historic gold standard treatment for patients with localized kidney cancer, treating small renal masses with partial nephrectomy (PN) has become the standard of care with oncologic outcomes comparable to RN.[1–4] PN has also gained favor as it may decrease the likelihood of developing chronic kidney disease (CKD) after extirpative surgery[5–7] and this advantage has become important in light of recent evidence linking CKD with an increased risk of death, cardiovascular events, and hospitalizations.[8,9] As the risk of developing CKD has been reported to be as high as 65% after RN and between 10%-25% after PN,[10,11] the American Urological Association (AUA) guidelines for the treatment of small renal masses recommend PN, and other nephron-sparing approaches, when feasible.[12] Although increased utilization of PN may mitigate the risk of surgically induced CKD, the rising incidence of kidney cancer, and incidental small renal masses in particular, argues for a greater understanding of the factors associated with the development of CKD after any nephrectomy.

Accepted for publication August 2013

Acknowledgement
JTL is supported by Award Number DK089086 from the National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIDDK or the NIH.

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Prior studies have demonstrated that patient age, preoperative renal function, and surgical approach (RN versus PN) were independent risk factors for CKD in patients undergoing nephrectomy.[11,12] Furthermore, diabetes mellitus and hypertension have been shown to also increase the risk of new onset CKD in certain cohorts.[13] However, these studies are limited by the possibility of selection bias through inclusion of patients who spanned several decades with pre-existing kidney disease. An additional limitation is that these studies have been externally validated.

Our hypothesis was that clinical factors may help predict the development of significant CKD after kidney cancer surgery. We present data a multivariable model that predicts the risk of developing stage 3 or greater CKD after nephrectomy from a contemporary cohort of patients with normal to near-normal baseline renal function.

Materials and methods

Patient selection

An Institutional Review Board approved, prospectively maintained database of all patients treated with both partial and radical nephrectomy was queried for all patients who underwent RN or PN since the start of data collection in 2007. An independent series of patients at the Veteran's Administration Palo Alto Health Care System who underwent RN or PN by a single surgeon was used as a validation dataset. There was no crossover of patients or surgeons between our database and this validation dataset.

Patient characteristics

Chart review was conducted to ascertain patient characteristics including age, sex, race/ethnicity, smoking history as defined as having ever smoked cigarettes, hypertension history as having a diagnosis of hypertension at the time of surgery, diabetes history as defined as having a diagnosis of diabetes at the time of surgery. Tumor size was ascertained by the maximum dimension on pathologic analysis. Surgical access (laparoscopic or open), approach (PN or RN), ischemia time was extracted from the operative reports.

Outcome measures

CKD was defined according to the National Kidney Foundation classification: stage 1 = GFR > 90, stage 2a = GFR 75-89, stage 2b = GFR 60-74, stage 3a GFR 45-59, stage 3b = GFR 30-44, stage 4 = GFR 15-29, stage 5 = GFR < 15. To estimate the risk of developing de novo stage 3 or greater CKD after nephrectomy, this analysis was restricted to patients with normal preoperative renal function which we defined as an eGFR ≥ 60 mL/min/1.73 m^2 by the abbreviated MDRD equation,[14] therefore excluding those with preoperative stage 3 or greater CKD. Postoperative eGFR was based on the last measured serum creatinine available in the electronic medical record. Patient records with less than 30 days of follow up were excluded to eliminate confounding by those whose renal function had not yet reached a post-nephrectomy steady state.

Statistical analysis

Patient age (years), preoperative eGFR (mL/min/1.73 m^2), ischemia time (minutes) among partial nephrectomies, and pathologic tumor size (cm) were modeled as continuous variables. Tumor size was log-transformed to meet normality assumptions. All continuous variables were linear to the log odds and therefore met the linearity assumption of logistic regression. Categorical predictors were surgical approach (RN or PN), surgical access (robotic, laparoscopic, or open), race (White, Black, Asian, or other), sex (male or female), and the presence of hypertension (no or yes) and diabetes (no or yes). The outcome variable was postoperative CKD (yes or no), which we defined as having a postoperative eGFR < 60 (stage 3 CKD or higher). Univariable analysis was performed to test for predictors of postoperative CKD.[11] For continuous variables, Student's t-test or a nonparametric equivalent was used to compare the distribution of values between those who did and did not develop postoperative CKD. For categorical variables, the chi-square test was performed. Because there were no missing values for the parameters modeled, we performed a complete case analysis. Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, NC, USA). All tests of significance were two-sided and a $p \leq 0.05$ was considered significant.

Logistic regression

Univariable analysis was performed to identify potential predictors of CKD. Those with significant p values were then used in unconditional logistic regression. The outcome was the development of CKD, i.e., postoperative eGFR < 60. Multivariable models were fitted using backward parameter selection to eliminate nonsignificant predictors from the final model. Interaction terms between the continuous variables and each categorical variable were used to test for effect modification, but none were significant. We assessed model fit using the likelihood ratio chi-square test and model performance using the concordance statistic and the area under the curve.

TABLE 1. **Patient demographics**

	Model		Validation		p value
Total patients	144		52		
Mean age, yr (SD)	57.2	(13.2)	61.7	(8.2)	0.02
Gender, n (%)					< 0.0001
Male	90	(62.5%)	49	(94.2%)	
Female	54	(37.5%)	3	(5.8%)	
Race, n (%)					0.03
White	96	(66.7%)	38	(73.1%)	
Asian	22	(15.3%)	1	(1.9%)	
Black	5	(3.5%)	4	(7.7%)	
Other	21	(14.5%)	9	(17.3%)	
Comorbidities, n (%)					
Hypertension	82	(56.9%)	30	(57.7%)	0.91
Diabetes mellitus	21	(14.6%)	16	(30.8%)	0.01
Tumor size, cm (SD)	5.8	(4.6)	5.0	(3.2)	0.21
Surgical approach, n (%)					0.0003
Radical nephrectomy	95	(66.0%)	22	(42.3%)	
Partial nephrectomy	49	(44.0%)	30	(57.7%)	
Ischemia time among PN, min (SD)	32	(11)	12	(14)	< 0.0001
Surgical approach, n (%)					0.001
Laparoscopic	94	(65.3%)	13	(25.0%)	
Open	46	(31.9%)	22	(42.3%)	
Robot assisted	4	(2.8%)	17	(32.7%)	
Mean preop eGFR, mL/min/1.73 m^2 (SD)	85	(18)	88	(16)	0.25
Mean postop eGFR, mL/min/1.73 m^2 (SD)	56	(18)	68	(20)	< 0.0001
Preoperative CKD stage					0.63
Stage 1 (eGFR ≥ 90)	43	(29.9%)	18	(34.6%)	
Stage 2a (eGFR 75-89)	63	(43.8%)	23	(44.2%)	
Stage 2b (eGFR 60-89)	38	(26.3%)	11	(21.2%)	
Postoperative CKD stage					< 0.0001
Stage 1 (eGFR ≥ 90)	5	(3.5%)	8	(15.4%)	
Stage 2a (eGFR 75-89)	16	(11.1%)	9	(17.3%)	
Stage 2b (eGFR 60-74)	33	(22.9%)	15	(28.8%)	
Stage 3a (eGFR 45-59)	55	(38.2%)	11	(21.2%)	
Stage 3b (eGFR 30-44)	26	(18.1%)	9	(17.3%)	
Stage 4 (eGFR 15-29)	5	(3.5%)	0	(0%)	
Stage 5 (eGFR < 15)	4	(2.7%)	0	(0%)	
Mean follow up, days (SD)	399	(311)	615	(408)	0.003
Patients with new CKD (stage ≥ 3), n (%)	90	(62.5%)	20	(38.5%)	0.0003

Internal validation

We internally validated the model using a 10-fold bootstrap cross-validation technique. The data were partitioned into 10 subsets; each subset was sequentially withheld and used to test the performance of a model built from the remaining 9 subsets. The area under the curve of the resultant model was used to determine model fit.

External validation

Next, we tested the performance of our model in an independent cohort of patients treated at the Veteran's Affairs Palo Alto Health Care System, identified using the same inclusion and exclusion criteria. Of the 63 cases from this series of patients, 52 were eligible for inclusion.

Results

Our primary analytic cohort included 144 out of 218 patients who met the inclusion criteria for this study. In the same period, 52 out of 63 patients meeting the same criteria were identified for our external validation cohort. The baseline characteristics of these cohorts are listed in Table 1. In the primary cohort, the mean age was 57.2 (SD 13.2) years. The ratio of men to women was approximately 2 to 1. Whites accounted for two-thirds of the cohort. Of note, there were a significant number of Asians (15.3%) which reflects the demographics of the communities surrounding the treating institution. The prevalence of hypertension and diabetes in our cohort were 56.9% and 14.6%, respectively. The mean preoperative and postoperative eGFR were 85 (SD 18) and 56 (SD 18) mL/min/1.73 m^2, respectively. The mean follow up was a little 399 days. Almost two-thirds of patients developed postoperative CKD (stage 3 or higher) while only 2.7% developed end stage renal disease.

The external validation cohort differed significantly from the cohort used to derive our predictive model. The patients in the validation dataset from the Veteran's Administration were older, more likely to be male, and more likely to be White, Table 1. Additionally, the patients in the validation cohort were more likely to have diabetes and more likely to undergo partial nephrectomy.

We performed univariable analysis to screen for variables associated with postoperative CKD. The variables tested and the corresponding p values are listed in Table 2, which showed significant differences between patients who developed CKD and those who did not in terms of age, preoperative GFR, surgical approach, sex, race, tumor size, and a history of hypertension. Nonsignificant variables were method of surgical access (laparoscopic versus open), warm ischemia time, and a history of diabetes.

Odds of developing postoperative CKD (stage 3 or higher) were then modeled as a function of the potentially significant predictors identified in the univariable analysis. In this first model, tumor size and hypertension were not statistically significant and were dropped; there was a trend toward significance for race, so it was retained. In the next model, sex and race lost significance and were dropped, leaving the final three parameters: age, preoperative GFR, and surgical approach. Parameters of this model along with the associated odds ratios are listed in Table 3. The AUC for this model was 0.798 (95% CI: 0.723-0.873).

Validation of the final model internally using a 10-fold cross-validation method yielded an AUC of 0.774 (95% CI: 0.695-0.853). This suggests good model fit and argues against overfitting. External validation of the final model yielded an AUC of 0.93 (95% CI: 0.86-0.99). The ROC curves for these validation analyses are plotted in Figures 1 and 2.

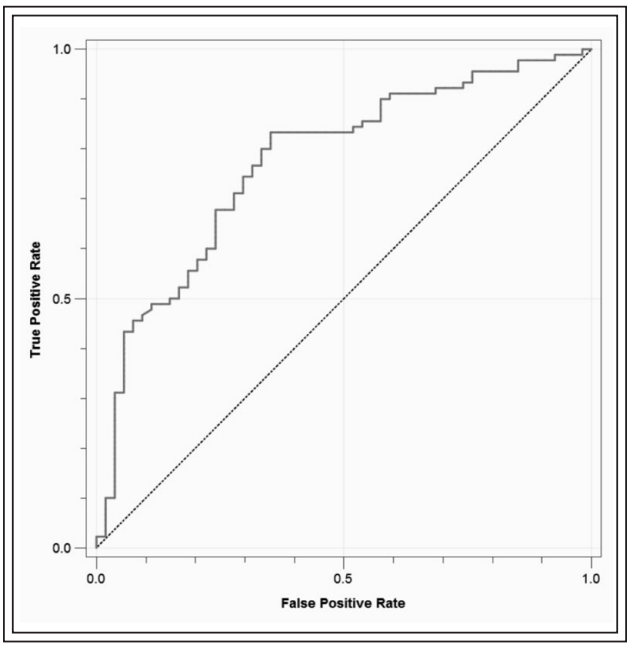

Figure 1. Performance of predictive model with internal validation.

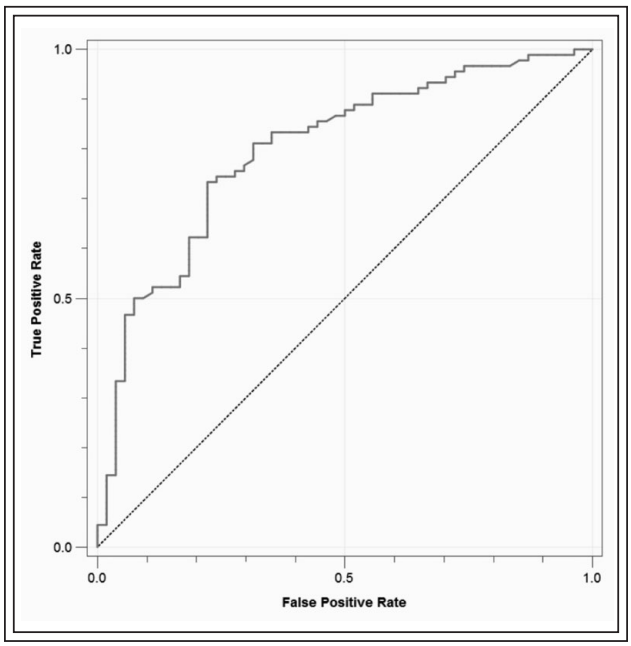

Figure 2. Performance of predictive model with external validation.

TABLE 2. **Univariable predictors of chronic kidney disease following nephrectomy**

Predictor	p value
Age	< 0.0001
Preoperative GFR	< 0.0001
Surgical approach (partial versus radical)	0.0005
Race	0.004
Hypertension	0.02
Sex	0.04
Tumor size	0.04
Access (laparoscopic versus open)	NS
Ischemia time (among partials)	NS
Diabetes mellitus	NS

TABLE 3. **Final multivariable model for risk of chronic kidney disease following nephrectomy**

Parameter	OR (95% CI)*	p value
Patient age	1.27 (1.07-1.51)	0.006
Preoperative eGFR	0.70 (0.56-0.89)	0.003
Radical nephrectomy	4.78 (2.08-10.99)	0.0002

*the OR for patient age and preoperative GFR are expressed in units of 5 years and 10 mL/min/1.73 m2, respectively. The probability of developing CKD in this model can be expressed in terms of the logistic function: $P = 1/1+\exp(-\beta)$ where β = (intercept + 0.483*age – 0.035*preoperative eGFR + 1.56*radical nephrectomy) and radical nephrectomy = 1 if the patient underwent RN and 0 if the patient underwent PN

Discussion

Estimating the risk of developing CKD following kidney cancer surgery is integral to the selection of patients for nephron-sparing surgery. PN has been shown to have oncologic equivalence with RN in the surgical treatment of small renal masses,[2] and its utilization is increasing. The risk of new onset postoperative CKD, defined as a glomerular filtration rate of < 60mL/min/1.73m^2, has driven urologists to further expand the use of PN. Thompson and associates have reported on PN of masses > 4 cm as a viable alternative to RN, when technically feasible, in an attempt to minimize the risk of CKD. In examining both overall and cancer specific survival between radical nephrectomy and partial nephrectomy for pT1b RCC, they found that there was no significant difference in overall survival.[15] However, the prevalence of CKD was significantly higher in the radical nephrectomy cohort and the presence of CKD was found to be significantly associated with both poorer overall and cancer specific survival. In a separate report on elective partial nephrectomy for T1b RCC, the authors found that the PN cohort had improved overall survival and that postoperative renal function again was a significant predictor of overall survival.[15] The strongest evidence to support partial nephrectomy comes from a population based study of 7138 patients under going surgery for clinical T1a renal cell carcinoma that showed improved overall survival. On the other hand, a recently published EORTC study comparing PN and RN did not show a significant difference in survival, although the study was terminated early for poor accrual.[16,17] Because of these seemingly contradictory results and the practical difficulty of accruing patients for randomized trials comparing RN and PN, studies comparing the sequelae of these surgical approaches may indirectly address this question.

CKD can affect health in previously unanticipated ways that extend beyond an increased risk of dialysis dependence, with deleterious effects on cardiovascular function and additional associated morbidity and mortality.[8,9] Weight and associates reported that, in a large single institutional cohort, postoperative eGFR was an independent predictor of overall survival and that decreasing postoperative eGFR was predictive for decreased overall survival and decreased cardiac specific survival.[18] In a large longitudinal cohort study of individuals with all stages of CKD, Smith et al estimated that individuals with CKD use 1.9 to 2.5 times more prescriptions, have 1.3 to 1.9 more outpatient visits, and are 1.6 to 2.2 more likely to be hospitalized compared to the general population.[19] In a study strictly focused on patients with SRMs, Huang et al confirmed that consequences of CKD are significant higher among patients managed with radical nephrectomy compared to partial nephrectomy.[20] The development of medical comorbidities is also associated with a decline in overall quality of life as individuals with CKD consistently report a lack of energy and an overall decreased sense of physical health.[21] More recently, some authors have suggested that surgically induced CKD from nephrectomy differs from medically induced CKD. They state that surgical CKD represents a single acute episode in which there is nephron loss, after which the patient goes back to his or her baseline state of health, whereas medical CKD results from a chronic medical conditions that persist indefinitely.[22] Although the history of

diabetes and hypertension did not independently predict the development of CKD in this study, our cohort was preselected to have normal to near-normal renal function preoperatively and, therefore, was less likely to suffer from or be at risk for medical CKD. Because our median follow up was approximately 1 year, it is too early to tell whether surgical CKD in our cohort led to an increased risk of hospitalizations, cardiovascular events, or death. However, this question merits further study once our data matures.

Previous authors have created models to predict for CKD following kidney cancer surgery and these studies have consistently shown that radical nephrectomy significantly predicted CKD in the follow up period.[6,10,12] In our study, we found that patient age, preoperative eGFR, and surgical approach were independent predictors of CKD after nephrectomy. Although race and sex were predictors in univariable analysis, they became non-significant in the multivariable models. This suggests that they do not independently predict the risk for developing CKD after correction for the other factors and were therefore not included in the final model. Currently, there is little evidence in the literature that addresses if patients with HTN and DM who undergo RN have a higher risk of CKD than those undergoing PN, although intuitively, it seems that a history of diabetes or hypertension would lead to a greater risk of CKD in the postoperative period. However, we did not observe this effect in these data. This may be due to several factors. First, we did not have available to us information on the severity, duration, and how well these medical comorbidities were controlled. A subset of these patients with severe or poorly controlled diabetes or hypertension may have had worse outcomes. Also, because we prescreened the study cohort to include only those with normal to near-normal renal function prior to surgery, many of the patients with poorly controlled diabetes or hypertension may have been selected out. Another possibility is that these factors are not independent predictors of CKD after controlling for the other clinical factors. From our results, we cannot conclude whether a history of diabetes or hypertension predisposes to worse outcomes in terms of renal function because the data available do not take into account severity or duration of these factors. It may, however, be prudent to attempt nephron-sparing approaches in these patients in the absence of compelling evidence to do otherwise.

Our study is unique in that, to our knowledge, this is the first study to attempt to quantitatively model the risk of postoperative CKD using preoperative characteristics in a contemporary cohort. Some have used multivariable logistic regression to identify factors associated with CKD, but did not quantify of the magnitude of the effect while others failed to validate their models, either internally with bootstrap cross-validation or externally with independent datasets.[12,13] While another group has developed a nomogram to predict the development of CKD after nephrectomy, they defined their outcomes in terms of creatinine, not in terms of eGFR,[23] which the National Kidney Foundation guidelines currently state is a more accurate measure of renal function.[24]

Another unique aspect of our study is that both internal and external validation was carried out and our model performed well in both analyses. The performance of our model in a cohort of Veterans treated in the VA health care system, suggests the generalizability of the model to groups with different baseline demographics and comorbidity. Because predictive regression models are at risk for over-fitting, a phenomenon in which associations between predictors and outcomes can be explained by inherent biases in a local cohort of patients rather than a true biological relationship, models must be validated before they can be used in cohorts that may have different baseline characteristics. Multiple groups have used bootstrap methods as an internal validation for a variety of clinical settings,[24–26] but bootstrap methods rely on the same data sets to both derive and test models, and can be limited in their ability to predict in a cohort that is different demographically. Other groups have used external cohorts to validate their predictive models,[27,28] but no study yet has used both internal and external validation cohorts.

This study has important limitations. The risk model we developed is based on a retrospective analysis from a single academic institution. This can potentially limit the generalizability of our results. However, that being said, the model performed robustly in an internal cross-validation as well as an external validation against an independent cohort. Also, the relatively small sample size of our study cohort created a more parsimonious model selection. However, the three predictors that we have identified agree with the findings of other groups and have been repeatedly cited as strong risk factors for CKD after nephrectomy. Furthermore, our model exhibited impressive discrimination (AUC = 0.798) though identifying other strong independent predictors to further refine this model is likely needed in the future, such as further exploration into emerging evidence regarding proteinuria and metabolic derangements in serum levels of calcium, phosphate, and bicarbonate leading to a higher risk of progression of CKD.[29] Finally, although the model we present in this study is simple, easy to use, and robust, it requires further external validation on larger cohorts for corroboration of its clinical utility.

Conclusions

Patient age, preoperative eGFR, and surgical approach, but not medical comorbidities, accurately predict the development of de novo CKD (stage 3 or greater) after nephrectomy. Further prospective studies and validation are needed to corroborate these findings in larger patient cohorts and to incorporate these results into preoperative counseling for patients undergoing kidney cancer surgery. □

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