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Original Article

External validation of the nomograms for predicting renal function at 1 year after partial nephrectomy with only preoperative factors

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Abstract: Nephron-sparing surgery has been widely used as treatment for small renal tumors if technically feasible. Compared with radical nephrectomy, partial nephrectomy confers less development of chronic kidney disease. Nevertheless, partial nephrectomy causes certain renal damage. Predictive tools of functional outcomes after partial nephrectomy are quickly developing. In our retrospective study, we assessed the accuracy and generalizability of two reported nomograms for predicting renal function at one year after partial nephrectomy with only preoperative factors. Our cohort consisted of a total of 107 patients. We calculated the preoperative and 1-year postoperative estimated glomerular filtration rate by modification of diet in renal disease and chronic kidney disease epidemiology collaboration formulas in patients undergoing partial nephrectomy. We applied the nomograms to each patient to the, calculated the adjusted coefficient of determination and analyzed the accuracy of the models, and the sensitivity and specificity to estimate postoperative chronic kidney disease. With modification of diet in renal disease and chronic kidney disease epidemiology collaboration formulas, the adjusted coefficients of determination were 0.75 and 0.62. The accuracies were 90.7% and 87.4%, the sensitivities to estimate postoperative chronic kidney disease were 50.0% and 30.8%, and the specificities were 95.0% and 97.6%, respectively. This external validation study showed that the nomograms for predicting renal function at one year after partial nephrectomy with only preoperative factors were applicable to a Taiwanese population. The nomograms have high accuracy and seem helpful in counseling and decision making before partial nephrectomy.

Keywords: Functional outcome, kidney tumor, nephron-sparing surgery, nomogram, partial nephrectomy

Introduction

In 1867, the first partial nephrectomy (PN) was performed by accident during an operation for liver cysts [1]. After a century, nephron-sparing surgery has become widely accepted as the standard treatment for small renal tumors if technically feasible even in stage III renal cell carcinoma (RCC). Compared with radical nephrectomy, PN confers less renal function loss, resulting in less development of chronic kidney disease (CKD), less cardiovascular events and improved overall survival rates [2]. Nevertheless, PN causes certain renal damage. In a literature review, PN was associated with approximately 10% of global renal function decline [3]. Newly acquired CKD was reported to develop in approximately a third of patients undergoing PN [4].

Development of CKD after PN can be attributable to multiple factors. Modifiable surgical factors are considerable and have been reported in many studies. Shortening ischemia time and minimizing excessive nephron loss leads to better long-term renal function [5]. PN by open, laparoscopic or robot-assisted methods may be associated with impaired postoperative renal function [6].

Unmodifiable demographic and tumor factors may play important roles. Nephrological diseases such as diabetes mellitus (DM), high blood pressure, obesity, and metabolic syndrome

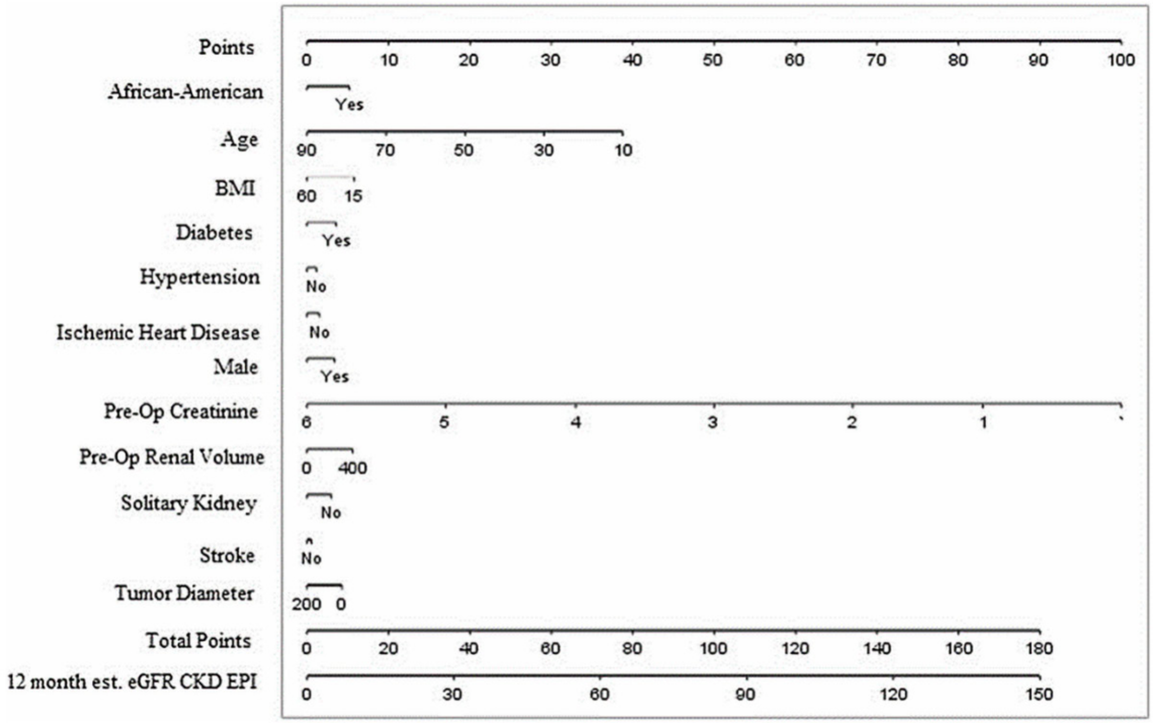

Figure 1. Nomogram for predicting renal function by CKD-EPI formula at 1 year: Row 1 refers to the point assignment for each preoperative covariate. Rows 2 to 13 represent the preoperative covariates included in the model. To use the nomogram, vertical lines are drawn from appropriate values in the preoperative covariates to row 1. Summation of assigned points for all preoperative covariates gives "Total Points", which is represented by row 14. Another vertical line from the final value of "Total Points" will indicate $eGFR_n$ by CKD-EPI formula at 1 year, as represented by row 15.

contribute to the development of CKD [5]. Lane et al. [7] analyzed 1169 patients undergoing PN, and found that increased age, gender, lower preoperative glomerular filtration rate (GFR), having a solitary kidney and tumor size significantly predicted lower postoperative GFR. Muramaki et al. [8] reported age, DM and preoperative estimated glomerular filtration rate (eGFR) as significant predictors of the postoperative development of CKD. In a review by Lorenzo et al. [9], preoperative quality of the parenchyma affects postoperative renal function, especially in the RCC population. When it comes to the risk of postoperative CKD, the patients' characteristics, parenchymal status and tumor nature must be taken into consideration.

Along with the understanding of postoperative renal function changes, predictive tools of functional outcomes have been developed. Shum et al. [10] recently designed two useful nomograms with internal validation, only using preoperative covariates for multivariate linear regression models, to predict eGFR one year after PN in mostly Caucasian and African-American population. The applicability of these nomograms in other ethnicities should be confirmed. We assessed the accuracy and generalizability of the nomograms in a Taiwanese population.

Materials and methods

This retrospective study consisted of a total of 107 patients undergoing PN for renal tumors regardless of tumor histology in the Mackay Memorial Hospital, Taiwan, between March 1994 and August 2017.

We excluded cases with: bilateral renal surgery, less than 1 year of postoperative follow-up, missing clinical variables, or no preoperative computed tomography (CT)/magnetic resonance imaging (MRI). All patients had complete information on the parameters in the nomograms including age, gender, body mass index (BMI), chronic medical disease, side and diameter of the tumor, preoperative and 1-year postoperative serum creatinine levels, ipsilateral

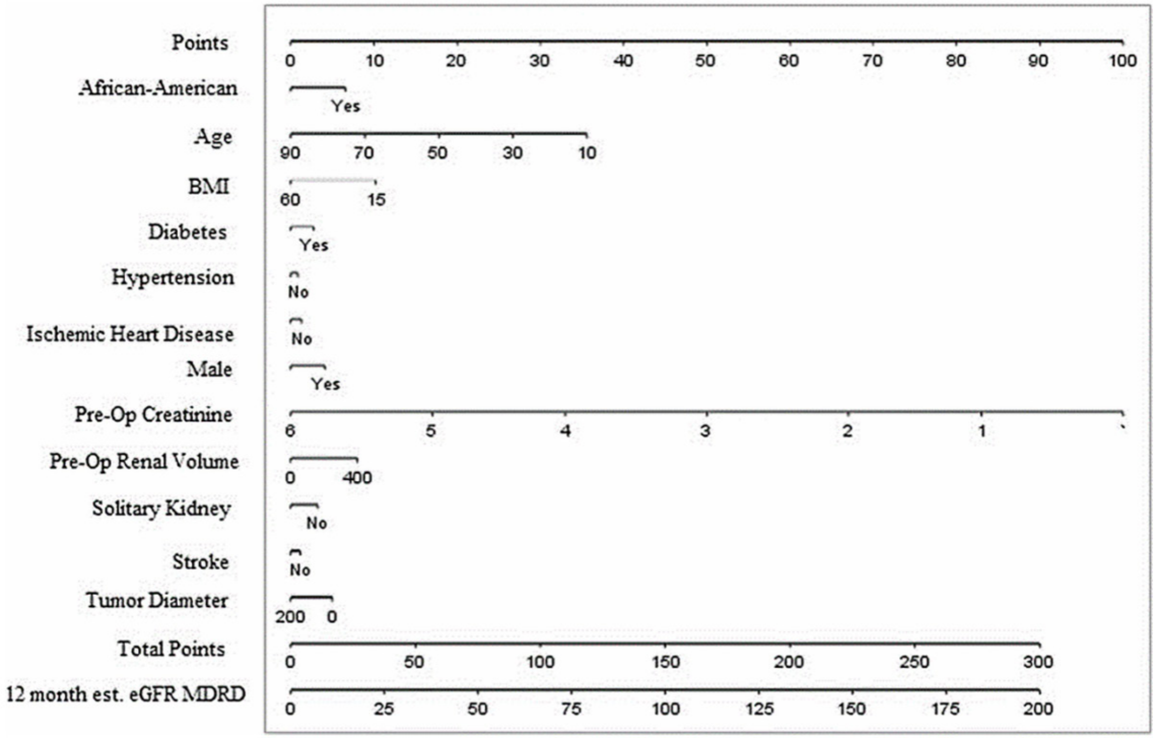

Figure 2. Nomogram for predicting renal function by MDRD formula at 1 year: Row 1 refers to the point assignment for each preoperative covariate. Rows 2 to 13 represent the preoperative covariates included in the model. To use the nomogram, vertical lines are drawn from appropriate values in the preoperative covariates to row 1. Summation of assigned points for all preoperative covariates gives "Total Points", which is represented by row 14. Another vertical line from the final value of "Total Points" will indicate $eGFR_n$ by MDRD formula at 1 year, as represented by row 15.

kidney volume, nephrometry score and solitary kidney status. Warm ischemia time and operation method were recorded. The measurement of ipsilateral kidney volume was based on CT/MRI using the ellipsoid formula *length*1 × *length*2 × *length*3 × π/6 [11]. We calculated the preoperative and 1-year postoperative eGFR by modification of diet in renal disease (MDRD) [12] and chronic kidney disease epidemiology collaboration (CKD-EPI) [13] formulas ($eGFR_{preop}$ and $eGFR_{postop}$). $eGFR_n$ was obtained by summing up the values of each variable in the nomograms (**Figures 1** and **2**). CKD was defined as eGFR less than 60 mL/min/1.73 m^2, that is, CKD stage 3 by the K/DOQI definition [14].

To externally validate these established nomograms, the obtained parameters of our patients were substituted into the nomograms. The main results, adjusted coefficient of determination, R^2, between $eGFR_{postop}$ and $eGFR_n$ were corrected by bootstrapping and performed with IBM SPSS Statistics Software version 25.0 (IBM Corp., Armonk, NY, USA). The accuracy was established on the proportion of $eGFR_n$ within ± 30% of $eGFR_{postop}$. We analyzed if the models were suitable for estimating postoperative CKD by the sensitivity and the specificity. The institutional review board approved this study (number: 19MMHIS007e).

Results

Fifty-four patients were included in our analysis. The patient characteristics are listed in **Table 1**. All patients were Taiwanese of Chinese Han origin. Mean (range) age was 55.2 (33-77) years. Twenty-one (38.9%) patients were female. Of the 54 patients, 21 (38.9%) had hypertension, 12 (22.2%) had DM, 3 had ischemic heart disease (5.6%) and 2 (3.7%) had previous stroke. All tumors were smaller than 7 cm in diameter, and the mean size (SD) was 3.8 (1.6) cm. Mean nephrometry score was 7.2. Mean ipsilateral kidney volume was 160.4 mL. Mean (SD) preoperative and 1-year postoperative serum creatinine levels were 0.93 (0.27) and 1.02 (0.32) mg/dl. Mean (SD) warm ischemia time was 24.2 (9.6) minutes.

Table 1. Patient characteristics

Patients, n	54
Age, mean, year (range)	55.2 (33-77)
Female gender, n (%)	21 (38.9)
BMI, mean, kg/m^2 ± SD	26.0 ± 4.4
Hypertension, n (%)	21 (38.9)
DM, n (%)	12 (22.2)
Ischemic heart disease, n (%)	3 (5.6)
Previous stroke, n (%)	2 (3.7)
Left-sided tumor, n (%)	26 (48.1)
Tumor diameter, mean, cm ± SD	3.8 ± 1.6
Nephrometry score, mean ± SD	7.2 ± 1.6
Solitary kidney status, n (%)	2 (3.7)
Preoperative volume of ipsilateral kidney, mean, mL ± SD	160.4 ± 43.2
Preoperative creatinine level, mean, mg/dL ± SD	0.93 ± 0.27
Postoperative creatinine level, mean, mg/dL ± SD	1.02 ± 0.32
Warm ischemia time, mean, minute ± SD	24.2 ± 9.6
Surgical method, n (%)	
Open	39 (72.2)
Laparoscopic	6 (11.1)
Robotic	9 (16.7)

BMI = body mass index; SD = standard deviation; DM = diabetes mellitus.

Table 2. Renal function by CKD-EPI formula

	Preoperative	Nomogram	1-year postoperative
eGFR, mean, mL/min/1.73 m^2, ± SD	85.9 ± 21.4	78.3 ± 15.5	79.1 ± 23.0
CKD staging, n (%)			
Stage 1	24 (44.4)	14 (25.9)	18 (33.3)
Stage 2	21 (38.9)	31 (57.4)	22 (40.7)
Stage 3	9 (16.7)	9 (16.7)	13 (24.1)
Stage 4	0 (0)	0 (0)	1 (1.9)
Stage 5	0 (0)	0 (0)	0 (0)
Decline in eGFR, mean, mL/min/1.73 m^2 ± SD			6.7 ± 8.5
Decline in eGFR, mean, %			8.4 ± 10.1
Decline in eGFR >10%, n (%)			26 (48.1)

CKD-EPI = chronic kidney disease epidemiology collaboration; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; CKD stage 1 = > = 90 mL/min/1.73 m^2; CKD stage 2 = 60 to <90 mL/min/1.73 m^2; CKD stage 3 = 30 to <60 mL/min/1.73 m^2; CKD stage 4 = 15 to <30 mL/min/1.73 m^2; CKD stage 5 = <15 mL/min/1.73 m^2; SD = standard deviation.

Twenty-six of 54 (48.1%) patients had a decrease in eGFR >10% at postoperative 1 year. Five out of 54 (9.3%) patients developed new-onset CKD (**Tables 2** and **3**). In all patients with postoperative CKD, only 7 in the CKD-EPI nomogram and 4 in the MDRD nomogram were accurately estimated to have postoperative CKD preoperatively. The sensitivities to estimate postoperative CKD from the CKD-EPI and MDRD nomograms were 50.0% and 30.8%, respectively. In contrast, the specificities were up to 95.0% and 97.6%. The accuracy of nomograms was 90.7% and 87.4%. The adjusted R^2 between $eGFR_{postop}$ and $eGFR_n$ were 0.75 and 0.62 (**Figures 3** and **4**).

Discussion

As PN has become the standard treatment for small renal masses, [15] more and more studies analyzing the factors influencing the functional outcomes are attempting to predict the

Table 3. Renal function by MDRD formula

	Preoperative	Nomogram	1-year postoperative
eGFR, mean, mL/min/1.73 m^2, ± SD	87.5 ± 25.2	79.1 ± 14.6	79.0 ± 24.2
CKD staging, n (%)			
Stage 1	24 (44.4)	14 (25.9)	18 (33.3)
Stage 2	22 (40.7)	35 (64.8)	23 (42.6)
Stage 3	8 (14.8)	5 (9.3)	12 (22.2)
Stage 4	0 (0)	0 (0)	1 (1.9)
Stage 5	0 (0)	0 (0)	0 (0)
Decline in eGFR, mean, mL/min/1.73 m^2 ± SD			8.4 ± 13.3
Decline in eGFR, mean, %			9.3
Decline in eGFR >10%, n (%)			26 (48.1)

MDRD = modification of diet in renal disease; eGFR = estimated glomerular filtration rate; CKD stage 1 = > = 90 mL/min/1.73 m^2; CKD stage 2 = 60 to <90 mL/min/1.73 m^2; CKD stage 3 = 30 to <60 mL/min/1.73 m^2; CKD stage 4 = 15 to <30 mL/min/1.73 m^2; CKD stage 5 = <15 mL/min/1.73 m^2; SD = standard deviation.

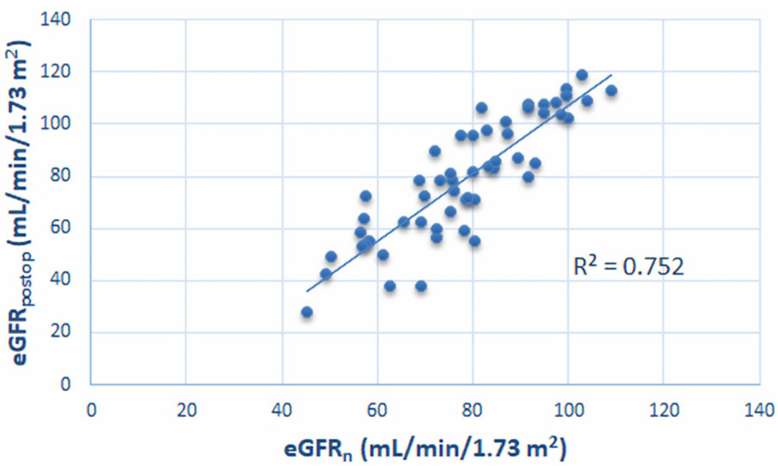

Figure 3. The scatter plot and coefficient of determination between eGFR$_{postop}$ and eGFR$_n$ by CKD-EPI nomogram.

postoperative renal function and the risk of CKD has been reported.

The majority of published models for prediction of post-PN functional outcomes require not only preoperative but also intraoperative or postoperative factors. Percentage of kidney volume change was involved as a variable in a nomogram in 2006 to predict the 7-year probability of renal insufficiency in patients undergoing radical or PN [16]. Alberto et al. [17] created a nomogram to effectively predict ≥25% reduction of eGFR between 3 and 15 months after robot-assisted PN. Postoperative acute kidney injury was included as a significant predictor. Thus, these tools cannot be utilized before the operation. Peritumoral Artery Scoring System [18] can predict function outcome after laparoscopic PN preoperatively. However, it requires a three-dimensional volume rendering on CT arteriography; that possibly decreases its usability.

The nomograms to estimate GFRs at one year after PN designed by Shum et al. have the advantage of only using preoperative covariates. It helps the physicians and the patients make comprehensive discussions and have proper expectation during decision making. Although bootstrap-corrected internal validations in their study provide reliable positive results, external validation is essential.

In this study, we performed external validation of the nomograms in an Asian population. The nomograms were constructed based on 486 patients from an American institutional database consisting of mostly Caucasian and African-American men; in contrast, our study included Taiwanese patients only. Race is a parameter in the MDRD and the CKD-EPI formulas, and is widely known for its influence on the prevalence and the progression rate of CKD [19], also a significant demographic predictor in the nomograms. Despite ethnic differences, these predictive models seem to be applicable to our patients.

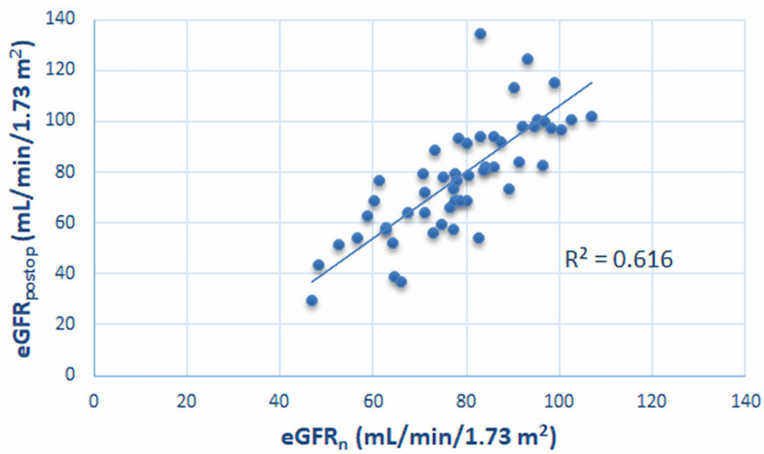

Figure 4. The scatter plot and coefficient of determination between eGFR$_{postop}$ and eGFR$_n$ by MDRD nomogram.

The coefficients of determination, R^2, used to measure how much of the proportion of eGFR$_{postop}$ was replicated and explained by the models, were 0.62 and 0.75, slightly higher than the 0.61 and 0.70 in the internal validations, calculated by the MDRD and the CKD-EPI formulas, respectively. These values display practical and trustworthy models for the clinicians to estimate about two-thirds of variances of postoperative functional outcomes, depending only on the available preoperative parameters.

More than 90 percent of eGFR$_n$ were within ± 30% of eGFR$_{postop}$, demonstrating the great accuracy of the nomograms. Both nomograms have excellent specificities to identify postoperative CKD. That is, if eGFR$_n$ was less than 60 mL/min/1.73 m^2, the physician should be aware of the possibility of postoperative renal function impairment. On the other hand, eGFR$_n$ was prone to be overestimated in the patients with poor renal function. We therefore cannot assure patients that they can be free from CKD even if they have high eGFR$_n$ due to the low sensitivity to identify CKD patients.

The main limitation of our study is the small size and the simple nature of our cohort. Further research involving larger and more variable populations are necessary to represent the whole Asian population. Second, the internal and external validations were built on the coefficient of determination between eGFR$_{postop}$ and eGFR$_n$. However, eGFR$_{postop}$ does not equal the actual postoperative renal function. Validating the nomograms by GFR measured by standard methods such as the clearance of exogenous filtration markers as ^{125}I-iothalamate or ^{99m}Tc-DTPA to increase accuracy may be considered [20]. We found it difficult to draw many lines and add the values of the nomogram. As mentioned in Shum's article, a web-based version of these nomograms is needed.

Conclusions

This external validation study showed that the nomograms for predicting renal function at one year after partial nephrectomy with only preoperative factors were applicable to a Taiwanese population. The nomograms have high accuracy and seem helpful in counseling and decision making before partial nephrectomy.

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Disclosure of conflict of interest

None.

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