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Clinical predictors of the estimated glomerular filtration rate 1 year after radical nephrectomy in Japanese patients

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Purpose: To evaluate renal function 1 year after radical nephrectomy (RN) for renal cell carcinoma, the preoperative predictors of postnephrectomy renal function were investigated by sex, and equations to predict the estimated glomerular filtration rate (eGFR) 1 year after RN were developed.

Materials and Methods: A total of 525 patients who underwent RN between May 2007 and August 2011 at Tohoku University Hospital and its affiliated hospitals were prospectively evaluated. Overall, 422 patients were analyzed in this study.

Results: Independent preoperative factors associated with postnephrectomy renal function were different in males and females. Preoperative eGFR, age, tumor size, and body mass index (BMI) were independent factors in males, while tumor size and BMI were not independent factors in females. The equations developed to predict eGFR 1 year after RN were: Predicted eGFR in males (mL/min/1.73 m^2)=27.99-(0.196×age)+(0.497×eGFR)+(0.744×tumor size)-(0.339×BMI); and predicted eGFR in females=44.57-(0.275×age)+(0.298×eGFR). The equations were validated in the validation dataset (R^2=0.63, p<0.0001 and R^2=0.31, p<0.0001, respectively).

Conclusions: The developed equations by sex enable better prediction of eGFR 1 year after RN. The equations will be useful for preoperative patient counseling and selection of the type of surgical procedure in elective partial or RN cases.

Keywords: Glomerular filtration rate; Nephrectomy; Renal cell carcinoma; Renal insufficiency

INTRODUCTION

Strong associations have been reported between chronic kidney disease (CKD) and outcomes such as the development of ischemic cardiovascular disease and heart failure, as well as all-cause mortality. Many patients are at risk for CKD immediately after radical nephrectomy (RN) for the treatment of renal cell carcinoma (RCC), and the prevalence of CKD increases steadily thereafter [1,2]. Although RN has long been the standard treatment for renal cell tumors, partial nephrectomy (PN) is now the appropriate treatment option based on its provision of equivalent cancer control

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and better preservation of long-term renal function [2-6]. There has been a drastic trend toward minimally invasive surgery, such as laparoscopic and robotic PNs. However, PN including a minimally invasive approach is associated with significant complications [7,8]. A recent prospective randomized study comparing the oncologic outcomes of elective PN and RN for low-stage RCC showed equally excellent oncologic outcomes, but in the intent-to treat population, PN was significantly less effective than RN in terms of overall survival [9]. Although PN substantially reduced the incidence of moderate renal dysfunction, the incidences of advanced kidney disease and kidney failure were nearly identical in the two treatment arms [10]. The studies suggest that a subset of patients with low-stage RCC do not benefit from PN in terms of complications, renal function, or survival. Thus, it is essential to accurately assess the likelihood of CKD after RN when choosing the optimal surgical procedure in RCC patients presenting for elective surgery.

In the present study, the predictors of postnephrectomy renal function were investigated by sex, and equations to predict the estimated glomerular filtration rate (eGFR) after RN were developed for males and females, respectively. To the best of our knowledge, no previous studies have shown a difference in the predictors of postnephrectomy renal function between males and females.

MATERIALS AND METHODS

1. Study design and patients

In 2007, we started a prospective study to investigate prognostic factors and renal functional outcome of RCC patients undergoing RN or PN. All RCC cases in Miyagi prefecture, Japan were prospectively registered in Tohoku University and affiliated hospitals. Follow-up data on renal function as well as oncological outcome were collected yearly for 5 years after surgery and a large computerized database was constructed. The study was not registered in the University Hospital Medical Information Network Clinical Trials Registry in Japan. The present study focused on 1-year renal functional outcome after RN. Between May 2007 and August 2011, 702 consecutive RCC patients undergoing RN or PN were registered, and 525 patients undergoing RN were analyzed in this study. Of them, 44 patients on hemodialysis, 16 patients with incomplete preoperative data, and 43 patients who died within 1 year or were lost to follow-up were excluded. Thus, a total of 422 patients including 40 cases undergoing cytoreductive nephrectomy were analyzed in this study. Tumor stage was determined according to the 2002 American Joint Committee on Cancer TNM classification. The patients were randomly divided into 2 separate datasets, the training dataset of 255 patients and the internal validation dataset of 167 patients. Preoperative clinical variables in this study included age, tumor size, BMI, and preoperative eGFR. Renal function was estimated based on the GFR calculation using the Modification of Diet in Renal Disease (MDRD) equation recently modified for Japanese patients by The Japanese Society of Nephrology, as: $\text{eGFR mL/min/1.73 m}^2=194\times \text{SCr}^{-1.094}\times \text{age}^{-0.287}\times 0.739$ (if female) [11].

2. Statistical analysis

The equations to predict eGFR one year after RN were derived from the training dataset by sex using a stepwise regression model. That is, the equation for male was derived from male patients consisting of the training dataset (n=180). The regression coefficients determined in the training dataset were then applied to obtain predicted eGFR in the validation dataset sample consisting of the remaining patients. That is, male equation was applied to male patients in the validation dataset (n=116). Similar analyses were done in females. Separate equations were developed for males and females, and the predicted postnephrectomy eGFR values were compared with the actual postnephrectomy eGFR values in the validation dataset sample to evaluate the performance of each prediction equation. The metrics for comparison included bias, precision, accuracy, and R-squared (R^2). Bias of the equations was expressed as the median difference between actual postnephrectomy eGFR and predicted eGFR. Precision of the equation was expressed as the interquartile range for the differences. Accuracy was expressed as the percentage of participants with predicted eGFR 15% (P_{15}) and 30% (P_{30}) greater/less than the actual postnephrectomy eGFR [11-13]. Confidence intervals (CIs) were calculated by bootstrap methods (100 bootstraps) [14].

A nonparametric test (Wilcoxon rank-sum test) was used to compare all median values between the training and validation datasets. Pearson's chi-square test was used to compare all percentages. All statistical analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC, USA), with $p<0.05$ considered significant.

All patients gave their written, informed consent to participate in the study, which was approved by the Institutional Review Board of Tohoku University Hospital (approval number: 2007-449).

RESULTS

The rate of change in eGFR before and 1 year after RN is shown in Table 1. There was a trend that eGFR reductions increased with smaller tumor size (p<0.001) and higher BMI (p=0.0145).

Table 2A compared the clinical characteristics between the training and validation datasets. There were no significant differences in age, sex, tumor size, BMI, preoperative eGFR, and clinical TNM stage distribution between the 2 groups. Table 2B compared clinical variables by sex in each data set, showing that BMI was significantly higher for males than females in both datasets.

With application of the stepwise regression model in the training dataset, age (p=0.0015) and BMI (p=0.0299) were inverse factors and preoperative eGFR (p<0.0001) and tumor

Table 1. Comparison of the eGFR change before and 1 year after radical nephrectomy in the combined dataset

Variable	eGFR before nephrectomy	eGFR after nephrectomy	Median rate of change (%)	p-value
Total	71.45 (12.2–138.0)	47.11 (3.5–112.4)	35.5	
Tumor size[a] (cm)				<0.001
≤4.8	72.9	46.2	37.5	
≥4.9	69.3	47.9	31.3	
Age (y)[a]				0.1338
≤64	76.6	50.3	34.2	
≥65	66.6	42.5	36.1	
Sex				0.3772
Male	71.2	47.0	35.7	
Female	72.1	47.3	34.0	
Body mass index[a] (kg/m^2)				0.0145
≤24	71.6	48.1	34.7	
≥25	71.2	45.3	36.2	

Values are presented as median (range) or percent.
eGFR, estimated glomerular filtration rate.
[a]:The patients were divided into 2 groups by each median value.

Table 2A. Comparison of the clinical characteristics of the training and validation datasets

Variable	Training dataset	Validation dataset	p-value
Age (y)	65 (24–84)	63 (35–84)	0.0854
Sex			0.8046
Male	180	116	
Female	75	51	
BMI (kg/m^2)	23.3 (14.4–34.8)	23.6 (16.7–42.3)	0.7546
Preop eGFR	71.18 (12.2–131.1)	71.87 (13.7–138.0)	0.786
0–29	5 (2)	5 (3)	
30–59	64 (25)	38 (23)	
60–89	152 (60)	100 (60)	
≥90	34 (13)	24 (14)	
Tumor size (cm)	4.5 (0.8–16)	5.0 (0.5–17.4)	0.3069
T classification			0.4661
1	176 (69)	113 (68)	
2	32 (13)	25 (15)	
3	41 (16)	27 (16)	
4	6 (2)	2 (1)	
N classification			0.0833
0	244 (96)	153 (91)	
1 or 2	11 (4)	14 (9)	
M classification			0.5661
0	229 (90)	147 (88)	
1	26 (10)	20 (12)	

Values are presented as median (range) or number (%) unless otherwise indicated.
BMI, body mass index; Preop eGFR, preoperative estimated glomerular filtration rate (mL/min/1.73 m^2).

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Table 2B. Comparison of the clinicopathologic variables by sex in each dataset

Variable	Training dataset	p-value	Validation dataset	p-value
Sex				
Male	180		116	
Female	75		51	
Age (y)		0.9339		0.0559
Male	65 (24–84)		61 (35–84)	
Female	67 (29–84)		67 (35–82)	
BMI (kg/m^2)		0.0464		0.0107
Male	23.9 (14.4–34.8)		23.8 (16.8–42.3)	
Female	22.9 (15.9–32.8)		22.7 (16.7–42.3)	
Preop eGFR		0.1151		0.5102
Male	70.3 (12.2–131)		72.5 (13.7–138)	
Female	73.5 (44.0–124)		71.6 (30.0–130)	
Tumor size (cm)		0.6925		0.1304
Male	4.5 (0.8–16)		4.8 (0.5–14)	
Female	4.6 (1.3–11)		5.5 (2.0–17)	

Values are presented as median (range).
BMI, body mass index; Preop eGFR, preoperative estimated glomerular filtration rate (mL/min/1.73 m^2).

Table 3. Intercepts and coefficients for the equation used to predict postnephrectomy eGFR

Training dataset	Intercept	Coefficient of continuous parameters			
		Age	eGFR	Tumor size	BMI
Equation for males	27.99	-0.196	0.497	0.744	-0.339
Equation for females	44.57	-0.275	0.298		

BMI, body mass index; eGFR, estimated glomerular filtration rate.
Equation for males: predicted eGFR=27.99-(0.196×age)+(0.497×eGFR)+(0.744×tumor size)-(0.339×BMI).
Equation for females: predicted eGFR=44.57-(0.275×age)+(0.298×eGFR).

Table 4. Performance of the predicted-eGFR equations

Validation dataset	Bias (95% CI)	Precision	Accuracy %		R^2 (95% CI)
		IQR of the difference (95% CI)	Within 15% of eGFR after RN (95% CI)	Within 30% of eGFR after RN (95% CI)	
Equation for males	4.3 (3.4–6.1)	7.2 (5.3–9.3)	63.8 (54.7–72.0)	87.9 (80.8–92.7)	0.62 (0.46–0.74)
Equation for females	8.2 (7.0–10.9)	7.7 (5.1–10.9)	43.1 (30.5–43.3)	88.2 (76.6–94.5)	0.31 (0.15–0.54)

eGFR, estimated glomerular filtration rate; CI, confidence interval; IQR, interquartile range.

size ($p<0.0001$) were positive factors that were significantly and independently associated with eGFR 1 year after RN in males. In females, age ($p<0.0008$) was an inverse factor and preoperative eGFR ($p<0.0001$) was a positive factor, while tumor size ($p=0.5003$) and BMI ($p=0.5617$) were not significant factors associated with eGFR 1 year after RN. Then, 2 new equations to predict eGFR 1 year after RN were derived: a 4-variable equation for males and a 2-variable equation for females (Table 3).

The performances of the derived equations were evaluated using the validation dataset, as listed in Table 4. For the equation for males, bias was 4.3 mL/min/1.73 m^2, and P_{15} and P_{30} were 63.8% and 87.9%, respectively. For the equation for females, bias was 8.2 mL/min/1.73 m^2, and P_{15} and P_{30} were 43.1% and 88.2%, respectively.

Compared with the equation for females, the equation for males showed significantly lower bias ($p=0.0046$), improved accuracy within 15% ($p=0.0129$), and R^2 ($p<0.0001$).

The correlations between predicted eGFR using each equation and actual eGFR 1 year after RN were evaluated in the combined dataset, as shown in Fig. 1. The equation for males showed better performance than that for females.

DISCUSSION

More accurate assessment of the likelihood of CKD after RN is essential when choosing the optimal surgical procedure in RCC patients presenting for elective surgery. The present study showed that decreased preoperative eGFR and increased age are significant predictors of deteriorating

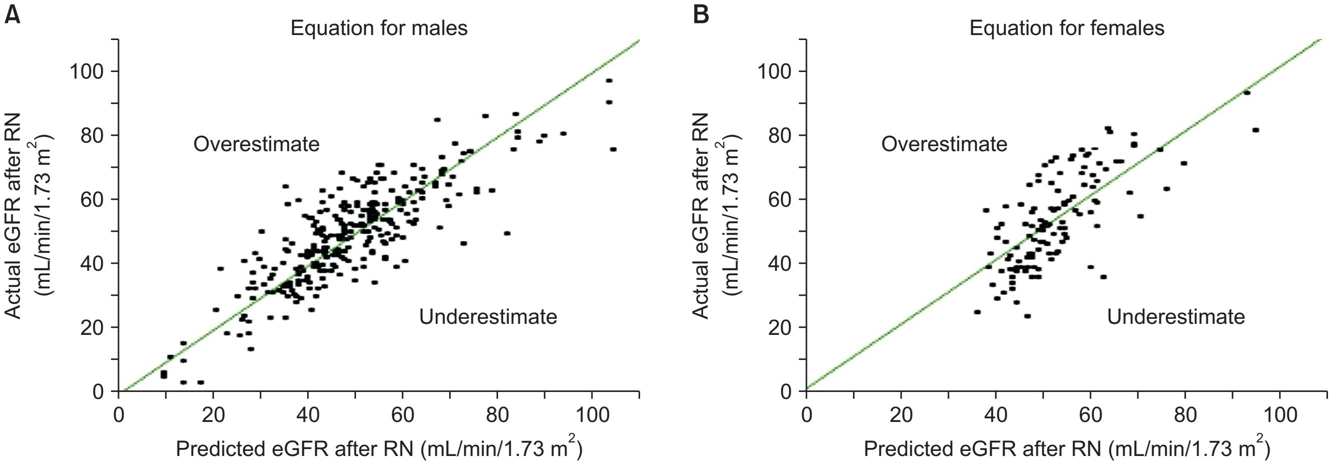

Fig. 1. (A) Correlation between predicted estimated glomerular filtration rate (eGFR) using the equation for males and actual eGFR 1 year after radical nephrectomy (RN) in the combination dataset ($R^2=0.66$, $p<0.0001$). (B) Correlation between predicted eGFR using the equation for females and actual eGFR 1 year after RN in the combination dataset ($R^2=0.34$, $p<0.0001$).

renal function after RN in both males and females, whereas smaller tumor size and higher BMI are significant predictors only in males.

In prior studies, Ohno et al. [15] reported that increased age (60 years or greater), smaller tumor size (7 cm or less), and preoperative lower eGFR were significant risk factors for new-onset renal insufficiency in patients undergoing RN, findings very similar to the present ones. In their study, however, these risk factors were derived without regard to sex difference. To the best of our knowledge, the current study is the first to show that tumor size and BMI are significant predictors of deteriorating renal function after RN only in males.

Yokoyama et al. [16] reported that renal function deteriorates immediately after RN and improves slightly, but significantly, thereafter in Japanese patients, suggesting that, when a decrement in renal function occurs, as in nephrectomy, compensation occurs in the remaining contralateral nephrons in an attempt to maintain renal function. It has been hypothesized that this compensatory mechanism may develop insidiously in larger tumors due to the decrement of nephrons. On the other hand, factors such as age and obesity, well-known risk factors for atherosclerosis [17-19], can cause the compensatory mechanisms to malfunction, resulting in the development of renal insufficiency after RN. This hypothesis may explain why advanced age, BMI, and small tumor size are risk factors for the development of post-RN CKD. In fact, the long-term renal consequences of kidney donation by living donors, older age and higher BMI were associated with reduced GFR [20].

In the present study, BMI and tumor size were significant risk predictors only in males. Possible explanations include the effect of endogenous sex hormones on the development of atherosclerosis [21]. Estrogen appears to have a beneficial effect on atherosclerotic processes through a combination of effects, including changes in the lipid profile and endothelial nitric oxide generation [22]. Men are reported to show a significant decline in the GFR and effective renal plasma flow between the ages of 20 and 50 years; this result is not seen in women, who are probably protected by estrogens in the premenopausal period [23]. Some studies have indicated that male sex is risk factor of decreased renal function after donor nephrectomy [24-27], Lim et al. [26] pointed out sex hormones are involved in the reduction of kidney function after donor nephrectomy in their study. Ibrahim et al. [20] reported that, through long-term follow-up after kidney donation, albuminuria was less likely to develop in females. Animal experiments using uninephrectomy adult rats demonstrated that there was glomerular and tubular damage in the male remnant kidneys, whereas female remnant kidneys were intact [28]. Another is the difference in smoking prevalence between males and females, the younger adoption of cigarette smoking, and the more than three times smoking prevalence among males compared to females [29]. These clinical and experimental studies suggest that there are differences in the renal compensatory ability between the sexes.

Yokoyama et al. [30] first reported the equation to predict eGFR 3 years after RN. They showed age, presence of diabetes mellitus, and preoperative eGFR were significant predictors of postnephrectomy eGFR. In addition to the previous study, the present study resulted in 2 new equations to predict eGFR 1 year after RN by sex, since the independent factors associated with postnephrectomy eGFR differed between the sexes. The 4-variable equation for males and the 2-variable equation for females can be recommended for use in clinical practice. These equations were well validated in the validation dataset.

There were significant differences in bias, precision, and accuracy within 15% of actual GFR between the equations for males and females in the present study. Postnephrectomy renal function can be more accurately predicted in males than in females, and further study with a larger patient population is needed to obtain a more accurate equation.

The present study has some limitations. First, the equations were developed mainly from elderly patients and a relatively small number of subjects, and it may not perform well in young patients.

The equation to predict postoperative eGFR was not good enough to predict outcome in females (R^2=0.32), probably due to relatively small study population. We recognize that the equation is one of the models on the way of development, but our model predicts actual eGFR as continuous outcome on individual basis, which can be utilized for preoperative patient counseling and decision making for the type of surgical procedure in elective partial or RN cases.

Second, data on comorbidities and smoking prevalence were not evaluated. Comorbidities such as DM, HT and smoking prevalence are very important factors of renal function after radical nephrectomy. The database included information on some of the comorbidities, but the present analysis did not include these factors, because it is difficult to quantify the degree of comorbidities and incorporate them into the prediction equation. Further study is needed to determine the accuracy of predicted eGFR considering comorbidities and smoking prevalence.

Third, renal function was estimated using the MDRD equation modified for Japanese patients. The present equations cannot be applied to other races, but it is possible to modify them to race-specific equations in a similar manner to that done in the present study. Despite these limitations, this is the first time that it has been shown that predictors of postnephrectomy renal function differed between males and females. The present equations may be useful for preoperative patient counseling and selection of the type of surgical procedure in elective partial or RN cases.

CONCLUSIONS

Equations to predict postoperative eGFR in Japanese RN patients, namely, predicted eGFR in males (mL/min/1.73 m^2)=27.99-(0.196×age)+(0.497×eGFR)+(0.744×tumor size)-(0.339×BMI), and predicted eGFR in females=44.57-(0.275×age)+(0.298×eGFR), were developed. We believe that these equations will be useful for preoperative patient counseling and selection of the type of surgical procedure in elective partial or RN cases.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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