



Preserved Kidney Volume, Body Mass Index, and Age Are Significant Preoperative Factors for Predicting Estimated Glomerular Filtration Rate in Living Kidney Donors at 1 Year After Donation

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ABSTRACT

Background. Securing postdonation renal function in the lifetime of donors is a consequential subject for physicians, and precise prediction of postdonation renal function would be considerably beneficial when judging the feasibility of kidney donation. The aim of this study was to investigate the optimum model for predicting eGFR at 1 year after kidney donation.

Methods. We enrolled 101 living-related kidney donors for the development cohort and 44 for the external validation cohort. All patients in each cohort underwent thin-sliced (1 mm) enhanced computed tomography (CT) scans. We excluded individuals with diabetes, glucose intolerance, or albuminuria from this study. We evaluated preoperative factors including age, sex, hypertension, body mass index (BMI), serum uric acid, baseline eGFR, and body surface area (BSA)-adjusted preserved kidney volume (PKV) by using 3-dimensional reconstruction of thin-sliced enhanced CT images. To detect independent predictors, we performed multivariable regression analysis.

Results. The multivariable regression analysis revealed that age, BMI, predonation eGFR, and BSA-adjusted PKV were independent predictors of eGFR at 1 year after kidney donation (correlation coefficient: -0.15 , -0.476 , 0.521 , 0.127 , respectively). A strong correlation between predicted eGFR and observed eGFR was obtained in the development cohort ($r = 0.839$, $P < .0001$). The significance of this predictive model was also confirmed with the external validation cohort ($r = 0.797$, $P < .0001$).

Conclusions. Age, BMI, predonation eGFR, and BSA-adjusted PKV may be useful for precisely predicting eGFR at 1 year after living kidney donation and be helpful to determine the feasibility of kidney donation from marginal donors.

LIVING-RELATED kidney transplantation has become increasingly prevalent because of the serious worldwide issues surrounding the shortage of deceased donors. On the other hand, some living kidney donors are at the risk

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of developing chronic kidney disease. It used to be thought that the risks of cardiovascular disease or mortality after kidney donation in living kidney donors were comparable to those in the healthy general population [1–3]; however, several studies have suggested that the risk in kidney donors is unexpectedly higher than in healthy controls, given strict inclusion criteria [4–6]. In a recent Norwegian report, the authors set strict exclusion criteria for age, body mass index (BMI), blood pressure (BP), BP medications, diabetes, and cardiovascular disease for donors and controls. They argued that kidney transplant donors had a much higher risk of developing end-stage renal disease than controls (hazard ratio, 11.38) [4]. Therefore, strict approval criteria are needed for living kidney donors to minimize short- and long-term risks encountered after kidney donation.

Recent guidelines for the preoperative assessment of kidney transplant donors proposed permissible criteria for predonation renal function, age, albuminuria, hematuria, BP, BMI, glucose intolerance, dyslipidemia, and so on [7,8]. The 2017 Kidney Disease: Improving Global Outcomes clinical practice guidelines on the evaluation and care of living kidney donors set forth that predonation glomerular filtration rate (GFR) should be higher than 90 mL/min/1.73 m² [8]. The guidelines also mention that if the GFR of a living donor candidate is between 60 to 89 mL/min/1.73 m², donation approval should be individually decided, considering each demographic and health profile.

Predictive models for postdonation renal function in living kidney donors with marginal predonation renal function would help physicians judge the feasibility of kidney donation from these individuals. The aim of this study was to investigate the optimum predictive model for an estimated GFR (eGFR) level at 1 year after kidney donation by using preoperative factors. We employed a newly advocated preoperative factor, the calculated kidney volume of 3-dimensional (3-D) reconstructed computed tomography (CT) image, instead of renal scintigraphy, because CT volumetry reported that this method was superior to renal scintigraphy for predicting postdonation renal function [9]. We investigated the significance of preserved kidney volume (PKV) in combination with other conventional preoperative factors to establish the optimum predictive model for postdonation renal function and evaluated the efficacy of this model using an external validation cohort.

MATERIAL AND METHODS

Ethics Statement

This study was conducted in compliance with the ethical standards of the Declaration of Helsinki and was approved by the research ethics committee of Keio University School of Medicine (authorization number 2018-0130) and Toho University Omori Medical Center (authorization number M18005). The requirement for written consent from participants was waived due to the retrospective approach and noninvasive nature of the study procedures.

Patient Selection and Study Design

To enroll the development cohort, we retrospectively reviewed 144 living kidney donors who underwent donor nephrectomies at Keio University Hospital between April 2000 and September 2014 and selected 101 patients who underwent 1 mm thin-sliced enhanced CT before transplantation. To enroll the external validation cohort, we selected 44 living donors who underwent donor nephrectomies at Toho University Omori Medical Center between January 2016 and December 2017. We excluded those who were not followed for >1 year post-donation in both the development and validation cohorts. We also excluded individuals with diabetes, glucose intolerance, and those with urine albumin ≥ 30 mg/gCr. Predonation evaluation of renal function in donors was conducted by calculating 24-hour creatinine clearance and eGFR. Since 24-hour urine collection was not carried out in all patients at postoperative periods, we used eGFR for the assessment of postdonation renal function. eGFR was calculated using the Modification of Diet in Renal Disease equation for Japanese patients [10]. We also defined patients with hypertension in patients who took 1 or more anti-hypertensive drugs.

CT Volumetry

To confirm universality of CT volumetry, we used a different operating system in each institution. At Keio University Hospital, dynamic CT was performed using 16- or 64-multidetector CT scanners (LightSpeed Pro16, LightSpeed VCT, BrightSpeed, and Discovery CT750 HD, GE Healthcare, Waukesha, Wis, United States) with a bolus-tracking technique. Iodinated contrast media (iohexol, Omnipaque 300, Daiichi Sankyo, Tokyo, Japan) at a dose of 2 mL/kg was injected for 30 seconds using a power injector following unenhanced CT scan and 1 mm sliced axial images were obtained. To reconstruct 3-D images and calculate volume, we transferred CT images of the nephrographic phase to a workstation (AW server 2.0-12.0, GE Healthcare). The 3-D reconstructed image was automatically obtained by collecting voxel units of the same CT values as renal parenchyma and adjacent structures including renal cysts, the collecting system, or renal vessels were eliminated. At Toho University Omori Medical Center, we used different type of CT scanner (Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany) and analyzing workstation (AZE Virtual Place Fuujin, AZE Co, Tokyo, Japan).

Statistical Analyses

Demographic and clinical data for continuous variables are presented as medians and distribution ranges, and those for categorical variables are presented as proportions (Table 1). Comparison of each variable between the development and validation cohorts was performed by using the Wilcoxon rank sum test for non-normally distributed continuous variables and the *t* test for normally distributed continuous variables. Comparison of categorical variables was performed by using χ^2 tests. To investigate significant preoperative factors that can predict eGFR at 1 year after kidney donation, we used univariate and multivariable regression analyses using the data in the development cohort (Table 2). To confirm universality of the established predictive equation for eGFR at 1 year after kidney donation, we applied the equation to the external validation cohort and investigated the correlation between the predicted eGFR and observed eGFR by Spearman's rank correlation analyses (Fig 1). Probability (*P*) values of <.05 were regarded as statistically significant. We performed statistical analyses using JMP Pro v 13.2.0 (SAS Institute, Inc., Cary, NC, United States) and

Table 1. Demographic and Clinical Characteristics of the Development and External Validation Cohorts

Variables	Development Cohort (n = 101)	External Validation Cohort (n = 44)	P Value
Age (years)	57 (29–79)	54 (31–76)	.1899
Sex (female)	47 (47%)	25 (61%)	.1188
Height (m)	1.63 (1.47–1.81)	1.61 (1.47–1.88)	.6875
Weight (kg)	58.0 (39–93.7)	57.4 (42.6–95.3)	.5971
BMI (kg/m ²)	22.7 (15.7–31.8)	22.8 (18.5–30.1)	.7356
Hypertension	21 (21%)	7 (17%)	.6137
Preserved kidney volume (cm ³)	171.1 (103.6–247.5)	151.2 (110.7–281.7)	.033
Preserved kidney volume/body surface area (cm ³ /m ²)	101.4 (76.2–138.8)	93.7 (74.4–132)	.0054
Preoperative serum creatinine (mg/dL)	0.75 (0.41–1.11)	0.70 (0.52–0.92)	.1255
Preoperative creatinine clearance (mL/min/1.73 m ²)	115.5 (74.3–175.4)	106.5 (85.3–199.4)	.5673
Preoperative uric acid (mg/dL)	5.4 (0.7–8.6)	5.6 (3.2–8.7)	.4125
Preoperative eGFR (mL/min/1.73 m ²)	72.3 (48.3–116.9)	75.5 (51.8–110.2)	.3242
1-year eGFR (mL/min/1.73 m ²)	47.8 (29.7–92.4)	46.8 (32.4–67.4)	.8784
eGFR decline ratio	0.363 (0.162–0.535)	0.362 (0.148–0.494)	.6268

Data are n (%) or median (range).

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.

drew statistical figures using GraphPad Prism v 5.0 (GraphPad Software, San Diego, Calif, United States).

RESULTS

Comparison of Demographic and Clinical Characteristics Between the Development and Validation Cohorts

Table 1 demonstrates the demographic and clinical characteristics of 101 patients included in the development cohort and 44 patients included in the validation cohort. Predonation variables including age, sex, height, weight, BMI, hypertension, serum creatinine, creatinine clearance, and eGFR (other than PKV) were not significantly different between the cohorts. PKV and body surface area (BSA)-adjusted PKV in the development cohort was significantly higher than those in the validation cohort (171.1 vs 151.2 cm³, $P = .033$; 101.4 vs 93.7 cm³, $P = .0054$, respectively). This difference may have resulted from differences in the analyzing workstations used by each institution. Post-donation variables, including observed eGFR and the decline ratio of eGFR at 1 year after kidney donation, were not different between each cohort.

Independent Preoperative Factors That Affect eGFR at 1 Year After Kidney Donation in the Development Cohort

We performed regression analyses to investigate significant predonation factors that could predict eGFR at 1 year after kidney donation in the development cohort. We used BSA-adjusted PKV (cm³/m²) as a variable because, in this study, eGFR was adjusted by BSA (mL/min/1.73 m²). Univariate regression analyses revealed that age, hypertension, BMI, preoperative eGFR, and BSA-adjusted PKV were significant predictive factors (Coefficient [95% confidence interval], P value: $-0.353 [-0.532, -0.174]$, 0.0002 ; $2.821 [0.509, 5.133]$, 0.0173 ; $-0.788 [-1.398, -0.179]$, 0.0118 ; $0.610 [0.531, 0.690]$, $<.0001$; $0.086 [0.023, 0.148]$, $.0076$; respectively) (**Table 2**). Sex and serum uric acid level were not significant predictive factors. We subsequently performed multivariable regression analysis to assess independent predictors by introducing all variables included in the univariate analyses. Age, BMI, preoperative eGFR, and BSA-adjusted PKV were significant independent predonation factors that could predict eGFR at 1 year after kidney donation (Coefficient [95% confidence interval], P value: $-0.150 [-0.277, -0.024]$, 0.0205 ; -0.476

Table 2. Univariate and Multivariable Regression Analysis for Predicting eGFR at 1 Year After Kidney Donation

	Univariate Analysis		Multivariable Analysis (Including All Covariates)		Multivariable Analysis (Only Independent Covariates)	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Age (years)	-0.353 (-0.532, -0.174)	.0002	-0.150 (-0.277, -0.024)	.0205	-0.133 (-0.259, -0.007)	.038
Sex (female)	0.398 (-1.537, 2.332)	.6842	-0.461 (-1.765, 0.843)	.4841		
Hypertension	2.821 (0.509, 5.133)	.0173	0.617 (-0.692, 1.925)	.3517		
BMI (kg/m ²)	-0.788 (-1.398, -0.179)	.0118	-0.476 (-0.874, -0.079)	.0195	-0.514 (-0.887, -0.140)	.008
Preoperative uric acid	-1.277 (-2.668, 0.114)	.0716	-0.408 (-1.344, 0.537)	.3883		
Preoperative eGFR (mL/min/1.73 m ²)	0.610 (0.531, 0.690)	<.0001	0.521 (0.429, 0.612)	<.0001	0.510 (0.410, 0.610)	<.0001
Preserved kidney volume/body surface area (cm ³ /m ²)	0.347 (0.195, 0.498)	<.0001	0.127 (0.027, 0.227)	.0137	0.118 (0.020, 0.216)	.019

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate.

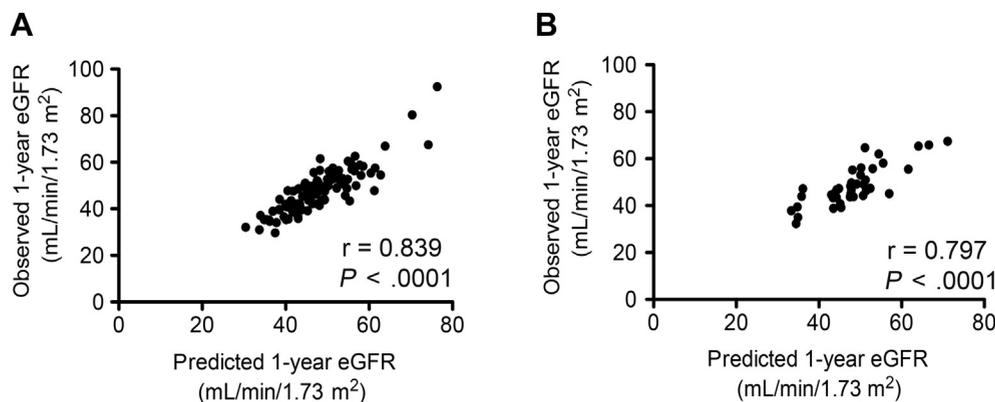


Fig 1. The correlation analysis between the predicted and observed eGFR at 1 year after kidney donation by Spearman's rank correlation analyses. **(A)** The dot plot represents the analysis in the development cohort. **(B)** The dot plot represents the analysis in the external validation cohort.

$[-0.874, -0.079], 0.0195; 0.521 [0.429, 0.612], <.0001; 0.127 [0.027, 0.227], .0137$; respectively).

Correlation of Predicted and Observed eGFR at 1 Year After Kidney Donation Both in the Development and Validated Cohorts

We established the predictive equation using coefficients that were obtained in a multivariable analysis including only independent covariates (Table 2): predicted eGFR = $17.316 + (-0.133 \times \text{Age}) + (-0.514 \times \text{BMI}) + (0.118 \times \text{BSA-adjusted PKV}) + (0.510 \times \text{predonation eGFR})$. We subsequently compared predicted eGFR with observed eGFR at 1 year after kidney donation. Predicted eGFR was significantly correlated with observed eGFR in the development cohort ($r = 0.839, P < .0001$) (Fig 1A). A strong correlation between predicted eGFR and observed eGFR was also obtained in the external validation cohort ($r = 0.797, P < .0001$) (Fig 1B).

DISCUSSION

At 1 year after kidney donation, eGFR could be predicted with high accuracy by age, BMI, predonation eGFR, and BSA-adjusted PKV in living kidney donors. These findings were also confirmed in an external validation cohort. Use of these factors during predonation assessments should assist physicians in identifying individuals suitable for living kidney donation, especially in cases where the donor's preoperative renal function is marginal.

The usefulness of kidney volumetry by CT scan before heminephrectomy is a recent topic of active discussion. When comparing the 3 methods for volumetry, including approximation by ellipsoid method, volumetry by manual setting of a region of interest, and the automated voxel count method performed by a dedicated workstation, the automated volumetry with a region of interest set by detecting CT values of the renal parenchyma has emerged as superior for estimating renal function [11]. Automated

volumetry has the advantage of being able to eliminate structures, which are adjacent to the renal parenchyma (eg, renal cyst, renal pelvis, or renal vessels). In this study, therefore, we used the automated volumetry system.

It was reported that age, BSA, preoperative eGFR, and preserved renal cortical volumetry were significant predictors of postnephrectomy renal function, although the patients in the study were not living kidney donors [12]. Introducing PKV factor as well as predonation renal function into the predictive equation may be critical because the magnitude of compensation in renal function after heminephrectomy differs from patients to patient. Lower PKV is reportedly a significant predictor of delayed renal functional recovery after kidney donation [13]. This is because kidney volume is closely related to glomerular-filtering surface area [14].

Among conventional predonation factors that may affect postdonation renal function, age, and BMI were independent predictors in this study. Age is a widely accepted predictive factor because it is more directly related to the extent of glomerular sclerosis. Previous reports have suggested that BMI or obesity were risk factors for renal function insufficiency in living kidney donors [15–17] and in nondonors [18,19]. However, the reason why obesity is related to renal function insufficiency in heminephrectomized patients remains undetermined. Rea et al found that obese donors exhibited enlarged glomerular surface area on histological analysis [20], and Goumenos et al also suggested a positive correlation between BMI and glomerular cross-sectional area [21]. Inferring from the evidence above, in patients with obesity, the glomeruli may be shifted into a hyperfiltration state before nephrectomy; thus, the magnitude of adaptive increase of GFR in these patients might be lower than those who are of normal weight. This may be the reason why BMI added independent information to age, predonation eGFR, and PKV for predicting postdonation eGFR. We speculated the reason why hypertension was not an independent predictor was that, in our patients, BP was strictly controlled by limited number of anti-hypertensive

drugs. This might have weakened the hypertension factor in this study.

CONCLUSIONS

When predonation renal function in living kidney donor candidates is marginal, a predictive model for postdonation renal function that includes donor age, predonation eGFR, BMI, and BSA-adjusted PKV may be helpful for physicians to determine the feasibility of kidney donation from individuals with marginal renal function.

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