Transplant International

ORIGINAL ARTICLE

Remaining kidney volume indexed to weight as a strong predictor of estimated glomerular filtration rate at 1 year and mid-term renal function after living-donor nephrectomy - a retrospective observational study

Diogo Nunes-Carneiro[1,2,3], Mariana Madanelo[1], Filipa Silva[4], Nicole Pestana[5], Catarina Ribeiro[6], Diogo Gil-Sousa[1], La Salete Martins[2,4], Manuela Almeida[2,4], Leonídio Dias[2,4], Jorge Malheiro[2,4], Vítor Cavadas[1], Antonio Castro-Henriques[2,4], Avelino Fraga[1,2,3] & Miguel Silva-Ramos[1,2]

1 Urology Department, Centro Hospitalar e Universitário do Porto, Porto, Portugal
2 Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal
3 i3S/INEB, Universidade do Porto, Porto, Portugal
4 Nephrology and Kidney Transplantation Department, Centro Hospitalar e Universitário do Porto, Porto, Portugal
5 Nephrology Department, Hospital Dr, Nelio Mendonça Funchal, Porto, Portugal
6 Nephrology Department, Centro Hospitalar de Vila Nova de Gaia e Espinho, Porto, Portugal

Correspondence
Diogo Nunes-Carneiro, Largo Prof. Abel Salazar 1, 4099-001 Porto, Portugal.
Tel.: +351 222 077 500;
fax: +351 222 030 411;
e-mails:
diogocarneiro.urologia@chporto.min-saude.pt;
diogonunescarneiro@gmail.com

ABSTRACT

The donors' estimated glomerular filtration rate (eGFR) after living nephrectomy has been a concern, particularly in donors with smaller kindeys. Therefore, we developed this retrospective observational study in 195 donors to determine the ability remaining kidney volume indexed to weight (RKV/W) to predict eGFR at 1 year through multivariate linear regression and to explore this relationship between annual eGFR change from 1 to 4 years postdonation evaluated by a linear mixed model. Comparing RKV/W tertiles (T1, T2, T3), RKV/W was a good predictor of 1-year eGFR which was significantly better in T3 donors. Gender, predonation eGFR, and RKV/W were independent predictors of eGFR at 1-year. In a subgroup with predonation eGFR < 90mL/min/1.73 m^2, a significant prediction of eGFR < 60mL/min/1.73 m^2 was detected in males with RKV/W ≤ 2.51cm^3/kg. Annual eGFR (ml/min/year) change from 1 to 4 years was + 0.77. RKV/W divided by tertiles (T1–T3) was the only significant predictor: T2 and T3 donors had an annual eGFR improvement opposing to T1. RKV/W was a good predictor of eGFR at 1 year, independently from predonation eGFR. A higher RKV/W was associated with improved eGFR at 1 year. A decline in eGFR on the four years after surgery was only noticeable in donors with RKV/W ≤ 2.13cm^3/kg.

Transplant International 2020; 33: 1262–1273

Key words
kidney volume, living donor, nephrectomy, transplantation

Received: 22 December 2019; Revision requested: 27 April 2020; Accepted: 22 June 2020;
Published online: 14 August 2020

Introduction

The prognosis of donors' glomerular filtration rate (GFR) after living-donor nephrectomy has been a subject of great concern for physicians. Several years ago, the major argument was that cardiovascular disease risk or overall mortality risk in kidney transplant donors was comparable to those in a matched nondonor population [1]. However, studies on kidney living donors have shown an increase in the serum creatinine level (SCr) by 20% above baseline

doi:10.1111/tri.13683

after radical nephrectomy (RN) [2]. It has also been shown that RN in patients results in functional adaptation and compensatory hypertrophy of the remaining kidney. The range of the GFR after RN has been reported to be 75–80% of its baseline level [3]. Studies after RN also showed that eGFR decreased immediately after the procedure, but improved slightly but significantly thereafter during a 5-year follow-up period [4]. Data from nondonor cohorts suggested that baseline estimated glomerular filtration rate (eGFR) is one of the strongest independent predictors of future kidney disease [5].

Many different equations and measurements have been previously used to calculate donor kidney function through the serum creatinine (SCr) value. The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula has been proposed to possibly be a more accurate assessment of healthy living donors [6]. Comparing with SCr, Cystatin C (CysC) is less affected by muscle mass, gender, race, and diet, and several equations incorporating CysC alone or with SCr have been proposed [7,8].

Kidney volume as a surrogate marker of nephron mass and renal function has been presented by many authors as a good predictor of recipient renal function. Many studies to date have investigated donor factors associated with recipient renal function and outcomes, though scarce data are available about factors associated with donor's renal function after nephrectomy [9-16].

Computed tomography (CT) is used for preoperative evaluation of living kidney donors. Apart from giving anatomic details of the kidney, vasculature, and collecting systems, it can also be used to reliably estimate kidney volume [10,17]. The degree to which remaining kidney volume (RKV) may associate with postdonation kidney function in relation to other donor factors such as weight, body mass index (BMI), and body surface area (BSA) is poorly understood [18,19].

Taking into account the importance of clear information about factors that affect the postdonation kidney function, we studied a cohort of living kidney donors to establish the relationship between RKV indexed to donor weight (RKV/W) and eGFR at 1 year. Additionally, we also explored its association with renal function compensation beyond 1 year, by analyzing the annual eGFR change until 4 years after donation.

Materials and methods

Study cohort

We retrospectively reviewed data from all donors who underwent living-donor nephrectomy consecutively at our institution between January 2008 and December 2017 (n = 210). After exclusion of 15 donors, ten whose CT scans were unavailable for our examination (performed outside our institution) and another 5 without evaluation of eGFR at 1 year and the remaining 195 donors defined our study cohort.

In all donors, age at donation, gender, weight, height, and predonation and 1 year after donation SCr were collected. The institutional review board at our institution approved this study (Ref.: 2017.154(131-DEFI/123-CES).

Renal function and kidney volume assessment

Serum creatinine-based CKD-EPI equation [20] was used to predict eGFR. CysC-based eGFR was also determined in donors with predonation CysC measurement (n = 133) with the respective CKD-EPI equation [21].

Body surface area (BSA) was calculated using the DuBois formula [22]. We explored RKV indexed to two anthropometric measurements: BSA and weight, calculating the ratio of remaining whole parenchymal kidney volume divided by BSA (RKV/BSA, cm^3/m^2) and W (RKV/W, cm^3/kg).

During the study, all potential living donors were evaluated with one of two multidetector-row CT scans available at our institution (a 64-detector GE VCT LightSpeed® or a 16-detector GE Brightspeed®) using the same image acquisition protocols. Images were obtained prior to contrast and after the administration of 100–150 ml of iodinated contrast media during the nephrographic (70–90 s) and excretory phases (approximately 240 s) of enhancement. This examination was usually done in less than three months of the nephrectomy in order to elucidate us about anatomic variants and rule out solid lesions and urolithiasis. Based on CT scan, we usually exclude kidney units with three or more arteries, with suspicious solid lesions and kidney stones (except cases of < 5mm solitary calyceal stone with no history of stone passage and low metabolic risk on 24-h urine analysis).

Volumes were measured through the voxel counting technique (the sum resulting from the tracing of the renal contours in sequential 2.5-mm transversal CT nephrographic images, excluding the renal sinus area) using the Osirix® (Pixmeo Sarl, Geneva, Switzerland) software.

Statistical analysis

Continuous data were described using mean ± standard deviation (SD) or median (interquartile range [IQR]),

and categorical data were expressed as number (and percentages). Categorical data including were compared using Pearson's chi-square test or Fisher's exact test, and continuous variables were compared with Student's t-test or Mann–Whitney U test, as appropriate. Correlation between eGFR values and RKV metrics are presented as Pearson's coefficient.

Linear prediction of eGFR and risk factors for an eGFR < 60 ml/min at 1-year were analyzed through a univariate and multivariable linear regression model. In order to establish comparisons between covariates regarding strength of association, the increment in continuous variables was assessed per standard deviation. To further explore the relationship between RKV/W and eGFR at 1 year, we used a restricted cubic regression spline basis matrix to graphically model (using the same multivariable model as above) the linear prediction of eGFR at 1 year, using the *adjustrcspline* command of *postrcspline* package for Stata.

Donor eGFR change between 1 and 4 years postdonation was assessed by univariate and multivariable linear mixed regression model that imputed subject-specific random effects (intercept and slope defined as eGFR at 1 year and time in years, respectively) on an unstructured covariance matrix. The dependent variable was all eGFR measurements, and the independent variables were entered as 2-way interaction terms between them and the time (in years) variable. All 195 donors were studied, and a median of 3 (IQR: 2–4) annual measurements of eGFR were available. All multivariable models were constructed by including variables with a univariate *P*-value < 0.150.

A 2-sided *P*-value < 0.05 was considered as statistically significant. Statistical calculations were performed using STATA/MP, version 15.1 (Stata Corp, College Station, TX).

Results

Study population

The population's characteristics are described in Table 1. We found a positive correlation between RKV and both predonation eGFR (r = 0.151 *P* = 0.035) and 1-year eGFR (r = 0.171 *P* = 0.017) and, in comparison, RKV indexed to anthropometric measurements (BSA and W) was more strongly correlated with eGFR measurements (Fig 1). RKV/W presented higher correlation with eGFR than RKW/BSA (Fig. 1). Given these results, we decided to use RKV/W as the RKV metric for the prediction of postdonation eGFR. Mean RKV/W was 2.30 ± 0.37 cm^3/kg.

w?>We analyzed donors' baseline characteristics considering RKV/W tertiles as presented in Table 1. Comparing donors in the first (T1) and second (T2) tertiles, the only significant differences observed were a higher CysC-based eGFR (*P* = 0.048) and a lower BMI (*P* = 0.019) in T2. On the other hand, those in the third tertile (T3) were younger (*P* = 0.003, *P* = 0.016) and had lower BMI and BSA (both *P* < 0.001) and a higher creatinine- (both *P* < 0.001) or cystatin-based (*P* < 0.001, *P* = 0.029) eGFR when compared with T1 (T1 vs T3) and T2 (T2 vs T3) donors, respectively. As expected, RKV, RKV/W, and RKV/BSA were significantly different between each tertile, with the exception of RKV comparison between T2 and T3 (*P* = 0.085).

Donors' mean eGFR at 1 year was 71.1 ± 14.5 ml/min/1.73 m^2, with a median of 69.8 ml/min/1.73 m^2 (IQR: 60.6–79.8). As shown in Fig. 2, T1 and T2 donors had similar of eGFR at 1 year, while those in T3 showed a significantly (both *P* < 0.001) higher value. Taking into account the nonlinear relationship between RKV/W tertiles and eGFR at 1 year, we explored the former as a continuous predictor variable in the regression analyses.

Linear prediction of eGFR at 1 year

All considered variables were significantly associated with eGFR at 1 year in univariate linear regression (Table S1). Multivariable analysis showed that independent predictors of eGFR at 1 year, ordered by the weight of their importance, were predonation eGFR (per SD = 3.36: β = 7.042; *P* < 0.001), gender (Female vsMale: β = 4.289; *P* = 0.012), and RKV/W (per SD = 0.37: β = 4.281; *P* < 0.001) (Table 2). Additionally, the prediction ability of model 2 (that included RKV/W) was significantly improved, in comparison with model 1 (which did not), with an increase of 6.2% between these models R^2.

A nonlinear association between eGFR at 1 year and RKV/W through restricted cubic spline regression was then explored graphically, using the same multivariable model discussed above. As depicted in Fig. 3 (*top left*), in the overall cohort, the predicted eGFR was above 60 ml/min, being noticeable that eGFR predicted values plateaued around 65–70 ml/min with values of RKV/W below 2.25 cm^3/kg while, above it, a linear increase in eGFR was observed. Given the curved relationship observed in this regression, the analysis of the quadratic effect of

Transplant International 2020; 33: 1262–1273

Table 1. Baseline population characteristics and divided by RKV/W tertiles

	Total n = 195	Tertile 1 (1.41–2.13) n = 65	Tertile 2 (2.14–2.40) n = 65	Tertile 3 (2.42–3.59) n = 65	P
Age, mean ± SD	48.0 ± 10.4	50.1 ± 9.7	49.2 ± 10.0	44.7 ± 11.0	**0.006****,***
Female gender, n (%)	142 (73)	48 (74)	43 (66)	51 (78)	0.281
Height (cm), median (IQR)	162 (158–169)	165 (158–170)	165 (159–170)	161 (157–167)	0.137*
Weight (kg), mean ± SD	67.9 ± 11.1	72.1 ± 10.0	69.8 ± 11.0	61.8 ± 9.6	**<0.001****,***
BMI (kg/m^2), mean ± SD	25.3 ± 3.4	26.8 ± 3.0	25.6 ± 3.1	23.5 ± 3.1	**<0.001***,**,***
BSA (m^2), mean ± SD	1.74 ± 0.17	1.78 ± 0.16	1.77 ± 0.17	1.66 ± 0.15	**<0.001****,***
Predonation serum creatinine (mg/dl), median (IQR)	0.70 (0.63–0.86)	0.75 (0.67–0.86)	0.73 (0.65–0.91)	0.64 (0.59–0.70)	**<0.001****,***
Predonation eGFR-SCr (ml/min/1.73 m^2), mean ± SD	100.3 ± 13.9	96.3 ± 13.1	97.0 ± 13.1	107.7 ± 12.5	**<0.001****,***
Predonation eGFR (ml/min/1.73 m^2), n (%)					
<90	43 (22)	22 (34)	16 (25)	5 (8)	**<0.001****,***
90–100	46 (24)	14 (22)	23 (35)	9 (14)	
≥100	106 (54)	29 (45)	26 (40)	51 (78)	
Predonation 24-h creatinine clearance available, n (%)†	171 (88)	55 (85)	59 (91)	57 (88)	0.565
Predonation 24-h creatinine clearance adjusted to BSA (ml/min/1.73 m^2), median (IQR)†	73.3 (61.6–85.6)	70.6 (61.0–79.0)	71.3 (59.8–80.8)	80.7 (68.8–89.8)	**0.003****,***
Predonation CysC (mg/l), median (IQR)‡	0.67 (0.61–0.75)	0.74 (0.65–0.78)	0.67 (0.61–0.74)	0.63 (0.57–0.68)	**<0.001***,**,***
Predonation eGFR-CysC (ml/min/1.73 m^2), median (IQR)‡	112.0 (104.9–122.9)	107.2 (100.2–114.2)	110.3 (105.9–122.9)	120.9 (108.4–128.8)	**<0.001***,**,***
Total kidney volume (cm^3), median (IQR)	307.3 (271.8–344.6)	272.3 (247.4–313.5)	317.3 (285.2–347.9)	332.1 (297.4–346.5)	**<0.001***,**
Right kidney remaining, n (%)	159 (82)	50 (77)	54 (83)	55 (85)	0.489
Remaining kidney volume (RKV, cm^3), median (IQR)	153.8 (134.8–173.6)	136.0 (119.2–156.0)	160.1 (141.5–175.8)	162.6 (149.2–183.8)	**<0.001***,**
RKV indexed to BSA (RKV/BSA, cm^3/m^2), mean ± SD	89.2 ± 12.8	77.6 ± 8.0	89.2 ± 6.9	100.8 ± 10.5	**<0.001***,**,***
RKV indexed to weight (RKV/W, cm^3/kg), mean ± SD	2.30 ± 0.37	1.93 ± 0.17	2.27 ± 0.08	2.72 ± 0.24	**<0.001***,**,***
eGFR at discharge (ml/min/1.73 m^2), mean ± SD	62.3 ± 18.9	60.2 ± 17.9	59.5 ± 16.5	67.1 ± 21.2	**0.043*****
eGFR at 1-y (ml/min/1.73 m^2), mean ± SD	71.1 ± 14.5	65.3 ± 12.1	67.6 ± 11.7	80.5 ± 14.7	**<0.001****,***
eGFR change from discharge to 1-y (ml/min/1.73 m^2), median (IQR)	+6.5 (−1.0 to 16.5)	+6.8 (0.6–11.7)	+3.5 (−1.9 to 20.0)	+8.5 (−0.8 to 27.1)	0.243
eGFR at 1-y < 60 ml/min, n (%)	45 (23)	24 (37)	17 (26)	4 (6)	**<0.001****,***

Bold indicates statistically significant P value.

T1, tertile 1; T2, tertile 2; T3, tertile 3; SD, standard deviation; IQR, inter-quartile range; BMI, body mass index, BSA, body surface area; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; CysC, serum cystatin C; RKV, remaining kidney volume.

*P < 0.05 for T1 vs T2.

**P < 0.05 for T1 vs T3.

***P < 0.05 for T2 vs T3.

†Data missing in 24 donors.

‡Data missing in 62 donors.

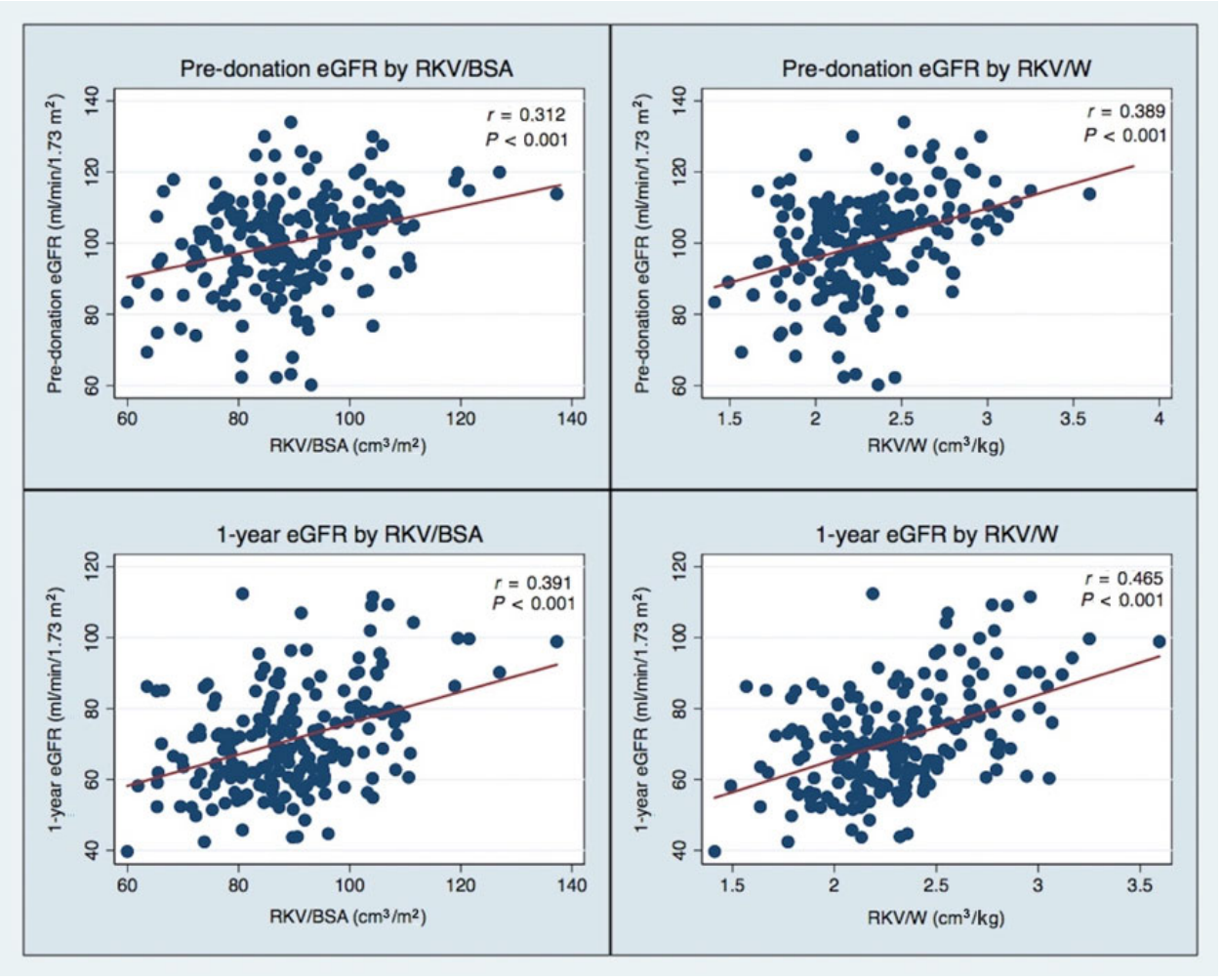

Figure 1 Scatterplots with regression lines representing the correlations. Top left, predonation eGFR and RKV/BSA. Top right, predonation eGFR and RKV/W. Bottom left, 1-year eGFR and RKV/BSA. Bottom right, 1-year eGFR and RKV/W.

RKV/W as an approximation of the spline model was added as model 3 in Table 2.

After stratification according to predonation eGFR, a trend towards an eGFR at 1 year < 60 ml/min was observed in a subgroup of donors with predonation eGFR < 90 ml/min/1.73 m^2 and a RKV/W ≤ 2.36 cm^3/kg (Fig. 3 *middle left*). In this subgroup, a similar observation was predicted for RKV/W ≤ 2.16cm^3/kg in females, while a significant prediction of eGFR at 1 year < 60 ml/min was detected in males with RKV/W ≤ 2.51 cm^3/kg (Fig. 3 *top right*), demonstrating that this subgroup of donors is particularly at risk of an "inadequate" eGFR 1-year postdonation.

Donor eGFR change after 1 year

Through mixed linear regression models, donor annual eGFR change from 1 year to 4 years after donation was analyzed (Table 3). Overall, annual eGFR change was + 0.77 ml/min/year, showing that an improvement in eGFR occurred on the mid-term after donation. Considering the same predictors analyzed above, performing univariate and multivariable analysis, only RKV/W tertiles were significantly associated with longitudinal annual change in eGFR. Marginal prediction of mean eGFR by RKV/W tertiles (Fig. 4 *left*) showed an eGFR improvement in donors in T2 and T3 longitudinally, while a decline in T1 was observed. Annual change in eGFR was −0.42, +1.61, and + 1.10 ml/min/year in T1, T2, and T3 donors, respectively (Fig. 4 *right*), with significant differences being observed between T2 ($P = 0.009$) and T3 ($P = 0.046$) in comparison with T1.

Discussion

In this study, we showed that RKV was independently correlated with eGFR before (r = 0.151, $P = 0.035$)

Transplant International 2020; 33: 1262–1273

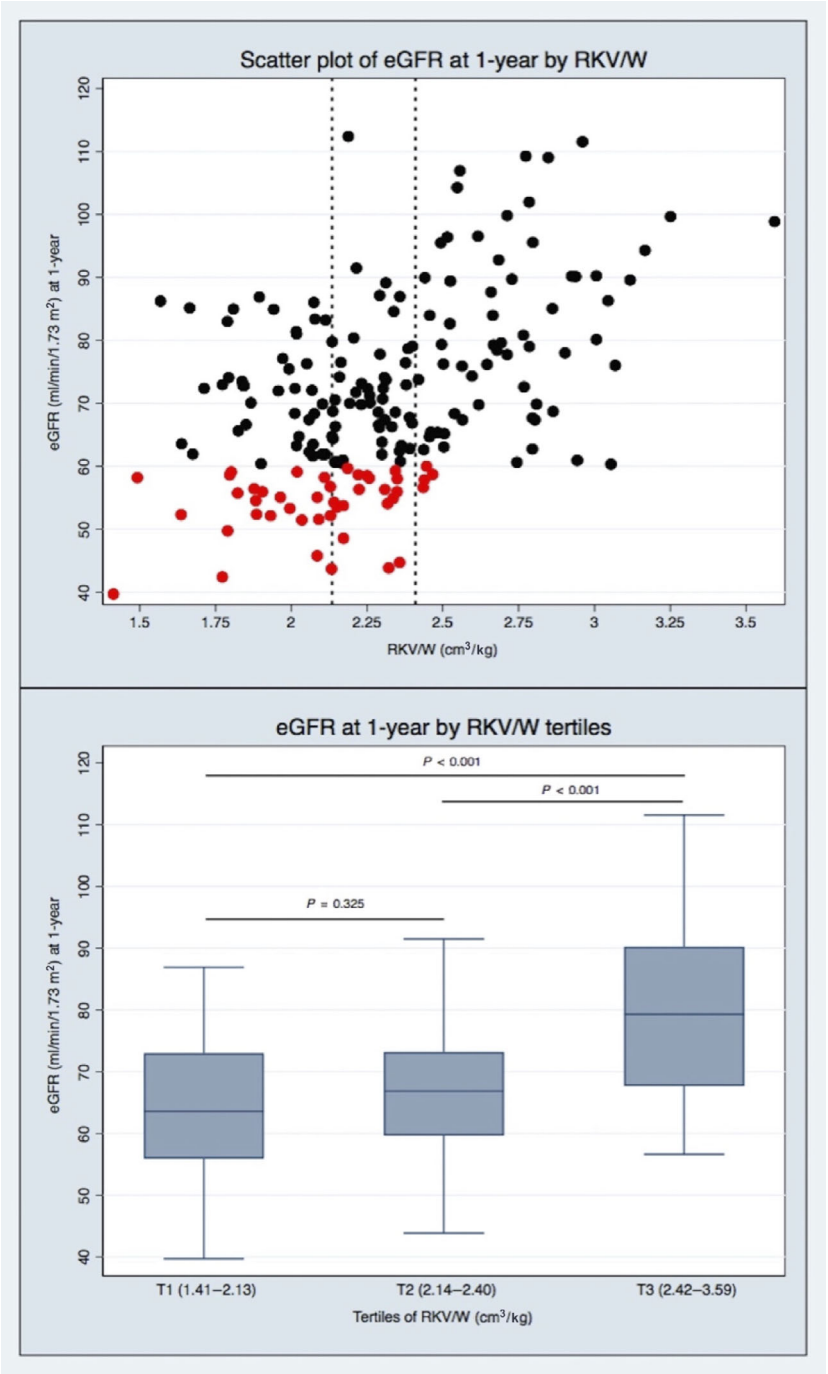

Figure 2 *Top*: scatterplot of the distribution of 1-year eGFR by RKV/W; eGFR values ≥ 60 ml/min are plotted in black and those < 60 ml/min in red. Dashed lines represent 33th and 67th percentiles of RKV/W. *Bottom*: Boxplots of 1-year eGFR by RKV/W tertiles. Boxes show the interquartile range of the values (median and percentile 25–75); whiskers show the lowest and the highest value within 1.5 times below or above the interquartile range, respectively.

and after 1 year of donation (r = 0.171, $P = 0.017$). We also found that RKV, adjusted to donor's weight and predonation eGFR (described as "volume dose" [15]), had positive and strong correlation with eGFR one year after donation, agreeing with most recent series [14,16,23]. A larger mass of nephrons remaining adjusted to donor's weight seems to predict a better long-term eGFR.

As is showed in Table 1, over the tertiles, the donor's showed a better health profile, such as younger age, tendentially more women, with lower weight and BMI, higher predonation eGFR (SCr and

Table 2. Multivariable predictors of eGFR 1 year by linear regression

	Multivariable model 1			Multivariable model 2			Multivariable model 3†		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
Age									
Per unit	−0.107	−0.282 to 0.068	0.228	−0.157	−0.332 to 0.009	0.064	−0.167	−0.332 to − 0.001	**0.049**
Per SD (10.4)	−1.119	−2.945 to 0.706		−1.639	−3.376 to 0.098		−1.739	−3.468 to − 0.011	
Female gender	3.368	−0.145 to 6.881	0.060	4.288	0.949–7.627	**0.012**	4.385	1.067–7.703	**0.01**
BMI									
Per unit	−0.089	−0.941	0.709	0.4	−0.973	0.106	0.425	−0.966	0.084
Per SD (3.36)	−0.301	−3.169		1.346	−3.273		1.429	−3.249	
Predonation eGFR									
Per unit	0.629	0.496–0.761	**<0.001**	0.508	0.374–0.642	**<0.001**	0.498	0.364–0.632	**<0.001**
Per SD (13.9)	8.717	6.879–10.556		7.042	5.179–8.904		6.902	5.045–8.759	
RKV/W									
Per unit	-	-	**-**	11.626	6.945–16.306	**<0.001**	-	-	**-**
Per SD (0.37)				4.281	2.557–6.005				
RKV/W*RKV/W†									
Per unit	-	-	**-**	-	-	**-**	2.558	1.586–3.529	**<0.001**
Per SD (1.76)							4.513	2.799–6.227	
Constant	−12.991	−44.985	0.256	−12.334	−47.127	0.303	1.311	−43.117	0.905
Model diagnostics									
VIF (mean)	1.24			1.37			1.38		
R^2 (%)*	45.3			51.5			52.2		

Bold indicates statistically significant *P* value.

BMI, body mass index; CI, confidence interval; RKV, renal kidney volume; SD, standard deviation; VIF, variance inflator factor.

*Model 2 vs 1: R2 change=+6.2%, $P < 0.001$. Model 3 vs 1: R2 change=+6.9%, $P < 0.001$. Model 3 vs 2: R^2 change=+0.7%, $P = 0.101$. *P*-values by LR tes.t

†Quadratic effect of RKV/W. Model 3 approximates the spline model presented in Fig. 3.

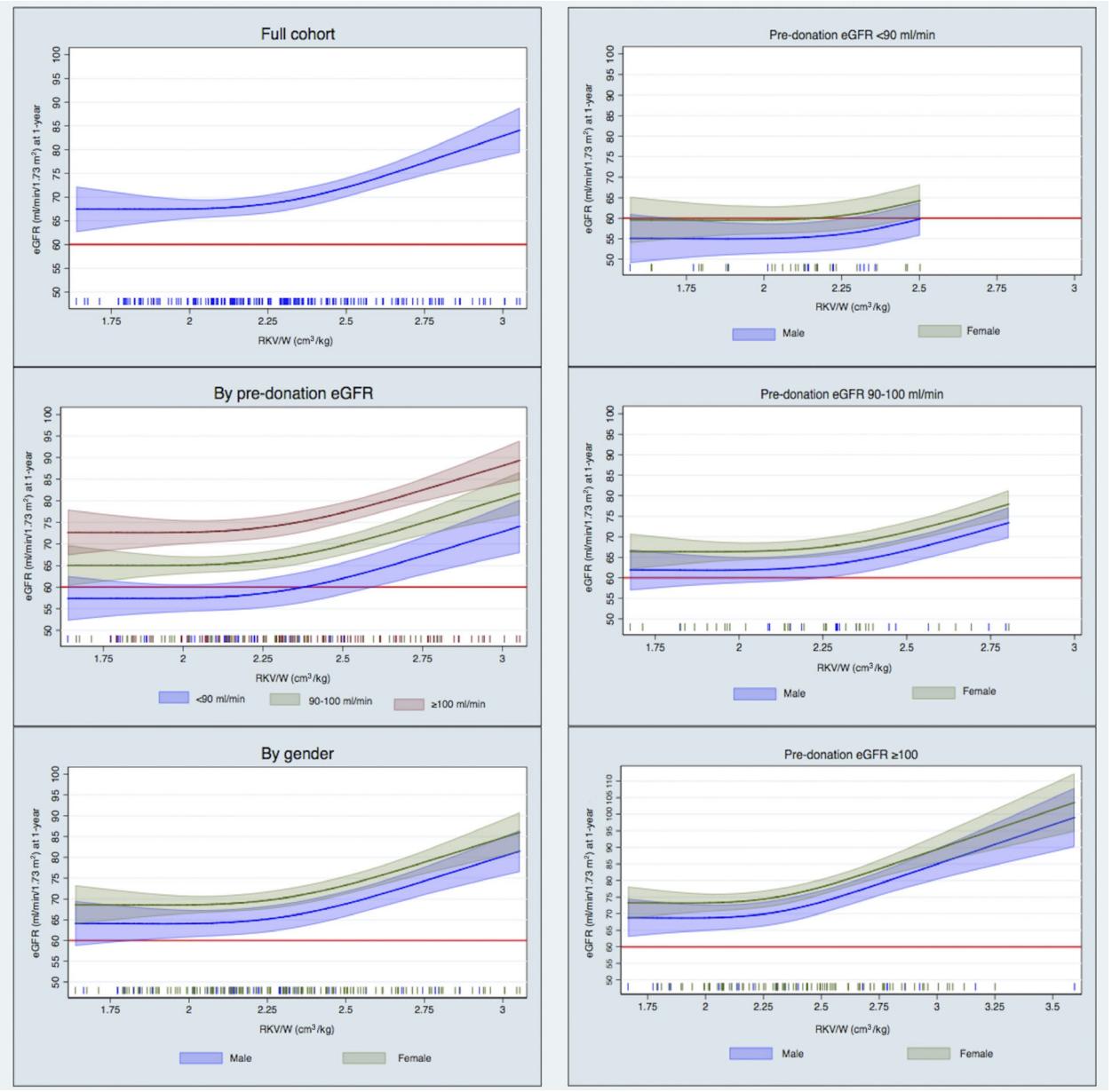

Figure 3 Linear prediction of 1-year eGFR by RKV/W values according with a restricted cubic spline multivariable (see Table S3) model. Left: *Top*, full cohort. *Middle*, by predonation eGFR (<90, 90–100, >100 ml/min/1.73 m^2). *Bottom*, by gender. Right: stratification for predonation eGFR group (<90, 90–100 and ≥ 100 ml/min) by gender. *Top*, predonation eGFR < 90 ml/min. *Middle*, predonation eGFR 90–100 ml/min.

CysC-based), and higher kidney volume. These characteristics were translated into a better renal function one year after donation as represented in Fig. 2. When we analyzed this population regarding to the first year eGFR, we observed a very homogenous group in T1 and T2, in opposition to a significantly better population regarding eGFR 1 year after donation in T3 (Fig. 2).

Predonation eGFR is one of the strongest predictors of 1-year postdonation renal function [24], and we showed that the predonation eGFR had a linear independent positive correlation with 1-year eGFR (each increase of 14 ml/min/1,73 m^2 in baseline eGFR decreased the risk of having eGFR < 60 ml/min/1,73 m^2 one year after donation by 69%) agreeing with these studies. Living-donor's population is composed by very healthy individuals: young (mean 48 years), low BMI (mean 25 kg/m^2), and good predonation eGFR (mean 100 ml/min/1.73 m^2) [25]. These findings could explain how eGFR plateaus around 65–70 ml/min/1,73 m^2 and

Table 3. Predictors of annual SCr-eGFR change (ml/min/year) from 1- to 4-years postdonation by linear mixed regression

	Univariate			Multivariable		
	β	95% CI	*P*	β	95% CI	*P*
Time (yearly)	0.77	0.13–1.40	**0.018**	−0.42	−1.52 to 0.68	0.452
Age per SD (10.4)	−5.99	−7.93 to −4.05)	**<0.001**	−1.74	−3.24 to −0.24)	**0.023**
Time*Age per SD (10.4)	−0.02	−0.67 to 0.63	0.952	-	-	-
Female (vs male) gender	5.00	0.33–9.66	**0.036**	1.22	−1.65 to 4.09	0.404
Time*Female (vs male) gender	−0.38	−1.86 to 1.10	0.615	-	-	-
Time*Male	1.05	−0.25 to 2.34				
Time* Female	0.67	−0.06 to 1.39				
BMI per SD (3.36)	−2.85	−4.93 to −0.76	**0.008**	1.06	−0.35 to 2.47	0.139
Time*BMI per SD (3.36)	0.17	−0.47 to 0.82	0.598	-	-	-
Predonation eGFR per SD (13.9)	9.49	7.98–11.01	**<0.001**	6.86	5.30–8.42	**<0.001**
Time*Predonation eGFR per SD (13.9)	−0.23	−0.89 to 0.43	0.498	-	-	-
RKV/W						
T2 vs T1	2.39	−2.21 to 7.00	0.308	2.28	−1.34 to 5.91	0.217
T3 vsT1	14.58	10.06–19.10	**<0.001**	9.19	5.27–13.11	**<0.001**
Time*RKV/W						
T2 vs T1	2.00	0.48–3.51	**0.015**	2.03	0.50–3.56	**0.009**
T3 vs T1	1.59	0.12–3.07	**0.034**	1.52	0.03–3.01	**0.046**
Time*T1	−0.48	−1.57 to 0.60		−0.42	−1.52 to 0.68	
Time*T2	1.51	0.46–2.57		1.61	0.54–2.67	
Time*T3	1.11	0.12–2.11		1.101.10	0.09–2.11	
Constant				16.69	−2.01 to 35.38	0.080

eGFR, estimated glomerular filtration rate; CI, confidence interval; SD, standard deviation; BMI, body mass index; RKV/W, remaining kidney volume indexed to donor's weight; T1, tertile 1; T2, tertile 2; T3, tertile 3. Interaction terms (Time*variable) and time variable (in bold) correspond to annual decline eGFR rate of the respective variable.

also an eGFR above 60 ml/min/1.73 m^2 for all RKV/W values in full cohort (Fig. 3 *top left*).

Being overconcerned with the target eGFR < 60 ml/min/1.73 m^2 after donation, without taking into account other factors could have unintended and detrimental consequences in selecting transplant candidates. In fact, there has been considerable debate over whether it is justifiable to consider or not healthy kidney donors with isolated eGFR values below 60 ml/min/1.73 m^2 as having chronic kidney disease (CKD) or vice versa [14,16,26]. Considering this, in our cohort, we showed that having predonation eGFR < 90 ml/min/1.73 m^2 is associated with a stronger trend towards an eGFR 1 year after donation < 60 ml/min/1.73 m^2, particularly in male donors with a ratio of RKV/W bellow 2.51 cm^2/kg (Fig. 3 *top right*). These findings allow us to safely propose donors with lower predonation eGFR, particularly when RKV/W is above 2,51cm^2/kg. This variable offers an added value to predonation eGFR improving the prediction of postdonation eGFR.

Given the 4 years follow-up of this cohort, we noted a distinct evolution in eGFR after 1 year of donation between T1 and T2, T3. The homogenous population we saw during the first year postdonation acquired a different behavior after the first year, in which T1 had a steady renal function decline (approximately −0.5 ml/min/1.73 m^2 each year) whereas the population of the second tertile experienced an improvement in function every year with a median yearly improvement of function of 1.6 ml/min/1.73 m^2 (Fig. 4 *left*). Although T1 donors experience a decline, it is still less marked than physiological decline with aging described in literature [27] underlining the steady and continuous process associated with remaining kidney adaptation and function recovery [3]. Differently, we observed that predonation eGFR was not significantly associated with eGFR decline after 1 year, emphasizing the added value that RKV/W may have in the prediction of postdonation eGFR trend beyond the first year, in contrast with predonation eGFR.

Comparing characteristics between tertiles, we found that T1 individuals had a significantly lower RKW when compared with T2 (138.8 ± 22.2 vs 158.2 ± 24.2cm^2, $P < 0{,}001$) while there was no difference between T2 and T3 regarding RKV (Table 1). Predonation SCr-

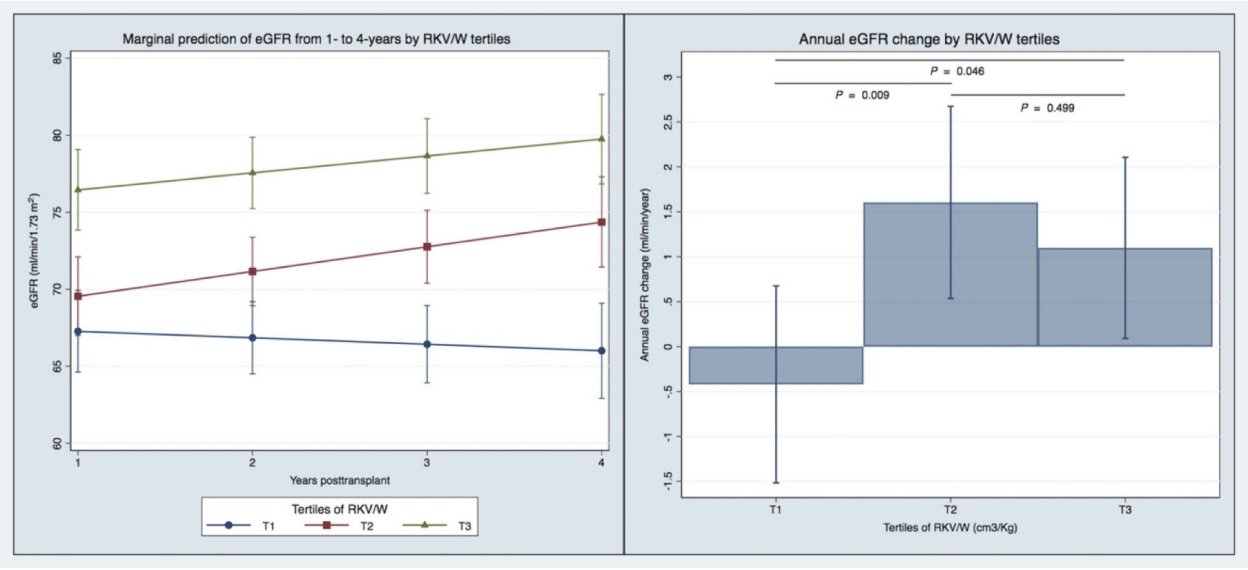

Figure 4 Change in donors eGFR from 1 to 4 years postdonation. *Left*, marginal mean prediction of eGFR at 1 to 4 years by RKV/W tertiles. *Right*, annual eGFR change by RKV/W tertiles.

based eGFR did not correlate with 4 years renal function when compared T1 vs T2 (P = 0,277) opposing the strong correlation found of predonation eGFR and short-term (1 year) renal function. In the same line, the predonation eGFR, determined through the serum CysC, was significantly higher in T1 when compared with the two other groups (0.74 vs 0.67 mg/l, P = 0.032) (Table 1). Even though the Cys measurements were not available in full cohort, the findings were equivalent when studied the population where we had the CysC data (Table S2 and Table S3). These findings could contribute for growing our knowledge because predonation eGFR seems to have a good correlation with first-year eGFR but this correlation is lost considering the first two tertiles from first to fourth year after donation. In this pool of donors (T1 and T2), CysC-based eGFR appeared as an useful tool to understand the differences between this population. Estimate GFR, measured by cystatin C, might be a better predictor of an eGFR improvement from the first year after donation associated with RKV/W when compared with SCr-based eGFR.

The current study has some important limitations. Though we controlled for important demographic factors and baseline eGFR, the retrospective, observational nature of the study design makes residual confounding factors plausible. The nature of this cohort, which is composed by young, very healthy donors may be not applicable when we are facing expanded criteria living donors. Additionally, data on postdonation albuminuria emergence and hypertension were not available for our analysis.

RKV/W was a potent predictor of both linear eGFR at 1 year, independently from predonation eGFR. Overall, a higher RKV/W was associated with improved eGFR at 1 year, although eGFR at 1 year plateaued around 65–70 ml/min in donors with RKV/W < 2.25 cm^3/kg. Importantly, a decline in eGFR after the first year was only noticeable in donors in the T1. Gender, RKV/W measured by CT scan and predonation eGFR were the three strongest predictors of worse renal function after donation. Regarding long-term eGFR, predonation SCr-based eGFR did not correlate with renal function after first year and donors with better predonation serum CysC-based eGFR seems to experience a continuous recovery of its renal function along the 4 years following the donation.

This information poses an important role during evaluation of potential donors, and it could predict the risk factors associated with lower postdonation eGFR. Furthermore, all this data will allow donors to give more conscious consent and provide clinicians more knowledge about the risks associated with living donation.

Authorship

DN-C: involved in research design, acquisition of the data, data analysis, and paper writing. MM and MS-R: performed research design and paper writing. FS, NP, CR, DG-S, LM, MA, and LD: involved in acquisition of

the data and data analysis. JM: involved in research design, acquisition of the data, data analysis, and paper writing. VC: performed research design, data analysis, and paper writing. AC-H and AF: involved in research design and data analysis.

Funding

No founding was received.

Conflict of interest

The authors declare no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Univariate predictors of eGFR 1-year by linear regression.

Table S2 Baseline characteristics by RKV/W tertiles, considering only donors with available pre-donation serum Cystatin C.

Table S3 Annual eGFR change (ml/min/year) from 1- to 4-years post-donation by linear mixed regression, considering only donors with available pre-donation serum Cystatin C (n = 133).

REFERENCES

1. Shinoda K, Morita S, Akita H, *et al*. Pre-donation BMI and preserved kidney volume can predict the cohort with unfavorable renal functional compensation at 1-year after kidney donation. *BMC Nephrol. BMC Nephrology* 2019; **20**: 1.
2. Najarian J. 20 years or more of follow-up of living kidney donors. *Lancet* 1992; **340**: 807.
3. Chung JS, Son NH, Byun S-S, *et al*. Trends in renal function after radical nephrectomy: a multicentre analysis. *BJU Int*. 2014; **113**: 408.
4. Kawamura N, Yokoyama M, Fujii Y, *et al*. Recovery of renal function after radical nephrectomy and risk factors for postoperative severe renal impairment: A Japanese multicenter longitudinal study. *Int J Urol* 2016; **23**: 219.
5. Grams ME, Sang Y, Levey AS, *et al*. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. *N Engl J Med* 2016; **374**: 411.
6. Shaffi K, Uhlig K, Perrone RD, *et al*. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. *Am J Kidney Dis* 2014; **63**: 1007.
7. Stevens LA, Schmid CH, Greene T, *et al*. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. *Am J Kidney Dis* 2010; **56**: 486.
8. Gaillard F, Legendre C, White CA. GFR Assessment of Living Kidney Donors Candidates. *Transplantation* 2019; **103**: 1.
9. Yanishi M, Kinoshita H, Yoshida T, *et al*. Comparison of live donor pre-transplant and recipient post-transplant renal volumes. *Clin Transplant* 2016; **30**: 613.
10. Dias J, Malheiro J, Almeida M, *et al*. CT-based renal volume and graft function after living-donor kidney transplantation: Is there a volume threshold to avoid? *Int Urol Nephrol* 2015; **47**: 851.
11. Yano M, Lin MF, Hoffman KA, Vijayan A, Pilgram TK, Narra VR. Renal Measurements on CT Angiograms: Correlation with Graft Function at Living Donor Renal Transplantation. *Radiology* 2012; **265**: 151.
12. Hugen CM, Polcari AJ, Farooq AV, Fitzgerald MP, Holt DR, Milner JE. Size Does Matter: Donor Renal Volume Predicts Recipient Function Following Live Donor Renal Transplantation. *J Urol* 2011; **185**: 605.
13. Huh KH, Yun M, Kim TS, *et al*. Measurement of Donor Kidney Functional Renal Volume and Glomerular Filtration Rate to Predict Allograft Function during the Post-Transplantation Period. *Nephron Clin Pract* 2009; **113**: c262.
14. Poggio ED, Hila S, Stephany B, *et al*. Donor kidney volume and outcomes following live donor kidney transplantation. *Am J Transplant* 2006; **6**: 616.
15. Sikora MB, Shaaban A, Beddhu S, *et al*. Effect of donor kidney volume on recipient outcome: does the "dose" matter? *Transplantation* 2012; **94**: 1124.
16. Hall IE, Shaaban A, Wei G, *et al*. Baseline living-donor kidney volume and function associate with 1-year post-nephrectomy kidney function. *Clin Transplant*. 2019; **33**: 1.
17. Hwang HS, Yoon HE, Park JH, *et al*. Noninvasive and direct measures of kidney size in kidney donors. *Am J Kidney Dis* 2011; **58**: 266.
18. Jeon HG, Lee SR, Joo DJ, *et al*. Predictors of kidney volume change and delayed kidney function recovery after donor nephrectomy. *J Urol*. 2010; **184**: 1057.
19. Taner T, Iqbal CW, Textor SC, Stegall MD, Ishitani MB. Compensatory hypertrophy of the remaining kidney in medically complex living kidney donors over the long term. *Transplantation* 2015; **99**: 555.
20. Levey AS, Stevens LA, Schmid CH, *et al*. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009; **150**: 604.
21. Inker LA, Schmid CH, Tighiouart H, *et al*. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med* 2012; **367**: 20.
22. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989; **5**: 303.
23. Coruh AG, Uzun C, Akkaya Z, Gulpinar B, Elhan A, Tuzuner A. Is There a Correlation with Pre-donation Kidney Volume and Renal Function in the Renal Transplant Recipient: A Volumetric Computed Tomography Study. *Transplant Proc* 2019; **51**: 2312.
24. Narasimhamurthy M, Smith LM, Machan JT, *et al*. Does size matter? Kidney transplant donor size

determines kidney function among living donors. *Clin Kidney J* 2017; **10**: 116.
25. Keys DO, Jackson S, Berglund D, Matas AJ. Kidney donor outcomes ≥ 50 years after donation. *Clin Transplant.* 2019; **33**: e12657.
26. Srinivas TR, Poggio ED. Do Living Kidney Donors Have CKD? *Adv Chronic Kidney Dis.* 2012; **19**: 229.
27. Glassock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. *Trans Am Clin Climatol Assoc* 2019; **120**: 419.