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ORIGINAL ARTICLE

# Renal volume assessed by magnetic resonance imaging volumetry correlates with renal function in living kidney donors pre- and postdonation: a retrospective cohort study

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## SUMMARY

Renal function of potential living kidney donors is routinely assessed with scintigraphy. Kidney anatomy is evaluated by imaging techniques such as magnetic resonance imaging (MRI). We evaluated if a MRI-based renal volumetry is a good predictor of kidney function pre- and postdonation. We retrospectively analyzed the renal volume (RV) in a MRI of 100 living kidney donors. RV was correlated with the tubular excretion rate (TER) of MAG3-scintigraphy, a measured creatinine clearance (CrCl), and the estimated glomerular filtration rate (eGFR) by Cockcroft-Gault (CG), CKD-EPI, and modification of diet in renal disease (MDRD) formula pre- and postdonation during a follow-up of 3 years. RV correlated significantly with the TER (total: $r = 0.6735$, $P < 0.0001$). Correlation between RV and renal function was the highest for eGFR by CG ($r = 0.5595$, $P < 0.0001$), in comparison with CrCl, MDRD-GFR, and CKD-EPI-GFR predonation. RV significantly correlated with CG-GFR postdonation and predicted CG-GFR until 3 years after donation. MRI renal volumetry might be an alternative technique for the evaluation of split renal function and prediction of renal function postdonation in living kidney donors.

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## Introduction

Renal transplantation is the therapy of choice in patients with end-stage renal disease (ESRD). It offers a better quality of life and significant survival benefit in comparison with other modalities of renal replacement therapy [1]. Transplantation after living kidney donation provides a better graft and patient outcome as compared to transplantation of deceased donor kidneys and is a valuable source to increase the donor pool [2].

Living kidney donation requires that healthy individuals undergo major surgery with no health benefit to themselves. Kidney donation inevitably leads to reduced renal function and recent evidence suggests that living kidney donors are at an increased risk of ESRD [3–5]. Predicting which donor will have renal dysfunction after donation remains challenging, particularly in those with no clinical evidence of disease at time of donation. An extensive donor assessment is therefore obligatory to ensure a safe procedure for the donor, to minimize the risk of ESRD after donation and guarantee a good organ quality for the recipient.

Investigations of the potential donor include a number of imaging techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) to evaluate the kidney anatomy, number and size of the renal arteries and veins and to exclude renal masses and calculi [6–8]. Renal function is evaluated by measurement of inulin clearance or equivalent nuclear methods such as nuclear GFR by $^{51}$Cr-ethylenediamine tetra acetic acid ($^{51}$Cr-EDTA), the endogeneous 24-h urine creatinine clearance (CrCl) and/or the estimations of glomerular filtration rate (eGFR) using Cockcroft-Gault (CG), chronic kidney disease epidemiology collaboration (CKD-EPI) and modification of diet in renal disease (MDRD) formula. The $^{99m}$Tc-labelled mercapto-acetyltriglycin (MAG3) scintigraphy is used to assess split renal function (SRF) [9–11] to ensure that the donor is left with the better functioning kidney if any disparity exists. Nuclear renal scintigraphy is widespread used, but has several limitations including exposure to radioisotopes.

Recent studies in living kidney donors showed that the single renal function can be evaluated preoperatively by CT-based analyses of the kidney volume [12–14]. The studies have shown a high concordance with nuclear renal scintigraphy suggesting that a comprehensive evaluation of living donor candidates is feasible using solely CT. However, CT has been associated with the risk of contrast exposure (contrast nephropathy), as well as the risk of radiation-induced malignancy [15]. Analysis of kidney volume, based on the predonation MRI, is a noninvasive and nonradiant alternative to assess renal volume.

The aim of this study was to assess if a predonation MRI-based volumetric assessment of the kidney volume can predict postdonation kidney function in living kidney donors within a follow-up of 3 years.

## Methods

### Study design and patients

We conducted a retrospective cohort study including 100 living kidney donors who donated a kidney between 2010 and 2014. Electronic charts of all patients were evaluated. All subjects were assessed by MAG3-scintigraphy and MRI imaging as standard of care evaluation before donation. Renal function was assessed by measurement of endogenous 24-h urine CrCl predonation. Estimated GFR was calculated using the CG [16], CKD-EPI [17], and MDRD [18] formula pre- and postdonation. Postdonation follow-up included a clinic visit and testing of kidney function at 14 days, 1, 2, and 3 years after donation.

### MAG3-scintigraphy

Renal scintigraphy was performed with 100 MBq $^{99m}$Tc-labelled MAG3 on a single head gamma camera (Signature; Siemens, Erlangen, Germany) equipped with a low-energy, high-resolution collimator. TER was assessed from measured activity concentrations in plasma samples corrected for the body surface according to the single sample method introduced by Bubeck *et al.* [10] Clearance values deduced from samples taken after 20 and 30 min after the $^{99m}$Tc-MAG3 administration were averaged to minimize errors [9]. Regions of interest (ROI) were drawn for each kidney and for a corresponding background, positioned just outside the kidney lower pole or between the kidneys, and real-time activity curves with subtracted background activity were generated for both kidneys. The functional distribution between the two kidneys (the split function) was estimated as relative activity content in the interval of 60–120 s from the injection. A difference of greater than 5% between both sides was considered to be of clinical significance.

### MRI volumetry

All patients underwent a standardized MRI protocol including unenhanced and contrast-enhanced sequences.



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The evaluation of the renal volume (RV) was performed semiautomatically using Syngo via (Siemens Healthcare, Erlangen, Germany). First of all, axial T1 fat sat vibe images of the renal parenchymal phase (Slice-Thickness: 2 mm) were uploaded and the outer contour of the kidneys was manually outlined on five to seven slices (red line Fig. 1a). Additionally, the signal intensity of the renal parenchyma as well as of the perirenal tissue was determined by drawing respective lines on the same slices (green line in Fig. 1a for renal parenchyma, not shown for perirenal tissue). The software then was able to automatically register the renal volume (blue line in Fig. 1b). In case of misregistration or renal cysts, a manual correction was performed.

### Statistics

Statistical analyses were performed using Graph Pad Prism® (GraphPad Software Inc., La Jolla, CA, USA). Descriptive statistics (number of cases and percentages for categorical variables, mean ± standard deviation (SD) for metric variables) were used to characterize the study population. Statistical significance was assumed at $P < 0.05$. Pearson's correlation coefficient was used to determine the correlation between quantitative data sets. To investigate differences between two selected groups, t-test was used for metric variables. A linear regression analysis was perfomed using random intercept models with individual intercepts per patient and variance components covariance structure. The relationship of the dependent variables (i) eGFR using the CG and (ii) CKD-EPI formula with the independent variables renal volume of the remaining kidney (remRV), TER of the remaining kidney (remTER), donor age (years) and gender (female versus male), body mass index (BMI), and time point (predonation and 14 days, 1, 2 and 3 years postdonation) was analyzed.

## Results

### Study population

In total, 100 living kidney donors were included in the study. Table 1 shows the characteristics of the study population at the time of donation. The mean age of the studied individuals was 54.96 ± 10.65 years. There were 44 men (44.0%) and 56 women (56.0%). The average BMI was 25.98 ± 3.80 kg/m$^{3.}$

### Renal function predonation

Predonation eGFR was 99.13 ± 28.50 ml/min/1.73 m$^2$, 86.78 ± 17.15 ml/min/1.73 m$^2$ and 87.33 ± 15.10 ml/min/1.73 m$^2$ by CG, MDRD and CKD-EPI formula, respectively. CrCl was 116.11 ± 34.58 ml/min.

The absolute total TER according to the renal MAG3-scintigram was 224.94 ± 39.94 ml/min, the left TER was 116.34 ± 23.57 ml/min and the right TER was 108.60 ± 20.19 ml/min. The TER of the remaining (remTER) kidney was 117.47 ± 22.86 ml/min. The split renal function expressed in percent of the total was 51.66 ± 3.96% (range 42–62%) for the left and 48.34 ± 3.96% (range 38–58%) for the right kidney. The left kidney was found to be dominant in 51 cases (51%). In 29 cases, the total TER was considered equal between both sides. The left kidney was donated in 48 (48%) cases.

### Renal volume analysis

The renal volume estimated following analysis of MRI imaging was analyzed for total (tRV), left (leftRV), right (rightRV), and remaining (remRV) renal volume. The results were as follows:

tRV: 338.50 ± 74.70 cm$^3$ (range 619.78–165.02),

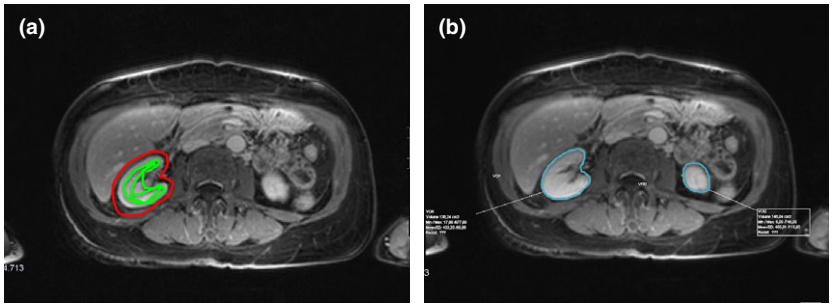


**Figure 1** Volumetric measurement of one patient. (a) First, the outer contour of the kidney was manually outlined (red line). The signal intensity of the renal parenchyma is determined by drawing respective lines on the same slices (green line). (b) The software automatically registered the renal volume (blue line).

**Table 1.** A linear regression analysis of Cockcroft-Gault-estimated GFR and the independent variables remaining renal volume, remaining tubular excretion rate, age, gender, and BMI using random intercept models with individual intercepts per patient and variance components covariance structure.

| | Unadjusted | | | | Adjusted for remTER | | | |
|---|---|---|---|---|---|---|---|---|
| Parameter | Estimate | SE | 95% CI | *P*-value | Estimate | SE | 95% CI | *P*-value |
| Intercept | 77.80 | 12.05 | 54.2–101.42 | <0.0001 | 80.08 | 10.70 | 59.10–101.05 | <0.0001 |
| remTER | 0.02 | 0.05 | −0.08 to 0.13 | 0.6763 | | | | |
| remRV | 0.14 | 0.04 | 0.06–0.21 | 0.0002 | 0.14 | 0.03 | 0.08–0.20 | <0.0001 |
| CreaCl (pre-donation) | 0.02 | 0.03 | −0.04 to 0.08 | 0.4493 | 0.02 | 0.03 | −0.04 to 0.08 | 0.4298 |
| CG-GFR pre-donation | 0 | | | | 0 | | | |
| CG-GFR (14 days) | −34.22 | 1.29 | −36.75 to 31.69 | <0.0001 | −34.22 | 1.29 | −36.75 to 31.69 | <0.0001 |
| CG-GFR (1 year) | −29.25 | 1.29 | −31.77 to 26.72 | <0.0001 | −29.25 | 1.29 | −31.77 to 26.72 | <0.0001 |
| CG-GFR [2 years) | −29.56 | 1.29 | −32.08 to −27.03 | <0.0001 | −29.56 | 1.29 | −32.08 to 27.03 | <0.0001 |
| CG-GFR (3 years) | −29.34 | 1.29 | −31.87 to −26.81 | <0.0001 | −29.34 | 1.29 | −31.87 to 26.81 | <0.0001 |
| Age | −1.08 | 0.10 | −1.27 to 0.88 | <0.0001 | −1.09 | 0.10 | −1.28 to −0.89 | <0.0001 |
| BMI | 1.95 | 0.28 | 1.41–2.50 | <0.0001 | 1.95 | 0.28 | 1.40–2.49 | <0.0001 |
| Gender | 2.59 | 2.25 | −1.82 to 7.00 | 0.2507 | 2.49 | 2.23 | −1.88 to 6.87 | 0.2647 |

CreaCl, creatinine clearance; SE, standard error; 95% CI, 95% confidence interval.

leftRV: 172.98 ± 40.28 $cm^3$ (range 85.11–316.17),
rightRV: 165.51 ± 36.50 $cm^3$ (range 79.91–303.61),
remRV: 171.38 ± 38.06 $cm^3$ (range 85.11–316.17)

The split renal volume expressed in percent of the total volume was 51.03 ± 2.68% (range 44.65–56.71%) for the left and 48.97 ± 2.68% (range 43.29–55.35%) for the right kidney.

There was agreement between the remRV and remTER as to which kidney was dominant in 66 of 100 (66%) cases. A difference of greater than 10% between both techniques, which we consider to be of clinical significance, was only observed in three of 100 (3%) patients.

### Correlation of renal volume and renal function predonation

We first assessed the degree of correlation between kidney volume by MRI volumetry and kidney function by MAG3-scintigraphy (TER). The Pearson correlation coefficient showed that total and remaining renal volume significantly correlated with total TER ($r = 0.6735$, $P < 0.0001$) and remTER ($r = 0.5877$, $P < 0.0001$), respectively (Fig. 2).

Secondly, we examined the accordance of total RV and eGFR as well as measured GFR. eGFR by CG ($r = 0.5595$, $P < 0.0001$) showed the best correlation with tRV predonation, as compared to eGFR by MDRD ($r = 0.3411$, $P = 0.0005$) and CDK-EPI ($r = 0.3319$, $P = 0.0007$) and CrCl ($r = 0.3621$, $P = 0.0002$) (Fig. 3).

### Kidney function postdonation

Postdonation GFR estimated by CG formula significantly decreased (by 34% on average) after donation from 99.13 ± 28.50 ml/min/1.73 $m^2$ before donation to 65.23 ± 17.65 ml/min/1.73 $m^2$ 14 days ($P < 0.0001$) postdonation. Thereafter, it slightly increased to 69.88 ± 19.67 ml/min/1.73 $m^2$ after 1 year ($P < 0.0001$) and remained stable at 2 years (69.56 ± 19.96 ml/min/1.73 $m^2$, $P = 0.7253$) and 3 years (69.78 ± 21.16 ml/min/1.73 $m^2$, $P = 0.8174$). None of the donors developed chronic kidney disease stage 4, 5 or, ESRD during follow-up (Fig. 4).

To determine predicted postdonation CG-GFR from preoperative imaging or nuclear scintigraphy, predonation CG-GFR was multiplied by percentage of remaining renal volume (%remRV) or remaining renal function (% remTER) for each technique. Predicted eGFR was significantly lower (eGFR%remRV: 50.20 ± 14,43 ml/min/1.73 $m^2$ and eGFR%remTER: 51.68 ± 14.84 ml/min/1.73 $m^2$, both $P < 0.0001$) in comparison with the observed postdonation CG-GFR of 65.23 ± 17.65 ml/min/1.73 $m^2$ 14 days after donation suggesting hyperperfusion of the remaining kidney at that early stage.

### Correlation of RV, TER, and renal function postdonation

As shown in Fig. 5, remRV significantly correlated with estimated eGFR by CG formula after 14 days



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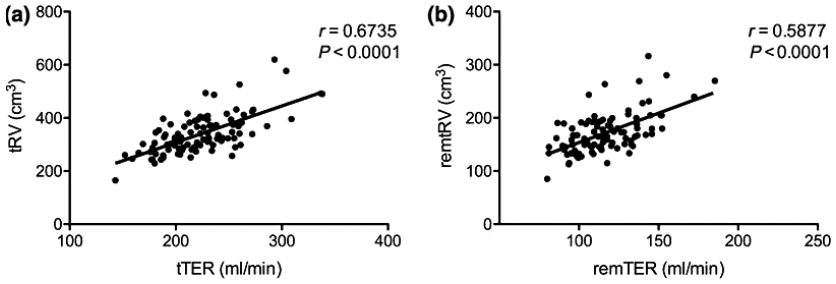


**Figure 2** Correlation of predonation (a) total renal volume and total tubular excretion rate; (b) remaining RV and remaining tubular excretion rate.

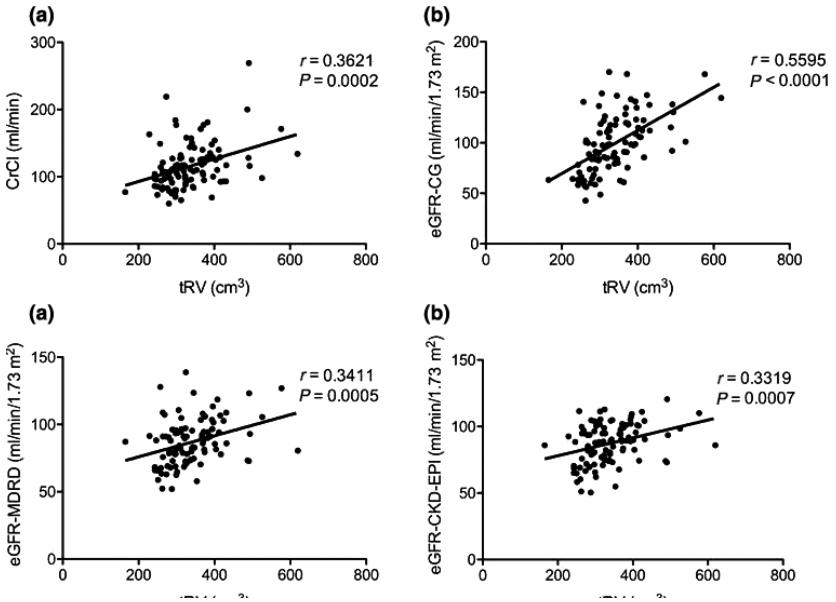


**Figure 3** Correlation of total renal volume and (a) endogenous 24-h urine creatinine clearance; (b) Estimated GFR (eGFR) by Cockcroft-Gault; (c) eGFR by modification of diet in renal disease formula; (d) eGFR by CKD-EPI predonation.

($r = 0.5696$, $P < 0.0001$, $n = 100$), 1 year ($r = 0.5427$, $P < 0.0001$, $n = 100$), 2 years ($r = 0.5185$, $P < 0.0001$, $n = 100$), and 3 years after donation ($r = 0.4804$, $P < 0.0001$, $n = 100$). However, the correlation weakened over time. The remRV did not correlate well with eGFR by CKD-EPI postdonation (14 days, $r = 0.3738$; 1 year $r = 0.2617$; 2 years $r = 0.2443$; 3 years, $r = 0.2091$ after donation).

Moreover, the split TER of the remaining kidney as assessed by predonation MAG3 Clearance correlated with CG-GFR at all four time points (14 days: $r = 0.4378$, $P < 0.0001$, $n = 100$; 1 year: $r = 0.4293$, $P < 0.0001$, $n = 100$; 2 year: $r = 0.4582$, $P < 0.0001$, $n = 100$; 3 years: $r = 0.4346$, $P < 0.0001$, $n = 100$) (Fig. 5).

### Factors predicting renal function postdonation

Predonation renal volume of the remaining kidney was significantly associated with postdonation renal function estimated by CG-GFR ($P = 0.0002$); while no associations were observed between predonation remaining kidney volume and kidney function estimated by MDRD-GFR or CKD-EPI-GFR. Further factors predicting renal function postdonation were donor age ($P < 0.0001$) and BMI ($P < 0.0001$). To our surprise, we did not observe a significant relation of donor gender or measured creatinine clearance predonation with postrenal eGFR estimated by CG or CKD-EPI Table 1.

## Discussion

To our knowledge, this is the first study that has analyzed the relationship between MRI volumetric measurements and postdonation residual renal function in live donors following donor nephrectomy. We demonstrate that MRI volumetric analysis of the remaining kidney correlates with split renal function evaluated by

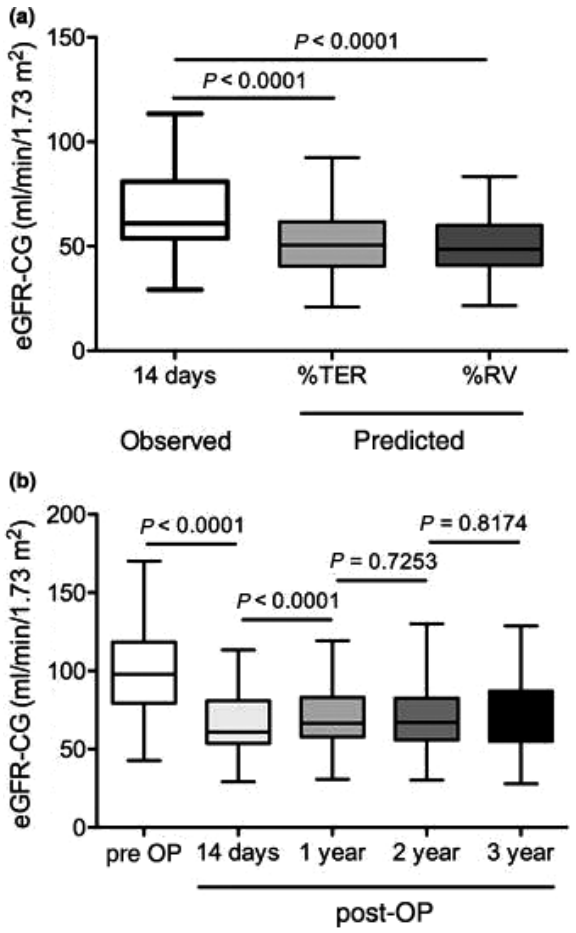


**Figure 4** (a) Difference between observed (Cockcroft-Gault) and predicted estimated GFR (eGFR) at 14 days follow-up. *P*-values are based on the *T*-test. (b) Estimated GFR by Cockcroft-Gault (eGFR-CG) predonation and at 14 days, 1, 2 and 3 years follow-up. *P*-values are based on the *T*-test.

MAG3-scintigraphy ($r = 0.5877$, $P < 0.0001$). Moreover, the remaining renal volume (remRV) correlates with eGFR by CG formula postdonation better than the remaining TER assessed by MAG3-scintigraphy. Using a linear regression model, we observed that remRV significantly predicts CG-GFR during a follow-up of 3 years postdonation. However, the predictive value is less powerful as compared to known factors influencing renal function such as age and BMI.

Kidney donation leads to reduced renal function and is associated with an increased risk of ESRD, as well as cardiovascular and all-cause mortality [4,19]. Therefore, an accurate assessment of split renal function is essential in living kidney donors predonation to decide which kidney can be donated and to ensure sufficient long-term renal function of both, donor and recipient. Analysis of kidney volume, based on the predonation MRI, is a noninvasive method. The routine use of MRI examination for the assessment of kidney vascular and parenchymal anatomy could therefore be an alternative for a renal scintigraphy to assess split renal function. In an ideal donor with normal renal function and anatomy, one would expect a split renal function and split renal volume of 50/50 between the right and left side. Owing the anatomical variations, a distribution between 45% and 55% on either side is considered normal. In the daily clinical use, a distribution of 40/60 or 20% deviation in split renal function by renal scintigraphy is accepted in the context of living kidney donation. Within our patient population, split renal function was 52% (range 42–62%) for the left and 48% (range 38–58%) for the right kidney. The percentage of the MRT volumetric split renal volume was 51% (range 45–57%) for the left and 49% (range 43–55%) for the right kidney. There was agreement between the remRV and the remTER in 66 of 100 (66%) cases. A difference of greater than 10% between both techniques was only observed in three of 100 (3%) patients.

Confirming the data of Wahba *et al.* [14] calculated eGFR by CG, MDRD or CKD-EPI formula compared to 24-h urine CrCl underestimated kidney function in healthy donors. The difference between CG-GFR and CrCl was 16.98 ml, between MDRD-GFR and CrCl was 29.33 ml, and between CKD-EPI-GFR and CrCl was 28.78 ml, respectively. The effect might be due to the fact that measurement of 24-h urine CrCl is influenced by tubular secretion of creatinine [20]. The KDIGO 2012 CKD guidelines recommend a two-stage testing of renal function in potential living kidney donors. Estimated GFR (eGFR) based on serum creatinine is the recommended initial test. In the North America, Europe, and Australia, the 2009 CKD-EPI creatinine equation should be used [21] as it was developed in a large data set in different populations, including renal patients as well as healthy individuals and pursues a better performance in the normal and higher ranges of GFR. In contrast, MDRD and CG equations were derived from populations with reduced GFR [16,18,22]. In our study, eGFR by CG correlated better with renal volume and TER predonation, as compared to MDRD and CKD-EPI or CrCl. Furthermore, CG-GFR significantly correlated with remRV after donation during the 3-year follow-up. The correlation of CG-GFR with remRV was higher than that with remTER demonstrating a superior ability to predict postdonation residual renal function for MRI volumetry as compared to MAG3-scintigraphy. The measurement of the remRV significantly predicted postrenal eGFR assessed by CG but not by CKD-EPI. This might be true to the effect

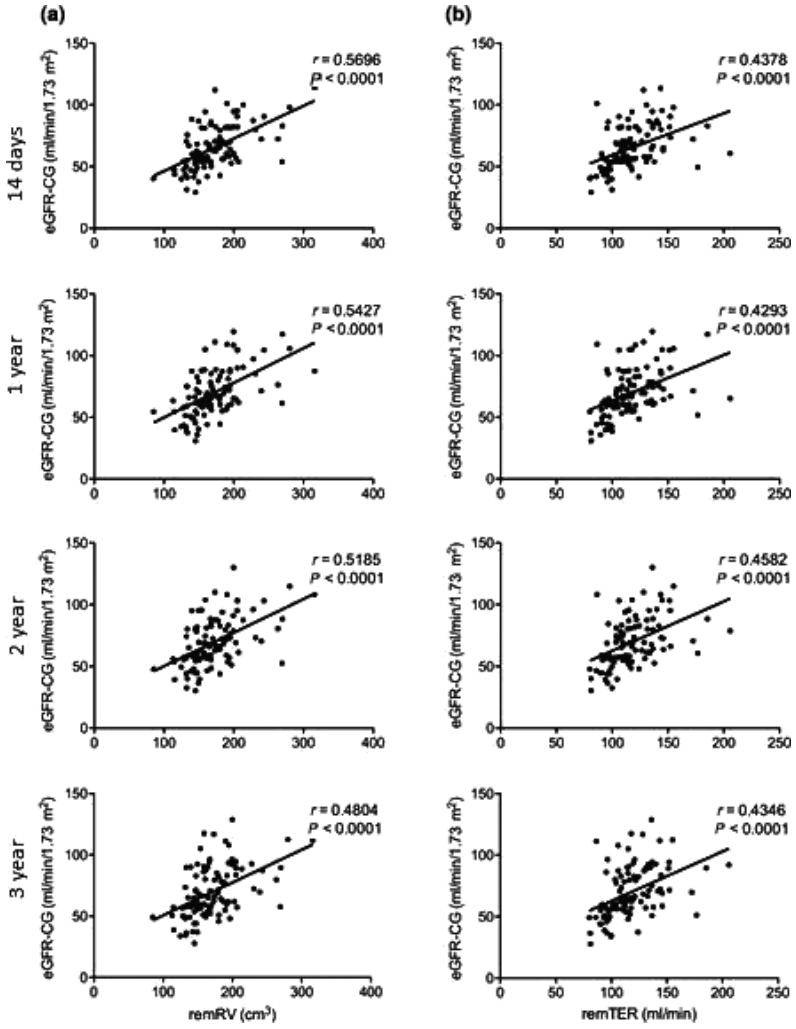


**Figure 5** Correlation of estimated GFR (eGFR) by Cockcroft-Gault (eGFR-CG) predonation and at 14 days, 1, 2, and 3 years with (a) remaining renal volume and (b) remaining tubular excretion rate.

that the removal of one kidney leads to a subsequent reduction in GFR within a range in that the CG-GFR equitation is more precise. In a population of 253 living kidney donors, Tent *et al.* could show that the CG performance significantly improved after donation, while the CKD-EPI performed slightly worse. The bias between measured GFR and estimated GFR was lowest for CG as compared to MDRD and CKD-EPI pre- and postdonation [23].

The correlation of CG-GFR with remRV and remTER decreased over time. This could be related to the improvement of renal function in donors. An increase of 20–34% in GFR after 1 week until 3 months has been reported after kidney donation or nephrectomy due to renal cell carcinoma [24–26]. In our study, eGFR by CG at 1 year was on average 5% higher than mean split eGFR 14 days after donor nephrectomy. However, remRV significantly predicted CG-GFR at all four time points after donation.

Limitations of the study are its relatively small sample size and the retrospective design of the analysis.

The advantage of volumetric measurements by MRI imaging is that it provides high-resolution 3D images without radiation exposure and the need for iodinated contrast agents, which may be nephrotoxic. MRI imaging provides good tissue contrast that facilitates segmentation of the kidney and extraction of volumetric information [27]. However, limitation of MRI imaging is that an inherently noisy method and effects such as patient positioning and field of view selection might influence image quality. Furthermore, the measurement of renal volume by manual contouring as conducted in this study is a time-consuming method and the measurement error is dependent on the number of available MRI slices. A clinical implementation of volumetric measurements requires thorough validation, and one existing cause for concern regarding this methodology is that the repeatability (i.e., test–retest reliability) of individual measurements is still largely unknown.

Based on previous findings and supported by the current findings, prediction of renal function after live

kidney donation might be possible by MRI volumetric analysis. Furthermore, MRI volumetric analysis could be used to asses split renal function in potential live kidney donors.

## Authorship

DL, AH, and AH: participated in research design, analysis, and interpretation of data. AC: analyzed the data and performed the linear regression analysis. DL, AH, and AR: participated in drafting and revising the article. BM, JW, MF and MS: participated in revising the article and provided intellectual content of critical importance to the work described.

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## Conflict of interest

The authors have declared no conflicts of interest.

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