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Estimated glomerular filtration rate for longitudinal follow-up of living kidney donors

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ABSTRACT

Background. Living kidney donor safety requires reliable long-term follow-up of renal function after donation. The current study aimed to define the precision and accuracy of post-donation estimated glomerular filtration rate (eGFR) slopes compared with measured GFR (mGFR) slopes.

Methods. In 349 donors (age 51 ± 10, 54% female), we analysed eGFR according to the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, Modification of Diet in Renal Disease (MDRD) and Cockcroft–Gault/body surface area (CG/BSA), creatinine clearance (CrCl) and mGFR (^{125}I-iothalamate) changes from 3 months until 5 years post-donation.

Results. Donors had a pre-donation mGFR of 116 ± 23 mL/min, at 3 months post-donation mGFR was 73 ± 14 mL/min and at 5 years it was 79 ± 16 mL/min. Between 3 months and 5 years post-donation, 28% of donors had a declining mGFR (−0.82 ± 0.79 mL/min/year), 47% were stable and 25% had an increasing mGFR. Overall, eGFR equations showed good slope estimates (bias $eGFR_{CKD\text{-}EPI}$ 0.13 ± 2.16 mL/min/year, $eGFR_{MDRD}$ 0.19 ± 2.10 mL/min/year, $eGFR_{CG/BSA}$ −0.08 ± 2.06 mL/min/year, CrCl −0.12 ± 4.75 mL/min/year), but in donors with a decreasing mGFR the slope was underestimated (bias $eGFR_{CKD\text{-}EPI}$ 1.41 ± 2.03 mL/min/year, $eGFR_{MDRD}$ 1.51 ± 1.96 mL/min/year, $eGFR_{CG/BSA}$ 1.20 ± 1.87 mL/min/year). The CrCl had a high imprecision [bias interquartile range −1.51–3.41 mL/min/year].

Conclusions. All eGFR equations underestimated GFR slopes in donors with a declining GFR between 3 months and 5 years post-donation. This study underlines the value of mGFR in the follow-up of donors with risk of progressive GFR loss.

Keywords: donor selection, glomerular filtration rate, kidney function, living kidney donation, renal function equations

INTRODUCTION

Due to a persistent donor organ shortage, selection criteria for potential living kidney donors have been liberalized, resulting in a higher proportion of marginal donors with more co-morbidities [1]. This might have an impact on donor outcomes, including accelerated renal function loss. Although the absolute risk for end-stage renal disease (ESRD) after donation is low (0.31–0.47%), the relative risk is high compared with matched controls (11.42–18.99 times) [2, 3].

Accurate follow-up and assessment of kidney function is essential to identify donors at risk for ESRD in a timely manner. Measured glomerular filtration rate (mGFR) using an exogenous marker is considered the optimal method for measuring kidney function [4]. However, its complexity and costs limit the availability of this technique in most centres worldwide. Alternatively, estimated GFR (eGFR) equations, including the Cockroft–Gault (CG), Modification of Diet in Renal Disease (MDRD) and eGFR according to the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, are considered reasonable alternatives [5]. However, eGFR equations that have been designed for and validated in populations with CKD, generally provide an underestimation of mGFR in the higher range [6–11]. Creatinine clearance (CrCl) may also be of use but generally shows a relatively large between-measurement variation [12].

Furthermore, to identify donors at risk for accelerated renal function loss, considering the course of renal function is preferable over a single point estimate [13]. Few studies have evaluated the longitudinal performance of eGFR equations [5, 14–16]. Therefore, the main aim of this study was to evaluate the performance of the most commonly used eGFR equations to detect changes in mGFR, with a particular focus on donors displaying a progressive decline in post-donation GFR.

MATERIALS AND METHODS

Study design

In this prospective cohort study we determined repeated mGFRs and eGFRs in 349 non-black living kidney donors who donated between 1994 and 2012 in the University Medical Center Groningen (Supplementary data, Figure S1). To comply with our donor selection criteria, all donors were normotensive or had an adequately regulated blood pressure with a maximum of two antihypertensive drugs. Furthermore, individuals with a history of diabetes (or an abnormal glucose tolerance test), kidney disease or cardiovascular events were excluded from kidney donation. At ∼4 months before donation and at 3 months, 5 years and 10 years (in a subgroup) after living kidney donation, mGFR was determined as the urinary clearance of ^{125}I-iothalamate [17]. The study was approved by the institutional ethical review board (METc 2014/077). All procedures were conducted in accordance with the Declarations of Helsinki and Istanbul.

Clinical and biochemical measurements

At all data collection visits, height, weight and blood pressure were measured. Serum creatinine (SCr) was measured routinely by enzymatic assay on the Roche Modular (Roche, Mannheim, Germany) from 1 March 2006. Before this date, samples were measured by Jaffé alkaline picrate assay on the Merck Mega Analyzer (Merck, Darmstadt, Germany). Values obtained by the Jaffé method were converted to allow comparison with the Roche method by the formula [$Y^{Roche} = (X^{Jaffé} - 8)/1.07$]. Urinary creatinine was measured from a 24-h urine specimen and CrCl was calculated as

$$\{\text{Urinary creatinine concentration (mg/dL)} \times \text{volume of 24-h urine (mL)}/[\text{urine collection time (min)}]/\text{plasma concentration (mg/dL)}\}.$$

Proteinuria was measured (g/24 h) using routine laboratory measurements from 24-h urine collection.

Renal function measurements

The mGFR was determined using ^{125}I-iothalamate and ^{131}I-hippurate infusion as previously described [18]. Briefly, measurements were with the participant in a semisupine position. After drawing a blood sample, ^{125}I-iothalamate and ^{131}I-hippurate infusions were started (0.04 mL/kg containing 0.04 MBq and 0.03 MBq, respectively). At 08:00 a.m., 0.6 MBq of ^{125}I-iothalamate was administered, followed by continuous infusion of 12 mL/h. After a 2-h stabilization period, baseline measurements were performed in a steady state of plasma tracer levels. Clearances were calculated as (U*V)/P and (I*V)/P, where U*V represents urinary excretion, I*V represents the infusion rate of the tracer and P represents the plasma tracer concentration per clearance period. To reduce the intertest coefficient of variation, we corrected for incomplete bladder emptying and dead space was achieved by multiplying the urinary ^{125}I-iothalamate clearances with plasma and urinary ^{131}I-hippurate clearance, as has been described previously [19]. Day-to-day variability of mGFR is 2.5% [19].

eGFR calculations

We used the abbreviated four-variable MDRD equation, repressed for standardized SCr samples [20]. The CKD-EPI equation was calculated as gender specific and stratified by creatinine levels [21]. The Cockcroft–Gault formula was calculated as [22] $eGFR_{CG} = (140 - age)$*body weight/(72*SCr) (*0.85 if female). The mGFR and $eGFR_{CG}$ were normalized for body surface area (BSA) according to Du Bois and Du Bois [23].

Statistical analysis

Data are reported as mean (standard deviation) for normally distributed variables and median [interquartile range (IQR)] for skewed data. Binary variables are shown as number (%). We investigated accuracy by calculating bias and root mean squared error (RMSE) and investigated precision by calculating the bias spread [mean (IQR)] and R^2 (Supplementary data, Figure S2). Bias for both absolute values (cross-sectional analysis) and slopes (longitudinal analysis) was calculated as eGFR − mGFR or CrCl − mGFR. Differences in bias were tested using a paired *t*-test. mGFR and eGFR/CrCl slopes were calculated as the difference in GFR between two time points divided by the time between these time points. Donors were divided into three groups according to their mGFR slope between 3 months and 5 years after donation: declining (mGFR slope <0 mL/min/year), stable (0–2 mL/min/year) or increasing (>2 mL/min/year). As a sensitivity analysis, we also dichotomized the mGFR slope (mGFR slope <0 mL/min/year and ≥0 mL/min/year). Differences in baseline characteristics per slope category were tested using one-way analysis of variance. We used Deming regression analysis to assess the association between the different eGFR/CrCl and mGFR slopes. Bland–Altman plots and density plots for the bias were used to evaluate the agreement between the slopes of the different formulas and mGFR.

In order to identify the main donor characteristics that determine the post-donation mGFR slope in our cohort, we applied a general linear mixed model using maximum likelihood estimation, with fixed effects for possible correlates and random effects for time. The covariance structure was determined for all possible correlates; ultimately an unstructured covariance matrix was used in the final model. We tested an interaction term between all determinants and time. Skewed variables were natural log transformed for the analyses. Statistical analyses were performed using SPSS version 22 for Windows (IBM, Armonk, NY, USA), R version 3.0.1 (R Project for Statistical Computing, Vienna, Austria), Stata (StataCorp, College Station, TX, USA) and GraphPad Prism 6 for Windows (GraphPad Software, La Jolla, CA, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

We included 349 living kidney donors (mean age at donation 51 ± 10 years, 46% male). The mean pre-donation $mGFR_{BSA}$ was 103 ± 16 mL/min/1.73 m^2 and the mean $mGFR_{BSA}$ at three months post-donation was 66 ± 11 mL/min/1.73 m^2. Other pre- and post-donation characteristics are shown in Table 1. At 5 years after donation, mean $mGFR_{BSA}$ was 69 ± 12 mL/min/1.73 m^2.

Table 1. Clinical characteristics of the living donors before and after donation

Variable	Pre-donation ($n = 349$)	Post-donation		
		3 months ($n = 349$)	5 years ($n = 349$)	10 years ($n = 94$)
Time after donation, years, median (IQR)	N/A	0.2 (0.1–0.2)	5.1 (5.0–5.6)	10.8 (10.1–11.7)
Age, years	51 ± 10	51 ± 10	57 ± 10	61 ± 9
Sex, female, *n* (%)	190 (54)	190 (54)	190 (54)	48 (51)
Height, cm	174 ± 9	174 ± 9	173 ± 9	173 ± 9
Weight, kg	80 ± 14	79 ± 14	82 ± 14	83 ± 17
BSA, m^2	1.94 ± 0.20	1.93 ± 0.19	1.96 ± 0.20	1.97 ± 0.23
BMI, kg/m^2	26 ± 4	26 ± 4	27 ± 4	28 ± 4
Serum creatinine, mg/dL	0.91 ± 0.16	1.27 ± 0.24	1.14 ± 0.22	1.14 ± 0.24
mGFR, mL/min	116 ± 23	73 ± 14	79 ± 16	78 ± 16
$mGFR_{BSA}$, mL/min/1.73 m^2	103 ± 16	66 ± 11	69 ± 12	68 ± 11.1
$eGFR_{CKD\text{-}EPI}$, mL/min/1.73 m^2	85 ± 14	57.7 ± 12	64 ± 13	623 ± 13
$eGFR_{MDRD}$, mL/min/1.73 m^2	83 ± 15	56.1 ± 11	63 ± 11	62 ± 11
$eGFR_{CG/BSA}$, mL/min/1.73 m^2	91 ± 18	64.1 ± 13	69 ± 15	66 ± 14
CrCl, mL/min	122 ± 45	82 ± 26	85 ± 23	88 ± 23
GFR change, mL/min	N/A	−42.6 ± 13.7[a]	5.4 ± 9.0[a]	2.9 ± 12.4[b]
Systolic blood pressure, mmHg	127 ± 14	125 ± 13	127 ± 14	132 ± 15
Diastolic blood pressure, mmHg	76 ± 9	77 ± 8.6	77 ± 9	78 ± 9
Number of antihypertensives, *n* (%)				
0	262 (75)	262 (75)	146 (42)	40 (43)
1	28 (8)	28 (8)	50 (14)	12 (13)
2	12 (3)	14 (4)	17 (5)	5 (5)
3	0 (0)	0 (0)	7 (2)	1 (1)
Unknown	48 (14)	46 (13)	129 (37)	36 (38)
Proteinuria, mg/L	0.09 ± 0.14	0.09 ± 0.13	0.10 ± 0.14	0.12 ± 0.26

Values presented as mean ± SD unless stated otherwise. BMI, body mass index.
[a]From previous measurement.
[b]Between 3 months post-donation and 10-year follow-up.

Creatinine-based eGFR data were available for all donors, whereas CrCl ($n = 267$) data were available in subgroups. In 94 donors, extended follow-up of a median of 11 (IQR 10–12) years post-donation was available, with a mean $mGFR_{BSA}$ of 68 ± 11 mL/min/1.73 m^2 at the end of follow-up.

Cross-sectional analysis

Both before and after donation, eGFR formulas showed an underestimation of the mGFR, with the $eGFR_{CG/BSA}$ having the lowest bias, indicating the best accuracy [pre-donation bias −12.4 ± 18.0 mL/min, post-donation (5 years) mean bias −1.4 ± 10.8 mL/min; Table 2]. For $eGFR_{MDRD}$, bias was significantly higher than for both $eGFR_{CKD\text{-}EPI}$ and $eGFR_{CG/BSA}$ ($P < 0.001$ for all analyses). The RMSE, a different measure of accuracy, was lowest for $eGFR_{CKD\text{-}EPI}$ (pre-donation RMSE 8.59, post-donation RMSE 5.25). The $eGFR_{CKD\text{-}EPI}$ showed the lowest IQR of bias, indicating the highest precision [pre-donation −27.3 to −6.6 mL/min; post-donation −14.0 to −1.9 mL/min; Table 2]. Both before and after donation, the R^2, a measure of model fit, was lowest for the $eGFR_{CKD\text{-}EPI}$ (pre-donation $R^2 = 0.44$, post-donation $R^2 = 0.53$). The CrCl showed an overestimation of renal function before and after donation (pre-donation bias 19 ± 44 mL/min, post-donation bias 17 ± 24 mL/min), with a large RMSE (pre-donation RMSE 12, post-donation RMSE 7.45).

Longitudinal analysis

A total of five (1.4%) living kidney donors in our cohort died with a functioning kidney during follow-up; none of the donors developed ESRD. In the 349 donors with available follow-up at 5 years, the mean mGFR slope was 1.03 ± 1.68 mL/min/1.73 m^2/year (Figure 1). A declining mGFR (slope <0 mL/min/year) was present in 97 donors (28%), a stable mGFR (slope 0–2 mL/min/year) in 164 donors (47%) and an increasing mGFR (slope >2 mL/min/year) in 88 donors (25%). Baseline characteristics of donors by slope of mGFR are given in Table 3. The characteristics of donors with a declining mGFR were not materially different from donors with a stable mGFR, but donors with an increasing mGFR were younger, more often male and had a higher baseline mGFR. At 5 years post-donation, donors with an increasing GFR slope had a significantly higher mGFR (declining 71 ± 14, stable 77 ± 14, increasing 90 ± 16; $P < 0.001$), indicating good 5-year kidney function (Table 4). Five years post-donation, only seven donors (2%) showed proteinuria >0.5 g/day, of which five had an increasing GFR and two a declining GFR. Donor characteristics at 3 months and 10 (subgroup) years after donation are shown in Supplementary data, Tables S1 and S2, respectively.

The $eGFR_{CKD\text{-}EPI}$ provided an accurate estimation of the mGFR slope in donors with a stable or increasing mGFR ($eGFR_{CKD\text{-}EPI}$ bias 0.02 ± 1.64 mL/min/year and −1.07 ± 2.42 mL/min/year, respectively) (Table 5). In these donors, the $eGFR_{MDRD}$ and $eGFR_{CG/BSA}$ displayed a slightly worse estimate, indicating a lower accuracy ($eGFR_{MDRD}$ bias 0.11 ± 1.57 mL/min/year and −1.09 ± 2.26 mL/min/year and $eGFR_{CG/BSA}$ bias −0.23 ± 1.87 mL/min/year and −1.22 ± 2.37 mL/min/year, respectively). However, in donors with a declining mGFR, all eGFR

Table 2. Cross-sectional comparison of pre- and post-donation eGFR with mGFR

Variable	Pre-donation ($n = 349$)	Post-donation		
		3 months ($n = 349$)	5 years ($n = 349$)	10 years ($n = 94$)
mGFR, mL/min	116 ± 23	73 ± 14	79 ± 16	78 ± 16
$mGFR_{BSA}$, mL/min/1.73 m^2	103 ± 16	66 ± 11	69 ± 12	68 ± 11.1
$eGFR_{CKD\text{-}EPI}$				
mL/min/1.73 m^2	85 ± 14	58 ± 12	64 ± 13	63 ± 13
Bias[a], mL/min/1.73 m^2	−17.7 ± 15.6	−7.8 ± 9.9	−5.7 ± 9.5	−6.1 ± 10.1
Bias[a], 25th–75th percentile	−27.3 to −6.6	−14.0 to −1.9	−12.8–0.5	−12.8–0.0
RMSE[b]	8.59	5.25	5.23	5.47
R^2[b]	0.44	0.53	0.62	0.37
$eGFR_{MDRD}$				
mL/min/1.73 m^2	83 ± 15	56 ± 11	62 ± 11	62 ± 11
Bias[a], mL/min/1.73 m^2	−20.1 ± 17.0	−9.4 ± 10.0	−6.9 ± 9.3	−6.4 ± 10.1
Bias[a], 25th–75th percentile	−30.6 to −9.4	−15.6 to −3.8	−12.3–0.9	−13.5 to −1.1
RMSE[b]	9.36	5.31	5.15	5.48
R^2[b]	0.31	0.50	0.52	0.35
$eGFR_{CG/BSA}$				
mL/min/1.73 m^2	91 ± 18	64.1 ± 13	69 ± 15	66 ± 14
Bias[a], mL/min/1.73 m^2	−12.4 ± 18.0	−1.4 ± 10.8	−0.5 ± 11.4	−2.5 ± 10.7
Bias[a], 25th–75th percentile	−24.0 to −2.8	−8.2–4.3	−8.4–6.7	−10.9–6.4
RMSE[b]	9.47	5.42	5.86	5.80
R^2[b]	0.24	0.50	0.52	0.35
CrCl	$n = 267$	$n = 267$	$n = 267$	$n = 56$
mL/min/1.73 m^2	122 ± 45	82 ± 26	85 ± 23	88 ± 23
Bias[a], mL/min/1.73 m^2	19 ± 44	17 ± 24	17 ± 20	21 ± 20
Bias[a], 25th–75th percentile	−2.7–38.4	4.7–28.3	3.8–28.5	9.8–36.1
RMSE[b]	12.15	7.45	7.39	8.08
R^2[b]	0.20	0.36	0.38	0.25

Values presented as mean ± SD.
[a]Bias from $mGFR_{BSA}$.
[b]Calculated from Deming regression line.

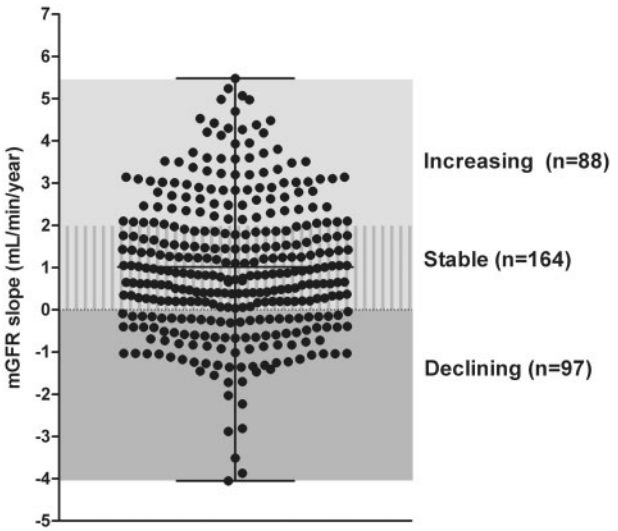

FIGURE 1: Donor mGFR slopes. Between 3 months and 5 years post-donation a declining mGFR (slope <0 mL/min/year) was present in 97 donors (28%), a stable mGFR (slope 0–2 mL/min/year) in 164 donors (47%) and an increasing mGFR (slope >2 mL/min/year) in 88 donors (25%).

equations systematically overestimated the slope (bias $eGFR_{CKD\text{-}EPI}$ 1.41 ± 2.03 mL/min/year, $eGFR_{MDRD}$ 1.51 ± 1.96 mL/min/year, $eGFR_{CG/BSA}$ 1.20 ± 1.87 mL/min/year); accordingly, bias was significantly different by slope category for all equations (all $P < 0.001$). The CrCl slope overall showed a low bias (0.77 ± 4.82 mL/min/year), especially in donors with a declining mGFR (bias −0.07 ± 4.01 mL/min/year) but has a large bias standard deviation and IQR, indicating imprecision (IQR −1.51–3.41]. Figure 2 shows histograms with a density plot of the bias for all formulas. In Figure 3 the relationship between eGFR/CrCl and mGFR slopes is shown using Bland–Altman plots, both for all donors and specifically for the donors with an mGFR decline. The RMSE, an alternative measure of accuracy, was best for $eGFR_{CKD\text{-}EPI}$ and CrCl, the model fit (R^2) was highest for $eGFR_{CG/BSA}$ (Table 5, Figure 4). In the subgroup of donors with extended follow-up, largely similar results were obtained (Supplementary data, Table S2). In a sensitivity analysis, we dichotomized the mGFR slope and found similar results (bias declining versus increasing mGFR, $P < 0.001$ for all equations).

Determinants of the mGFR slope

In univariable regression, the mGFR slope through 5 years post-donation was associated with pre-donation age (st. β −0.23, $P < 0.001$), height (st. β 0.04, $P < 0.001$), weight (st. β 0.10, $P = 0.05$) and SCr (st. β 0.15, $P = 0.004$), but not with pre-donation $mGFR_{BSA}$ (st. β 0.03, $P = 0.61$). Three months post-donation, $mGFR_{BSA}$ was also associated with the mGFR slope (st. β 0.02, $P = 0.004$). None of the pre-donation eGFR equations, nor blood pressure, antihypertensive use or proteinuria were associated with the mGFR slope. In a linear mixed

Table 3. Pre-donation characteristics per subgroup of mGFR slope (3 months–5 years after donation)

Variable	mGFR slope			P-value
	Declining ($n = 97$)	Stable ($n = 164$)	Increasing ($n = 88$)	
Age, years	52 ± 8	52 ± 10	47 ± 12	0.001
Sex, female, *n* (%)	59 (61)	99 (60)	32 (36)	<0.001
Height, cm	172 ± 8	174 ± 10	176 ± 8	0.004
Weight, kg	77 ± 13	79 ± 15	84 ± 13	0.005
BSA, m^2	1.90 ± 0.18	1.93 ± 0.21	2.00 ± 0.17	0.001
BMI, kg/m^2	26 ± 4	26 ± 4	27 ± 4	0.20
Serum creatinine, mg/dL	0.89 ± 0.15	0.89 ± 0.16	0.95 ± 0.16	0.003
mGFR, mL/min	114 ± 20	113 ± 22	122 ± 26	0.01
$mGFR_{BSA}$, mL/min/1.73 m^2	104 ± 15	102 ± 15	105 ± 19	0.17
$eGFR_{CKD\text{-}EPI}$, mL/min/1.73 m^2	85 ± 13	85 ± 14	87 ± 15	0.56
$eGFR_{MDRD}$, mL/min/1.73 m^2	82 ± 14	83 ± 16	84 ± 16	0.87
$eGFR_{CG/BSA}$, mL/min/1.73 m^2	89 ± 16	90 ± 18	94 ± 20	0.22
CrCl, mL/min	117 ± 40	127 ± 50	120 ± 40	0.33
Systolic blood pressure, mmHg	127 ± 13	127 ± 13	128 ± 15	0.80
Diastolic blood pressure, mmHg	76 ± 10	76 ± 8	78 ± 9	0.29
Use of antihypertensives, *n* (%)	11 (11)	16 (10)	13 (15)	0.44
Proteinuria, mg/L	0.09 ± 0.13	0.10 ± 0.15	0.09 ± 0.13	0.86

Values presented as mean ± SD. BMI, body mass index.

Table 4. Donor characteristics 5 years post-donation per subgroup of mGFR slope

Variable	All donors ($n = 349$)	mGFR slope			P-value
		Declining ($n = 97$)	Stable ($n = 164$)	Increasing ($n = 88$)	
Age, years	57 ± 10	58 ± 8	59 ± 10	53 ± 12	<0.001
Sex, female, *n* (%)	190 (54.4)	57 (62.6)	101 (59.4)	32 (36.4)	<0.001
Height, cm	173 ± 9	171 ± 9	173 ± 10	176 ± 9	0.003
Weight, kg	82 ± 14	79 ± 14	82 ± 15	87 ± 13	0.001
BSA, m^2	1.96 ± 0.20	1.91 ± 0.19	1.95 ± 0.21	2.03 ± 0.17	<0.001
BMI, kg/m^2	27 ± 4	27 ± 4	27 ± 4	28 ± 4	0.13
Serum creatinine, mg/dL	1.14 ± 0.22	1.15 ± 0.23	1.13 ± 0.21	1.13 ± 0.23	0.82
mGFR, mL/min	79 ± 16	71 ± 14	77 ± 14	90 ± 16	<0.001
$mGFR_{BSA}$, mL/min/1.73 m^2	69 ± 12	64 ± 11	68 ± 10	77 ± 12	<0.001
$eGFR_{CKD\text{-}EPI}$, mL/min/1.73 m^2	64 ± 13	61 ± 11	62 ± 11	70 ± 16	<0.001
$eGFR_{MDRD}$, mL/min/1.73 m^2	63 ± 11	60 ± 10	61 ± 10	68 ± 13	<0.001
$eGFR_{CG/BSA}$, mL/min/1.73 m^2	69 ± 15	65 ± 12	67 ± 14	77 ± 19	<0.001
CrCl, mL/min	85 ± 23	80 ± 20	84 ± 23	95 ± 26	<0.001
Systolic blood pressure, mmHg	127 ± 14	126 ± 14	129 ± 14	127 ± 14	0.21
Diastolic blood pressure, mmHg	77 ± 9	76 ± 10	77 ± 8	78 ± 10	0.23
Use of antihypertensives, *n* (%)	56 (16)	16 (17)	24 (15)	16 (18)	0.58
Proteinuria, mg/L	0.10 ± 0.14	0.08 ± 0.11	0.10 ± 0.14	0.12 ± 0.15	0.33
Proteinuria ≥0.5 g/day, *n* (%)	7 (2.0)	2 (2.4)	4 (2.4)	1 (1.3)	0.65

Values presented as mean ± SD. BMI, body mass index.

model using all available mGFR measurements we show that donor age is a significant predictor of GFR slope (Table 6), with a more negative slope in older donors. Also, the renal function estimates by the three eGFR formulas at baseline were predictors of the mGFR slope.

DISCUSSION

In this study we show that creatinine-based eGFR formulas or CrCl are unable to precisely detect renal function decline in living kidney donors. While, in general, eGFR equations provide an underestimation of the mGFR, all formulas fail to detect mGFR changes in donors with a progressively declining mGFR. The CrCl had a good estimate of the slope, but was very imprecise.

Over the past decade, liberalization of selection criteria has resulted in a growing contribution of older donors with more comorbidities to the living donor pool [1]. Several studies identified donor age as a major determinant of post-donation renal function [3, 24, 25], in line with our data revealing donor age as the main correlate of the mGFR slope. Together, these data underline the need for accurate and precise follow-up of renal function after nephrectomy, especially aimed at detection of renal function loss. We show that creatinine-based eGFR formulas and the CrCl do not fulfill this need, since all these

Table 5. Longitudinal comparison of eGFR slope with mGFR slope

Variable	Overall	mGFR slope			P-value[b]
		Declining ($n = 97$)	Stable ($n = 164$)	Increasing ($n = 88$)	
mGFR slope, mL/min/year	1.03 ± 1.68	−0.82 ± 0.79	0.93 ± 0.55	3.25 ± 1.09	<0.001
$eGFR_{CKD\text{-}EPI}$					
Slope, mL/min/1.73 m^2/year	1.16 ± 1.95	0.59 ± 1.88	0.95 ± 1.59	2.18 ± 2.25	<0.001
Bias, mL/min	0.13 ± 2.16	1.41 ± 2.03	0.02 ± 1.64	−1.07 ± 2.42	<0.001
Bias, 25th–75th percentile	−1.14–1.27	0.17–2.64	−1.13–0.90	−2.33 to −0.07	
RMSE[a]	1.30	1.60	0.83	1.86	
R^{2a}	0.14	N/A	N/A	N/A	
Slope according to eGFR, *n* (%)					
Declining	N/A	40 (41)	41 (25)	14 (16)	
Stable	N/A	38 (39)	84 (51)	28 (32)	
Increasing	N/A	19 (20)	39 (24)	46 (52)	
$eGFR_{MDRD}$					
Slope, mL/min/1.73 m^2/year	1.22 ± 1.83	0.69 ± 1.80	1.04 ± 1.52	2.16 ± 2.06	<0.001
Bias, mL/min	0.19 ± 2.10	1.51 ± 1.96	0.11 ± 1.57	−1.09 ± 2.26	<0.001
Bias, 25th–75th percentile	−0.98–1.35	0.36–2.76	−0.95–0.96	−2.26–0.03	
RMSE[a]	1.36	1.66	0.91	1.88	
R^{2a}	0.16	N/A	N/A	N/A	
Slope according to eGFR, *n* (%)					
Declining	N/A	36 (37)	32 (20)	13 (15)	
Stable	N/A	41 (42)	93 (57)	32 (36)	
Increasing	N/A	20 (21)	39 (24)	43 (49)	
$eGFR_{CG/BSA}$					
Slope, mL/min/1.73 m^2/year	0.95 ± 1.90	0.38 ± 1.73	0.70 ± 1.50	2.04 ± 2.28	<0.001
Bias, mL/min	−0.08 ± 2.06	1.20 ± 1.87	−0.23 ± 1.53	−1.22 ± 2.37	<0.001
Bias, 25th–75th percentile	−1.14–1.04	0.11–2.58	−1.06–0.69	−2.63 to −0.16	
RMSE[a]	1.32	1.61	0.86	1.88	
R^{2a}	0.20	N/A	N/A	N/A	
Slope according to eGFR, *n* (%)					
Declining	N/A	44 (45)	48 (29)	15 (17)	
Stable	N/A	35 (36)	87 (53)	34 (39)	
Increasing	N/A	18 (19)	29 (18)	39 (44)	
CrCl	$n = 267$	$n = 80$	$n = 129$	$n = 58$	
Slope, mL/min/1.73 m^2	0.77 ± 4.82	−0.07 ± 4.01	0.78 ± 4.01	1.92 ± 6.84	0.06
Bias, mL/min	−0.12 ± 4.75	0.74 ± 4.17	−0.12 ± 3.99	−1.30 ± 6.55	0.04
Bias, 25th–75th percentile	−2.54–2.15	−1.51–3.41	−2.26–2.05	−4.75 to −1.30	
RMSE[a]	1.23	0.53	0.48	0.85	
R^{2a}	0.31	N/A	N/A	N/A	
Slope according eGFR, *n* (%)					
Declining	N/A	38 (48)	52 (40)	22 (38)	
Stable	N/A	21 (26)	29 (23)	9 (16)	
Increasing	N/A	21 (26)	48 (37)	27 (47)	

Values presented as mean ± SD unless stated otherwise.
[a]Calculated from Deming regression (Figure 4).
[b]One-way analysis of variance for difference between three slope categories.

measures fail to adequately detect donors with progressive renal function loss. The eGFR formulas, and particularly the $eGFR_{MDRD}$ formula, show poor accuracy in donors with mGFR decline. The best formulas were the $eGFR_{CG/BSA}$ and the $eGFR_{CKD\text{-}EPI}$. CrCl, often used in living donor screening, was better able to estimate mGFR, but cannot be used alone due to its poor precision. Our findings are in line with prior studies on the longitudinal use of eGFR equations in other patient groups, including patients with diabetes and CKD [14, 15, 16, 26, 27], that show poor accuracy and underestimation of progressive renal function loss with eGFR equations. Previous studies on the use of eGFR in live kidney donors had a cross-sectional nature [6–11] and were in line with our current results. While eGFR slopes have been investigated in CKD [27], we are the first to evaluate the performance of eGFR in longitudinal follow-up of living kidney donors. Living kidney donors also have a lower GFR than non-donors but generally do not have CKD [28].

After kidney donation, vasodilatation occurs and renal reserve capacity is used to adapt to the single-kidney state [29], resulting in a single-kidney GFR of ∼66% of the prior two-kidney state instead of ∼50% of the two-kidney state [30]. This compensatory increase in GFR can persist for up to 15 years after donation [31]. Our findings are in line with this concept, since 252 (72%) donors had a positive mGFR slope. Donors with a positive mGFR slope were younger, more often male and had a higher baseline mGFR, as well as a higher mGFR 5 years post-donation, and they had no proteinuria. This is indicative of a

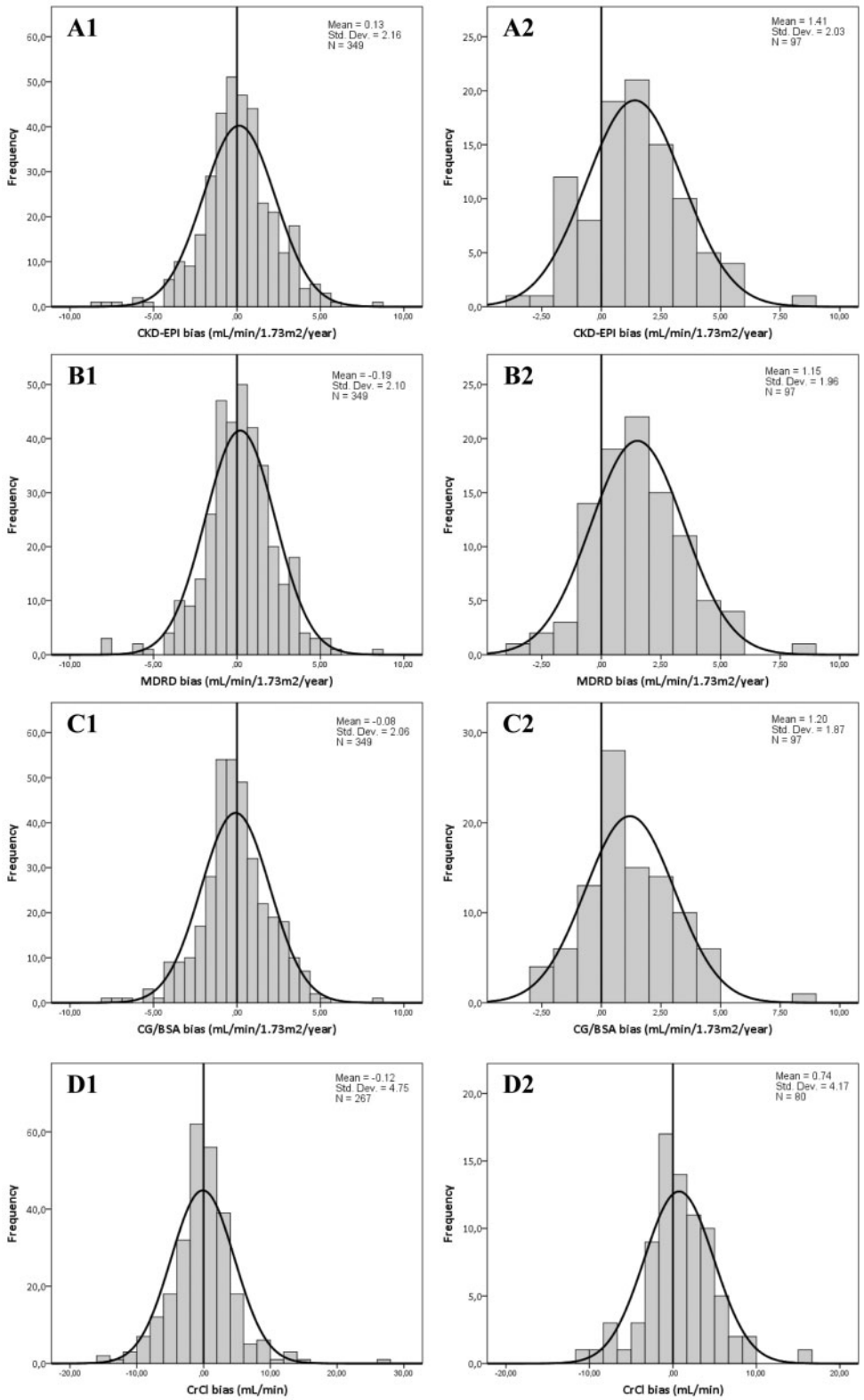

FIGURE 2: Bias distribution plot of eGFR formula and CrCl slopes. Bias distribution plots of (**A1**) $eGFR_{CKD\text{-}EPI}$, (**B1**) $eGFR_{MDRD}$, (**C1**) $eGFR_{CG/BSA}$ and (**D1**) CrCl in all donors and (**A2**) $eGFR_{CKD\text{-}EPI}$, (**B2**) $eGFR_{MDRD}$, (**C2**) $eGFR_{CG/BSA}$ and (**D2**) CrCl in donors with a declining mGFR.

'benign adaptive hyperfiltration' after living kidney donation, which has been described previously [32, 33] but has to be substantiated by longer follow-up. eGFR performed relatively well in these donors, with the $eGFR_{CKD\text{-}EPI}$ showing the lowest bias. However, 97 (28%) donors showed a declining GFR per year and 32 (9%) donors showed a decline of >0.96 mL/min/1.73 m^2, the average GFR decline with age [34]. We found that progressive renal function decline was associated with older age,

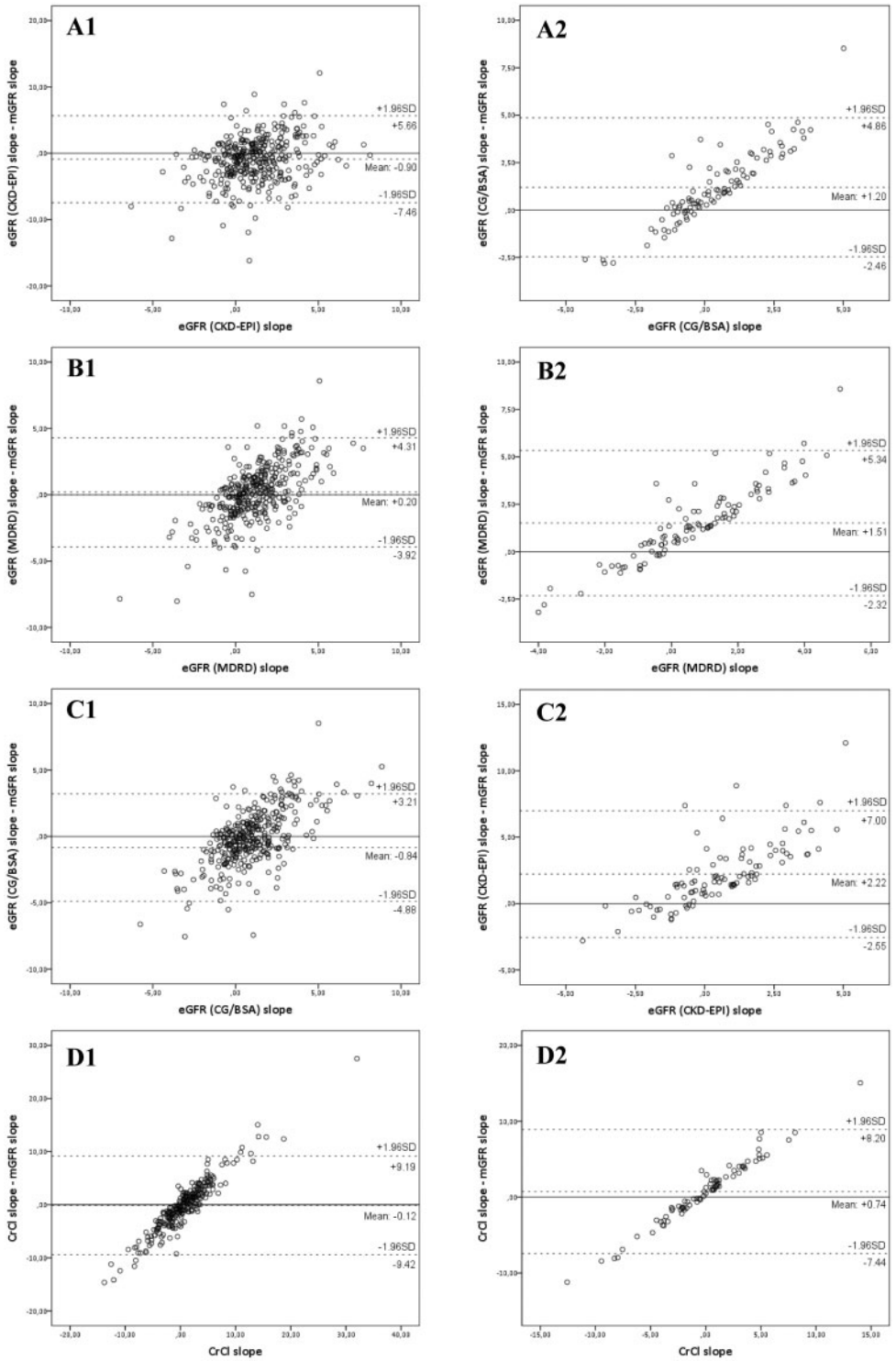

FIGURE 3: Bland–Altman plots of eGFR formula and CrCl slopes. Bland–Altman plots of (**A1**) $eGFR_{CKD\text{-}EPI}$, (**B1**) $eGFR_{MDRD}$, (**C1**) $eGFR_{CG/BSA}$ and (**D1**) CrCl in all donors and (**A2**) $eGFR_{CKD\text{-}EPI}$, (**B2**) $eGFR_{MDRD}$, (**C2**) $eGFR_{CG/BSA}$ and (**D2**) CrCl in donors with a declining mGFR.

implying that follow-up may be especially important in older donors. We found no association with proteinuria, which may be explained by the low levels of proteinuria in donors. Also, the GFR slope was not associated with hypertension, which is in line with previous studies [35, 36] and may be explained by the practice in which only low-risk hypertensive donor candidates are accepted.

Limitations of this study were that the cohort of donors mainly consisted of Caucasians, while black and Asian Indian donors have an increased ESRD risk [12, 37]. The implications of our study for non-white donors are unclear and require investigation in a separate study. Second, the duration of follow-up was moderate for the full cohort (5 years), with long-term follow-up available for a subgroup and a limited number of

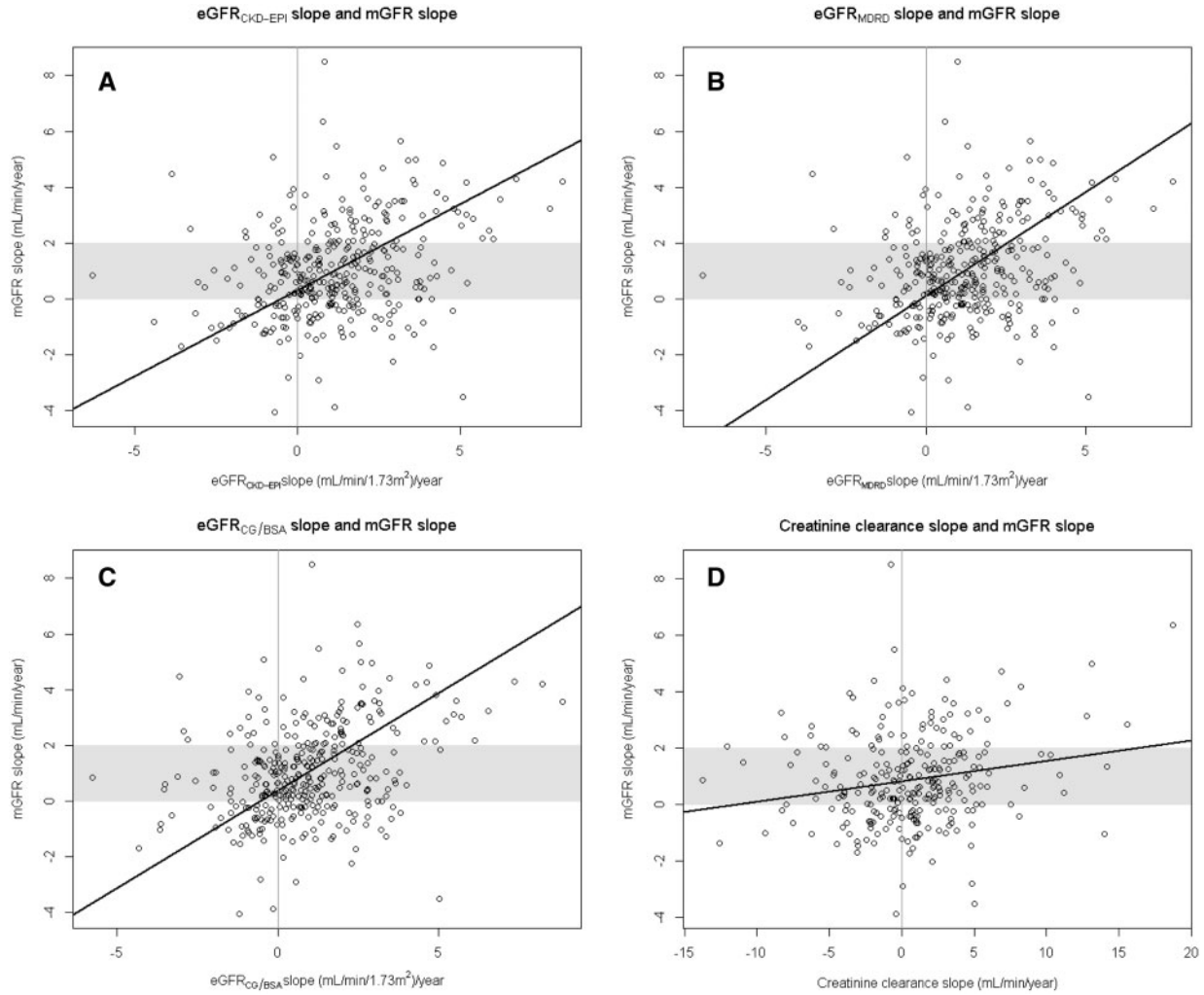

FIGURE 4: Deming regression plots of eGFR formula slopes. Scatterplots with Deming regression analysis line of **(A)** eGFR$_{CKD-EPI}$, **(B)** eGFR$_{MDRD}$, **(C)** eGFR$_{CG/BSA}$ and **(D)** CrCl with the 'stable' mGFR slope category marked in gray.

Table 6. Linear mixed models for pre-donation determinants of mGFR slope after donation

Variable	Estimate of variable			Interaction with time		
	Coefficient (mL/min)	95% CI	P-value	Coefficient (mL/min*year)	95% CI	P-value
Time	0.53	0.38–0.67	<0.001	NA	NA	NA
Age[a]	−0.67	−0.80 to −0.55	<0.001	−0.03	−0.04 to −0.01	<0.001
Sex[a]	10.53	7.76–13.30	<0.001	0.18	−0.12–0.47	0.24
Height[a]	0.78	0.64–0.92	<0.001	0.01	−0.003–0.03	0.10
Weight[a]	0.51	0.42–0.60	<0.001	0.004	−0.01–0.01	0.43
SBP[a]	−0.12	−0.22 to −0.01	0.0400	−0.01	−0.02–0.005	0.24
mGFR[a]	0.52	0.48–0.55	<0.001	0.003	−0.004–0.1	0.37
eGFR$_{CKD-EPI}$[a]	0.45	0.36–0.55	<0.001	0.01	0.003–0.2	0.01
eGFR$_{MDRD}$[a]	0.18	0.29–0.47	<0.001	0.01	0.001–0.02	0.03
eGFR$_{CG/BSA}$[a]	0.46	0.39–0.53	<0.001	0.01	0.003–0.02	0.006
CrCl[a]	0.43	0.10–0.17	<0.001	<0.001	−0.003–0.004	0.89

CI, confidence interval; SPB, systolic blood pressure.
[a]Variables were added to a linear mixed model (maximum likelihood estimation) with a fixed and random effect for time and unstructured covariance matrix. In all models, interactions with time were also calculated.

repeated measurements per donor. While this reduces the accuracy of the slope measurements, the intertest variation for our method of measuring GFR is <3% and standard error is <6 mL/min/year [19], minimizing the error of the slope. Given the compensatory increase in GFR during the first years after donation in most donors, the impact of our findings might have been greater after (even more) extended follow-up; this will be addressed in future studies. Still, our current data are in line

with previous cross-sectional studies in donors and longitudinal studies in other populations. The strengths of this study are the prospective study design with repeated mGFR measurements post-donation in a large group of living donors.

Future studies are needed to design more suitable tools to timely detect progressive renal function decline after living kidney donation. A combination of eGFR and repeated measurements of the 24-h CrCl, possibly in the context of a risk prediction tool also considering age and race, could be used as an alternative in centres where mGFR is unavailable. Proteinuria would be an important predictor [38] but is generally low in non-diabetic living kidney donors [39]. Other biomarkers (pro-enkephalin [40], β-trace protein, β_2 microglobulin [41, 42], urea excretion [43], copeptin [44] and CKD273 [45]) require validation as potential tools to predict post-donation renal function.

In conclusion, while creatinine-based eGFR formulas and CrCl had a reasonable overall performance in estimating renal function, they underestimated the slope of renal function in donors with progressive renal function loss (<0 mL/min/year between 3 months and 5 years post-donation), which was present in 28% of donors. Our data imply that eGFR changes should be interpreted with caution in living donors with an expected GFR decline. Particularly in older donors, who are at risk to develop progressive GFR loss, mGFR-based donor follow-up is preferable for timely detection of potential renal function decline.

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AUTHORS' CONTRIBUTIONS

This study was conceived and designed by M.v.L., G.N. and M.H.d.B. Data were acquired by M.v.L., A.B.W., J.d.V., J.-S.S., M.F.C.d.J., R.A.P., S.P.B., G.N., M.H.d.B. M.v.L., A.B.W., J.d.V. and G.N. M.H.d.B analysed and interpreted the data. The tables and figures were prepared by M.v.L., A.B.W. and J.d.V. Drafting of the manuscript and approval of the final version was done by M.v.L., G.N. and M.H.d.B. Critical revision of the manuscript for important intellectual content and approval of the final version was done by M.v.L., A.B.W., J.d.V., J.-S.S., M.F.C.d.J., R.A.P., S.P.B., G.N. and M.H.d.B.

CONFLICT OF INTEREST STATEMENT

R.A.P. reports grants from Astellas and Chiesi during the conduct of the study. The other authors do not have any conflicts of interest to declare. The results presented in this article have not been published previously in whole or part, except in abstract format.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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