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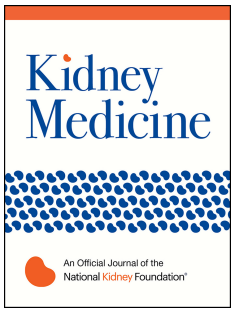

Timed Creatinine Clearance and Measured Glomerular Filtration Rate in Living Kidney Donors

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To the Editor:

Assessment of pre-donation glomerular filtration rate (GFR) is a key aspect of the evaluation of potential living kidney donors. In the United States, measurement of donor GFR is a regulatory requirement and most commonly assessed using 24-hour timed creatinine clearance ($CrCl_{24}$), despite the potential for error due to incorrectly timed urine sample collection and tubular creatinine secretion.[1,2] We aimed to determine the real-world performance of $CrCl_{24}$ in living donor candidates.

We performed a retrospective cross-sectional study of living kidney donor candidates evaluated at our center. This study was approved by the Columbia University Medical Center institutional review board (#AAAI1288). We identified 279 consecutive candidates who underwent cold iothalamate clearance testing from 2018-2021 for GFR assessment as part of living kidney donation evaluation. At our center, a GFR $\geq$80ml/min/1.73m^2 is used to determine suitability for donation for most candidates. Donor candidates were referred for iothalamate clearance testing if either CKD-EPI2009 creatinine-based estimated GFR (eGFR) or $CrCl_{24}$ were <90mL/min/1.73m^2, if the candidate was unable to perform a timed urinary collection, or if the testing was requested by the evaluating nephrologist. After excluding donors with incomplete data (see detailed methods in Item S1), we analyzed a final cohort of 212 donor candidates.

Demographic information was obtained from the medical record. Body surface area (BSA) was calculated using the Gehan & George formula.[3] Donor candidates performed ambulatory 24-hour urine collections, and $CrCl_{24}$ was calculated as the

product of 24-hour urinary creatinine concentration and urine volume divided by serum creatinine concentration, then adjusted for BSA. Serum creatinine and cystatin C values were used to calculate eGFR using the CKD-EPI2021 combined creatinine and cystatin C equation ($eGFR_{crcys}$).[4] "Measured" GFR (mGFR) was determined based on cold iothalamate clearance using the Bröchner-Mortensen correction and adjusted for BSA (Item S1).[5] Bias for each GFR estimate equation was calculated as [mGFR - estimate]. All GFR and bias values below are presented in units ml/min/1.73m^2.

Among 212 donor candidates analyzed, median age was 54 years, and 62% were female. Body size parameters are presented in Table 1. Median mGFR was 107 (IQR 95-120). Median weight-indexed 24-hour creatinine excretion was 21.9mg/kg (16.5-26.0) for males and 15.9 (12.8-18.7) for females, and median $CrCl_{24}$ was 73 (58-89). Median serum creatinine was 0.89mg/dL and median cystatin C was 0.8mg/L, corresponding to median $eGFR_{crcys}$ 97 (IQR 85-111). Scatterplots of mGFR versus $CrCl_{24}$ and $eGFR_{crcys}$ are shown in Figure 1. Overall, median bias for $CrCl_{24}$ was 33.9 (IQR 16.3-50.7), including 40.0 (20.5-63.3) for males and 32.1 (14.2-46) for females. Median bias for $eGFR_{crcys}$ was 10.5 (IQR -1.7 to 25.4), including 25.6 (13.4-36.0) for males and 2.7 (-11.0 to 13.6) for females.

Using a GFR-based donation eligibility threshold of 80, 119 (56%) donors had discordant classification using $CrCl_{24}$ versus mGFR (Table S1). Of these, 115 (54% of all candidates and 97% of those with discordant classification) had mGFR≥80 but $CrCl_{24}$<80, likely a reflection of the underlying selection bias of the cohort.

We next sought to determine whether urine collection adequacy (as reflected by weight-indexed 24-hour creatinine excretion) or similarity in $CrCl_{24}$ and $eGFR_{crcys}$ results

could be used as indicators of low $CrCl_{24}$ bias. Among males with creatinine excretion 20-25mg/kg (n=23) and females with creatinine excretion 15-20mg/kg (n=49), median bias was 32.2 (IQR 14.5-46.7) (Figure S1).

Only 70 (33%) candidates had $eGFR_{crcys}$ within 20% of $CrCl_{24}$. Although there was a positive relationship between the absolute bias of $CrCl_{24}$ and the absolute difference between $CrCl_{24}$ and $eGFR_{crcys}$ (r^2=0.34, p<0.001, Figure 1, Figure S2), $CrCl_{24}$ bias remained high even when the difference between both estimates was small: Even among the 89 donor candidates with $eGFR_{crcys}$ within 20 ml/min/1.73m^2 of $CrCl_{24}$, median bias was 22.1 (IQR 11.5 - 37.2), suggesting that similarity between CrCl24 and eGFRcrcys does not imply that $CrCl_{24}$ approximates mGFR well.

Given the large median bias we observed, $CrCl_{24}$ appears to be a suboptimal method of "measuring" GFR in a subset of potential living kidney donors despite current regulatory policies requiring GFR assessment using "isotopic methods or a creatinine clearance calculated from a 24-hour urine collection."[6] This inaccuracy likely stems from the challenges of accurately collecting timed urine samples in an ambulatory setting. Our study may be limited by selection bias, given that participants were healthy and only selected donor candidates were referred for iothalamate clearance testing, thereby enriching our cohorts for individuals with eGFR or CrCl that underestimated mGFR. Additionally, potential deviation of iothalamate-based mGFR from true GFR and may influence our results. However, given that $CrCl_{24}$ does not appear to accurately reflect GFR in a subset of candidates—and that $CrCl_{24}$ bias remained large even among those with creatinine excretion suggesting "adequate" urinary collection and those with agreement between $CrCl_{24}$ and $eGFR_{crcys}$ results— additional study is needed to

determine how to best evaluate kidney function during living kidney donor evaluations and identify which donor candidates may warrant more accurate GFR assessments.

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Supplementary Material

Figure S1. Bias of 24-hour timed creatinine clearance versus weight-indexed 24-hour creatinine excretion.

Figure S2. Absolute value of the bias of 24-hour timed creatinine clearance (CrCl24) versus the absolute difference between the 24-hour timed creatinine clearance and the estimated glomerular filtration rate based on the 2021 CKD-EPI creatinine-cystatin C equation (eGFRcrcys).

Item S1. Supplementary Methods

Table S1. Reclassification of glomerular filtrate rate (GFR) based donor eligibility using measured GFR versus timed creatinine clearance.

Descriptive Text for Online Delivery

Supplementary File (PDF)

Fig S1-S2, Item S1, Table S1

Article Information

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Table 1. Characteristics of Donor Candidates Analyzed

	All	Male	Female
n (col %) or median (IQR)	**n=212 (100%)**	**n=80 (38%)**	**n=132 (62%)**
Age, years	54 (43-61)	49 (37-58)	57 (47-62)
Race			
White	138 (65)	46 (58)	92 (70)
Black/African American	19 (9)	11 (14)	8 (6)
All others	55 (26)	23 (29)	32 (24)
Height, cm	168 (163-175)	175 (170-180)	163 (159-170)
Weight, kg	79 (66-88)	76 (63-85)	82 (74-93)
Body Mass Index, kg/m2	27 (24-31)	27 (24-30)	28 (24-32)
Body Surface Area, m2	2.06 (1.90-2.19)	2.16 (2.05-2.30)	1.98 (1.87-2.13)
24-hour creatinine excretion, g	1.29 (1.06-1.67)	1.75 (1.39-2.22)	1.16 (0.96-1.36)
Weight-indexed 24-hour creatinine excretion, mg/kg	17.4 (13.5-21.8)	21.9 (16.5-26.0)	15.9 (12.8-18.7)
Serum creatinine, mg/dL	0.89 (0.76-1.00)	1.07 (0.93-1.15)	0.81 (0.73-0.90)
Cystatin C, mg/L	0.8 (0.8-0.9)	0.8 (0.8-1.0)	0.8 (0.7-0.9)
GFR assessments, ml/min/1.73m2			
Measured GFR (iothalamate)	107 (95-120)	111 (100-123)	106 (91-117)
CKD-EPI 2021 (creatinine)	90 (77-104)	88 (79-103)	91 (76-104)
CKD-EPI 2012 (cystatin C)	99 (83-110)	105 (86-116)	98 (82-105)
CKD-EPI 2021 (combined)	97 (85-111)	85 (76-96)	106 (94-115)
Timed Creatinine Clearance	73 (58-89)	67 (54-86)	75 (63-89)

Abbreviations: GFR, glomerular filtration rate

Figure Legend

Figure 1. Measured glomerular filtration rate (GFR) versus 24-hour timed creatinine clearance (Panel A) and estimated GFR based on the CKD-EPI 2021 creatinine-cystatin C equation (eGFRcrcys) (Panel B). Red lines indicate 80 ml/min/1.73m2, a typical threshold used for suitability for living kidney donation.