

Kidney Function Prediction for Individuals Consider Living Kidney Donation

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Abbreviations:

ASN, American Society of Nephrology; **BMI**, body mass index; **eGFR**, estimated glomerular filtration rate; **HRSA**, The Health Resources and Services Administration; **IQR**, interquartile range; **KDIGO**, Kidney Disease: Improving Global Outcomes; **NKF**, National Kidney Foundation; **OPTN**, Organ Procurement and Transplantation Network; **P30**, percentage of estimates within 30% of the observed values; **SRTR**, Scientific Registry of Transplant Recipients.

ABSTRACT

Background: Individuals who donate a kidney lose 50% of their nephron mass. Kidney reserve capacity varies by individual characteristics. Reduced 6-month post-donation creatinine-based estimated glomerular filtration rate (eGFRcr) is associated with increased long-term risk of kidney failure. We sought to inform the individual predicted 6-month post-donation creatinine and expected eGFRcr using the race-free CKD-EPI 2021.

Methods: We examined the U.S. national cohort of living kidney donors between 01/2005-06/2019. We used donor demographic and health characteristics to develop the prediction model, which was validated by 10-fold cross-validation and temporal validation. We assessed bias, precision, and accuracy of model performance between race groups.

Results: Of 52494 donors included, median (IQR) predonation and 6-month post-donation creatinine and eGFRcr were 0.8 mg/dL (0.7, 0.9) and 101 mL/min/1.73m² (88, 112), and 1.2 mg/dL (1.0, 1.4) and 65 mL/min/1.73m² (56, 75), respectively. Our model had predictive R²=0.68 which was consistent in cross-validation (R²=0.68) and temporal validation (R²=0.71). The model retained correct classification of expected 6-month eGFRcr <50 or ≥50 mL/min/1.73m² in 90% of donors. The median (IQR) bias of expected 6-month eGFRcr was 2.02 mL/min/1.73m² (-3.86, 7.08) among Black donors and -0.82 mL/min/1.73m² (-7.06, 4.72) among non-Black donors. The expected 6-month eGFRcr was within 30% of observed eGFRcr among 95% of Black donors and among 97% non-Black donors.

Conclusions: We provide an accurate prediction of 6-month post-donation kidney function and a calculator for precision counseling of individuals considering kidney donation. Our tool helps improve decision-making for marginal donor candidates and identify those who need careful surveillance.

INTRODUCTION

Individuals who donate a kidney sacrifice 50% of their nephron mass following nephrectomy. Compensatory kidney function in the remnant kidney can vary by individual characteristics, such as age, sex, body size, and hypertension.¹⁻⁶ As such, individuals with similar pre-donation kidney function may not equally tolerate the insult of nephrectomy. Kidney reserve, the capacity of the kidney to raise glomerular filtration rate (GFR) in response to stressor stimuli, is determined by factors that may not be captured during donor evaluation.⁷⁻⁹ Lack of appropriate compensation in the remnant kidney can be consequential in the long-term risk of kidney failure, especially in the event of de novo disease.¹⁰⁻¹⁶ There is a need for tools to better inform decision-making for donor candidates and those with borderline predonation kidney function.

Most of the nephrons compensation in the remnant kidney occurs in the first 6 months post-donation.^{17,18} Each 10 mL/min/1.73m² reduction in creatinine-based estimated GFR (eGFRcr) at 6 months post-donation is associated with a 28% increased 15-year risk of kidney failure.¹⁹ Subclinical kidney pathology at the time of donation has been linked to lower eGFR, higher urine albumin, and new onset hypertension at 6 months post-donation.²⁰ Six-month post-donation serum creatinine, as the most commonly used laboratory biomarker of kidney function, can add an important value to the risk assessment tools for precision counseling of donor candidates.²¹⁻²³ Since kidney failure takes decades to develop in donors and is rare, 6-month post-donation kidney function can serve as a surrogate marker for the long-term risk.

To predict individualized post-donation kidney function, we utilized the US national registry of living kidney donors to identify the clinical characteristics associated with 6-month post-

donation creatinine and establish a publicly available online calculator of the individual predicted 6-month post-donation creatinine and expected eGFR_{cr} (CKD-EPI 2021).

METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. This dataset has previously been described elsewhere.²⁴ This study used deidentified data and was exempted by the University of California Irvine Institutional Review Board.

Study Population

The study population consisted of adult (≥ 18 -year-old) living kidney donors who donated a kidney between January 2005 and June 2019, and had a pre-donation creatinine that was reported to the OPTN, and at least one post-donation creatinine record reported to the OPTN at 6 months post-donation (± 3 months, to allow a range of reporting from transplant programs). We excluded donors with registry information on creatinine that would typically exclude the individual to be a donor candidate and was assumed to be a data entry error. We also excluded those who had missing variables (body mass index [BMI] and history of hypertension) (Supplementary Figure 1).

Covariables

We considered predonation creatinine, age, sex, BMI, height, history of hypertension, systolic blood pressure (BP), and history of smoking for development of the prediction model. Race was not included in the prediction model, consistent with the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) task force position that race is a social and not a biological construct.^{25,26}

Outcome

Six-month post-donation serum creatinine (6-month creatinine) was the outcome of interest. We chose to model serum creatinine rather than eGFR because it is a readily available lab measurement, and eGFR is a calculation based on creatinine which is the significantly changing biomarker of kidney function at 6 months post-donation. Further, this approach provides the opportunity to use the predicted 6-month creatinine in current or future creatinine-based equations to calculate the expected 6-month post-donation eGFRcr.

Development of the prediction model

We built multivariable linear regression models. We explored the distribution of creatinine in both its untransformed and logarithmic transformed format by plotting it against the quantiles of normal distribution, by the standardized normal probability plot, and the kernel density estimate (Stata diagnostic plots: kdensity, qnorm, pnorm). We compared the coefficient of determination (R^2) with the untransformed 6-month creatinine or its logarithmic transformation as outcome, and chose the untransformed form as our outcome since logarithmic transformed 6-month creatinine did not markedly increase the R^2 of models (higher R^2 signified that higher proportion of 6-month creatinine variance being explained by the model predictors). We confirmed no collinearity using the variance inflation factor (VIF). We plotted the augmented

complement plus residual plot (Stata post-estimation diagnostic plots: `acprplot`) of 6-month creatinine against continuous predictors (predonation creatinine, age, BMI, SBP) to examine for non-linearity, and to inform the final decision on spline nodes.²⁷ We considered interactions between predonation creatinine and age, predonation creatinine and sex, HTN and sex, HTN and age, and HTN and BMI. We determined the final predictors, presence and absence of interactions and spline nodes by comparing between models the extent of decrease in Akaike information criterion (AIC, lower signified better model fit) and the increase in adjusted R-squared (R^2).

Validation of prediction model

We validated the model by 10-fold cross-validation and temporal validation. For temporal validation we used donors who donated from 2005-2018 to derive the predicted value for donors who donated in 2019. For each validation procedure, we calculated the correlation between predicted and observed values of 6-month creatinine.

Sensitivity analysis

To check whether there are variables that should still be considered for the final modeling, and also to evaluate whether a better model could be yielded from a machine-learning approach, we performed Multiple Additive Regression Trees (MART) boosting algorithm with normal distribution after log-transformation of 6-month creatinine (Stata boosting regression: `boost`). Ten-fold cross validation was performed, and we assessed R^2 and determined whether the boosting approach improved prediction of 6-month creatinine.

Measures of performance

We assessed bias (median of the differences between predicted 6-month creatinine and observed 6-month creatinine), precision (interquartile range [IQR] of the bias), and accuracy (percentage of estimates within 30% of the observed values [P_{30}]). We also assessed differential bias, precision, and accuracy between race groups (Black and non-Black donors) to evaluate imbalance in the predicting capability of the model. We further assessed differential accuracy between race groups by evaluating the percentage of predicted 6-month creatinine within a specific range from the absolute observed values: ≤ 0.05 , $>0.05-\leq 0.09$, $>0.09-\leq 0.14$, $>0.14-\leq 0.2$, $>0.2-\leq 0.3$, and >0.3 mg/dL.

We calculated expected 6-month eGFRcr based on the predicted 6-month creatinine using the race-free CKD-EPI 2021 equation. We assessed bias (median of the differences between expected 6-month eGFRcr and observed 6-month eGFRcr, with a negative sign indicating an underestimation of the observed value and a positive sign indicating an overestimation of the observed value), precision (IQR of the bias), and accuracy (P_{30}). We also assessed differential bias, precision, and accuracy between race groups. We further assessed differential accuracy between race groups by evaluating the percentage of donors with 6-month eGFRcr lower than 50 or ≥ 50 mL/min/1.73m² classification given eGFR <50 is considered a key threshold for clinical decision making in donors.¹⁹

Statistical analysis

Confidence intervals were reported as per the method of Louis and Zeger.²⁸ All analyses were performed using Stata 17.0/MP (College Station, Texas).

RESULTS

Study Population

The study population included 52,494 donors, of whom 63% were female, 71% were White, 10% were Black, 14% were Hispanic, and 5% were Asian/other (Table 1). Median (IQR) age at donation was 43 years (34, 52), median (IQR) BMI was 26.6 (23.8, 29.6), and median (IQR) height was 167.6 cm (162.6, 175.3); 4% of participants had hypertension prior to donating. The median (IQR) predonation creatinine and 6-month creatinine were 0.8 mg/dL (0.7, 0.9), and 1.2 mg/dL (1.0, 1.4), respectively. Median (IQR) pre-donation and post-donation CKD-EPI 2021 eGFRcr were 101.0 (88, 112), and 65 (56, 75), respectively (Table 1).

Prediction and Validation

The final covariates included in the prediction model were predonation creatinine, predonation creatinine splines at 0.7 and 0.9, age, sex, BMI, BMI spline at 30, height, and history of hypertension. We included interaction term for predonation creatinine and sex (Table 2). The final model had a predictive discrimination with an R^2 of 0.68 (Pearson coefficient: 0.82). The R^2 of ten-fold validation and temporal validation were 0.68 and 0.71, respectively.

Sensitivity analysis

The boosting method achieved an R^2 of 0.70 using all data. The R^2 in the ten-fold validation is 0.68 (0.6784), which is comparable to the R^2 using linear regression (0.6790).

Prediction model performance

Among all donors, the median (IQR) bias of predicted 6-month creatinine was 0.01 mg/dL (-0.08, 0.09) mg/dL. The predicted 6-month creatinine was within 30% of the observed 6-month creatinine in 98.3% donors (Figure 1A). The median (IQR) bias of expected 6-month eGFRcr

(calculated based on the predicted 6-month creatinine) was $-0.50 \text{ mL/min/1.73m}^2$ $(-6.74, 4.96)$.

The expected 6-month eGFRcr was within 30% of observed 6-month eGFR in 96.9% of donors (Figure 1B). Our model retained correct classification of expected 6-month eGFR <50 or $\geq 50 \text{ mL/min/1.73m}^2$ in agreement with the observed 6-month eGFRcr in 90.4% of donors (Figure 1B).

When stratified by race groups, the median (IQR) bias of the predicted 6-month creatinine was -0.03 mg/dL $(-0.13, 0.06)$ among Black donors, and 0.01 $(-0.08, 0.10) \text{ mg/dL}$ among non-Black donors. The predicted 6-month creatinine was within 30% of the observed 6-month creatinine among 99.0% of Black donors and among 98.3% non-Black donors (Figure 2A). The predicted 6-month creatinine was within 0.2 mg/dL of the observed values among 82.0% of Black donors and 86.1% of non-Black donors (Supplementary Figure 2). The median (IQR) bias of expected 6-month eGFRcr (calculated based on the predicted 6-month creatinine) was $2.02 \text{ mL/min/1.73m}^2$ $(-3.86, 7.08)$ among Black donors and $-0.82 \text{ mL/min/1.73m}^2$ $(-7.06, 4.72)$ among non-Black donors. The expected 6-month eGFRcr was within 30% of observed eGFRcr among 95.1% of Black donors and among 97.1% non-Black donors (Figure 2B). The expected 6-month eGFR was correctly classified into <50 or $\geq 50 \text{ mL/min/1.73m}^2$ in agreement with the observed 6-month observed eGFRcr among 86.7% of Black donors and among 90.8% of non-Black donors (Figure 2B).

We applied the coefficients derived from the prediction model into case scenarios to illustrate the predicted post-donation kidney function at an individual level (Table 3).

DISCUSSION

In this national study of living kidney donors in the United States, we predicted the 6-month post-donation serum creatinine using predonation demographic and clinical characteristics ($R^2=0.68$). We calculated the expected 6-month eGFRcr based on the predicted 6-month creatinine using the race-free CKD-EPI 2021 equation (90% correct classification of 6-month eGFRcr lower than 50 or ≥ 50 mL/min/1.73m²). We have created a publicly available online calculator of the individual predicted 6-month post-donation creatinine and expected eGFRcr to help facilitate precise counseling of the individual considering living kidney donation and improve the selection process for those with borderline predonation kidney function.

We have previously reported that unlike predonation eGFRcr, lower 6-month postdonation eGFRcr is significantly associated with subsequent ESRD risk, a dose-response relationship especially for those with post-donation eGFRcr lower than 50 mL/min/1.73m². Others showed that individuals with a stronger early increase in post-donation eGFRcr have a significantly higher five-year postdonation eGFRcr, independent of predonation eGFRcr.²⁹ Our study provides a practical online tool to advance counseling for the individual considering living kidney donation.^{21,22} In contrast to prior studies in Europe that estimated 12-month post-donation eGFRcr with the Toulouse-Rangueil model (TRM), which was developed and validated in single-center studies with small sample sizes (n=133 to 400),³⁰⁻³² our study used data from all US living kidney donors (n=52,494) to develop and validate our predication model. Further, we found the TRM predicted values were statistically significantly different from observed values when using U.S. donor population, where the TRM model overestimated post-donation kidney function in U.S. cohort. While our calculator was developed in a U.S. donor population, it may have utility in other countries given our methods produce robust estimates that are independent of race.

Further, our predicted 6-month creatinine allows providers to use any of the creatinine-based equations to calculate the estimated 6-month post-donation eGFR_{Cr}.

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors recommends that donor candidates with GFR of ≥ 90 mL/min per 1.73 m^2 should be considered an acceptable level for kidney donation, while donor candidates with GFR 60 to 89 mL/min per 1.73 m^2 should be individualized based on demographic and health profile in relation to the transplant program's acceptable risk threshold.²³ Further, the OPTN informed consent policy for living kidney donors requires educating donor candidates regarding the expected post-donation kidney function and to include specifically that “on average, living donors will have a 25-35% permanent loss of kidney function after donation.”³³ Yet, these general recommendations do not help inform donor candidates about the expected post-donation kidney function at the individual level, especially for those with suboptimal predonation kidney function or a comorbidity such as obesity or hypertension, who may have reduced kidney reserve capacity. Prior studies reported that while older age and higher BMI did not affect predonation kidney reserve capacity, they are associated with loss of postdonation reserve capacity.⁸ Further, for younger donors in whom progressive post-donation kidney diseases may not begin until middle age, preservation of their kidney reserve is critical.¹ Transplant programs are increasingly more inclined to accept marginal donor candidates given the substantial decline in the number of donors over most of the last two decades.³⁴⁻³⁸ Providers can use our tool to better inform donor candidates and have close monitoring of those with expected borderline 6-month post-donation eGFR_{Cr}.

Our findings must be understood in the context of its limitations. Despite being the largest study predicting post-donation kidney function to date, we recognize the potential limitations of using registry-based data. In the absence of kidney biopsy information, we cannot definitively ascertain the presence of subclinical kidney disease at time of donation which can affect our findings.³⁹ Furthermore, we did not have information on donor genetics, e.g., APOL1 high-risk genotype in black donors is linked to greater decline in post-donation kidney function.⁴⁰ That said, key strengths of our study include the use of national registry data allowing us to produce reliable estimates given the diverse representativeness of the demographic and clinical characteristics of donors. Our approach using serum creatinine provides the opportunity to use the predicted 6-month creatinine in current, or future creatinine-based equations to calculate the estimated 6-month post-donation eGFR_{cr}. In addition, our study provides a practical risk calculator for donor candidates.

In conclusion, we have developed a robust model for 6-month post-donation kidney function and provided an online calculator to better inform discussion between providers and individuals when considering living kidney donation. Our tool has the potential to improve the selection process and decision-making for marginal donor candidates and help identify those who need more careful surveillance.

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DISCLOSURE

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Table 1. Baseline Characteristics of Living Kidney Donors in the United States from 2005 to 2019

Characteristic	n=52,494
Predonation serum creatinine, median (IQR)	0.8 (0.7, 0.9)
Predonation eGFR CKD EPI-2021, median (IQR)	101.0 (88, 112)
Age in years, median (IQR)	43 (34, 52)
18-29	15%
30-44	38%
45-59	38%
>=60	9%
Male, %	37%
Race category, %	
White	71%
Black	10%
Hispanic	14%
Asian or others	5%
BMI, median (IQR)	27 (24, 30)
Height, median cm (IQR)	168 (163, 175)
Systolic BP, median mm Hg (IQR)	120 (112-130)
HTN, %	4%
History of smoking, %	19%

Abbreviations: BMI: body mass index; eGFR, estimated glomerular filtration rate; HTN: hypertension; IQR, interquartile range

Table 2. Prediction model of 6 months post-donation serum creatinine among living kidney donors

Variables	lower 95% CI	Coefficient	upper 95% CI	p
Pre-donation creatinine ¹	0.0789	0.0819	0.0850	<0.001
-- Spline at 0.7 mg/dL	0.0088	0.0131	0.0175	<0.001
-- Spline at 0.9 mg/dL	-0.0200	-0.0158	-0.0116	<0.001
Age per decade ²	0.0229	0.0242	0.0255	<0.001
-- Spline at 55 years	-0.0127	-0.0072	-0.0016	0.011
Male sex (ref. female)	0.2297	0.3429	0.4561	<0.001
Interaction: male and predonation creatinine	-0.0523	-0.0359	-0.0195	<0.001
Interaction: male and predonation creatinine spline at 0.7 mg/dL	0.0299	0.0473	0.0648	<0.001
BMI ³	0.0150	0.0171	0.0192	<0.001
-- Spline at 30 kg/m ²	-0.0185	-0.0125	-0.0065	<0.001
Height ⁴	0.0112	0.0129	0.0146	<0.001
History of hypertension	0.0010	0.0075	0.0139	0.024

Abbreviations: BMI: body mass index.

¹SCr per 0.1 mg/dL increase

²Age per 10 years increase

³BMI per 5 kg/m² increase

⁴Height per 10 cm increase

Equation: 6-month post-donation serum creatinine = 0.06 + [0.8192 (– 0.3593 if male)]*(predonation creatinine) + [0.1311 (+ 0.4733 if male)]*(predonation creatinine – 0.7)*(predonation creatinine>0.7) – 0.1581*(predonation creatinine – 0.9)*(predonation creatinine>0.9) + 0.3429*(male) + 0.0034*(BMI) – 0.0025*(BMI – 30)*(BMI>30) + 0.0024*(age) – 0.0007*(age – 55)*(age>55) + 0.1290*(height in meters) + 0.0075*(hypertension)

Table 3. Case Scenario of predicated post-donation kidney function at an individual level, using the national registry of living kidney donors in the United States from 2005 to 2019

Predonation donor characteristics								Post-donation Predicted		Post-donation Observed	
Age year	Sex	Race	BMI	Height meter	HTN	Creatinine mg/dL	eGFRcr ml/min/1.73 m ²	Creatinine mg/dL	eGFRcr ml/min/1.73 m ²	Creatinine mg/dL	eGFRcr ml/min/1.73 m ²
26	male	Asian	24	1.74	no	0.6	137	1.05	100	1.00	106
26	female	Hispanic	22	1.61	no	0.6	127	0.90	90	0.90	90
26	female	Hispanic	34	1.68	no	0.6	127	0.94	86	0.98	81
26	male	Black	27	1.75	no	1	106	1.41	70	1.40	71
26	female	Black	27	1.60	no	1	80	1.26	60	1.31	58
68	male	White	23	1.78	no	0.8	96	1.29	60	1.30	60
68	male	White	28	1.70	yes	0.8	96	1.31	59	1.33	58
68	female	Black	32	1.65	no	0.8	80	1.21	49	1.20	49
68	female	White	21	1.6	no	0.9	70	1.26	47	1.20	49
68	female	White	32	1.75	yes	0.9	70	1.32	44	1.32	44

Abbreviations: BMI: body mass index; HTN: hypertension.

Figure 1A. Observed versus predicted 6-month post-donation serum creatinine.

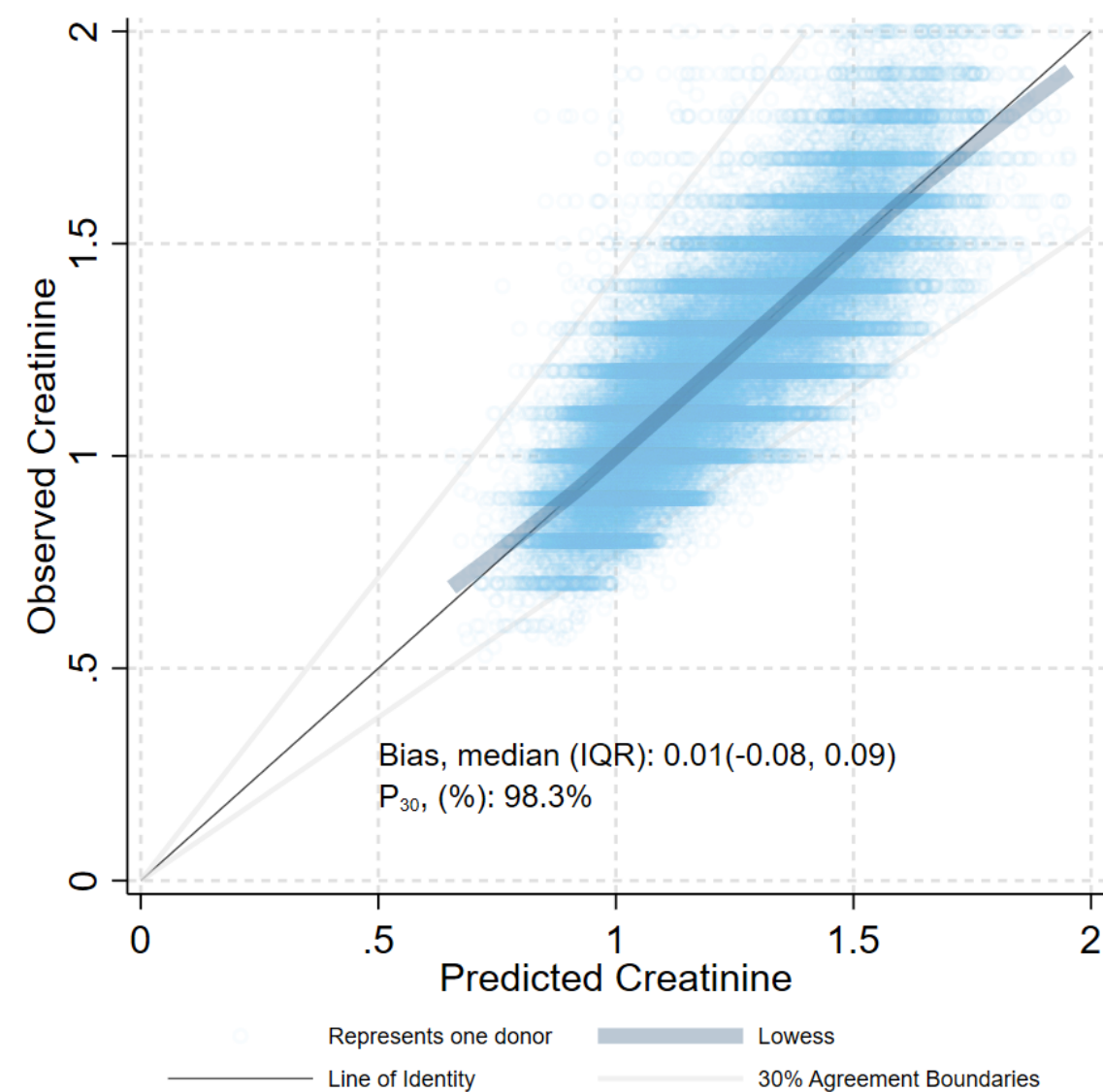
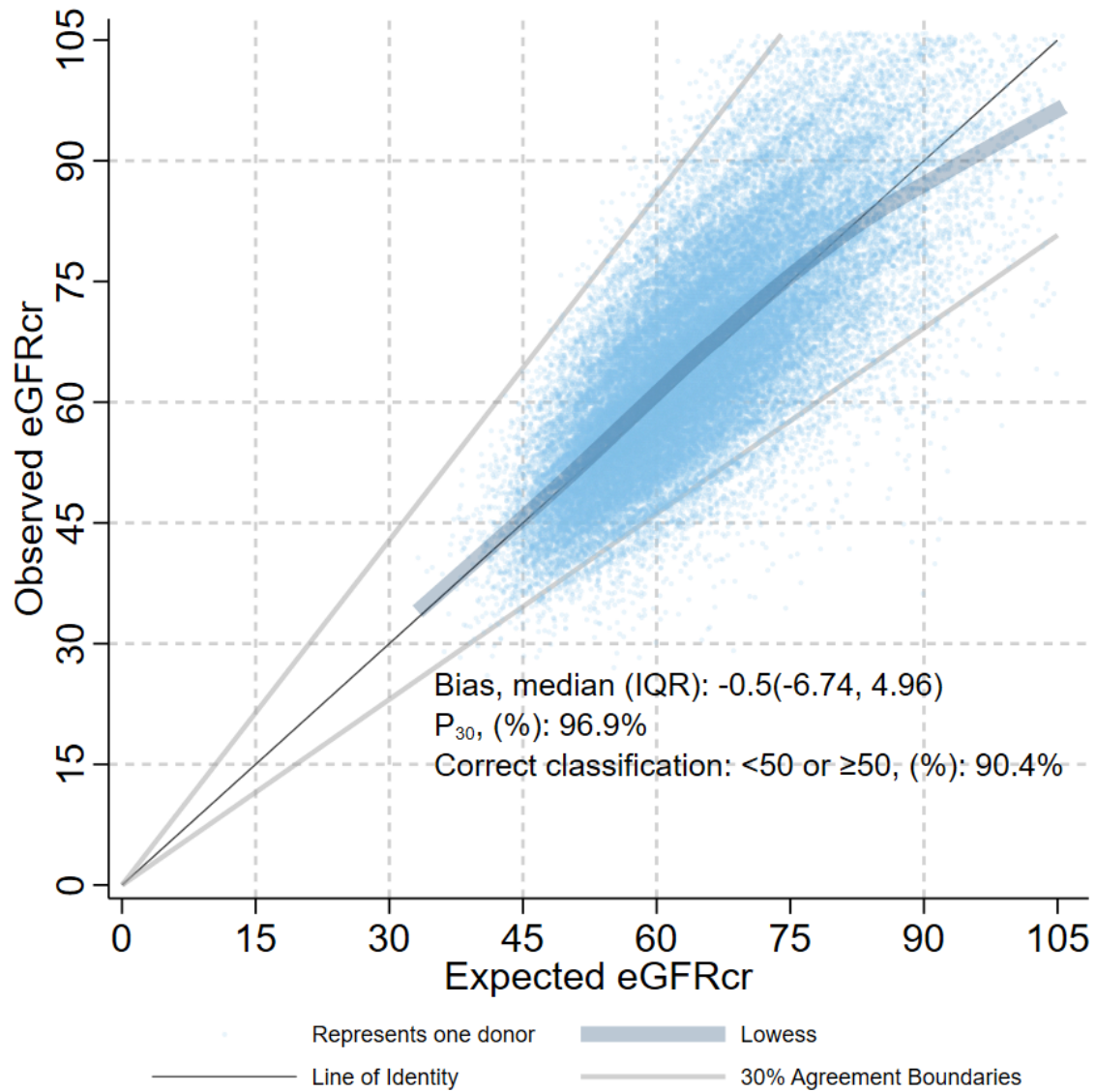


Figure 1B. Observed versus expected 6-month post-donation eGFRcr.



Calculated expected 6-month eGFRcr based on the predicted 6-month creatinine using the race-free equation CKD-EPI 2021; P₃₀, percentage of estimates within 30% of the observed values.

Figure 2A. Observed versus predicted 6-month post-donation serum creatinine stratified by donor race.

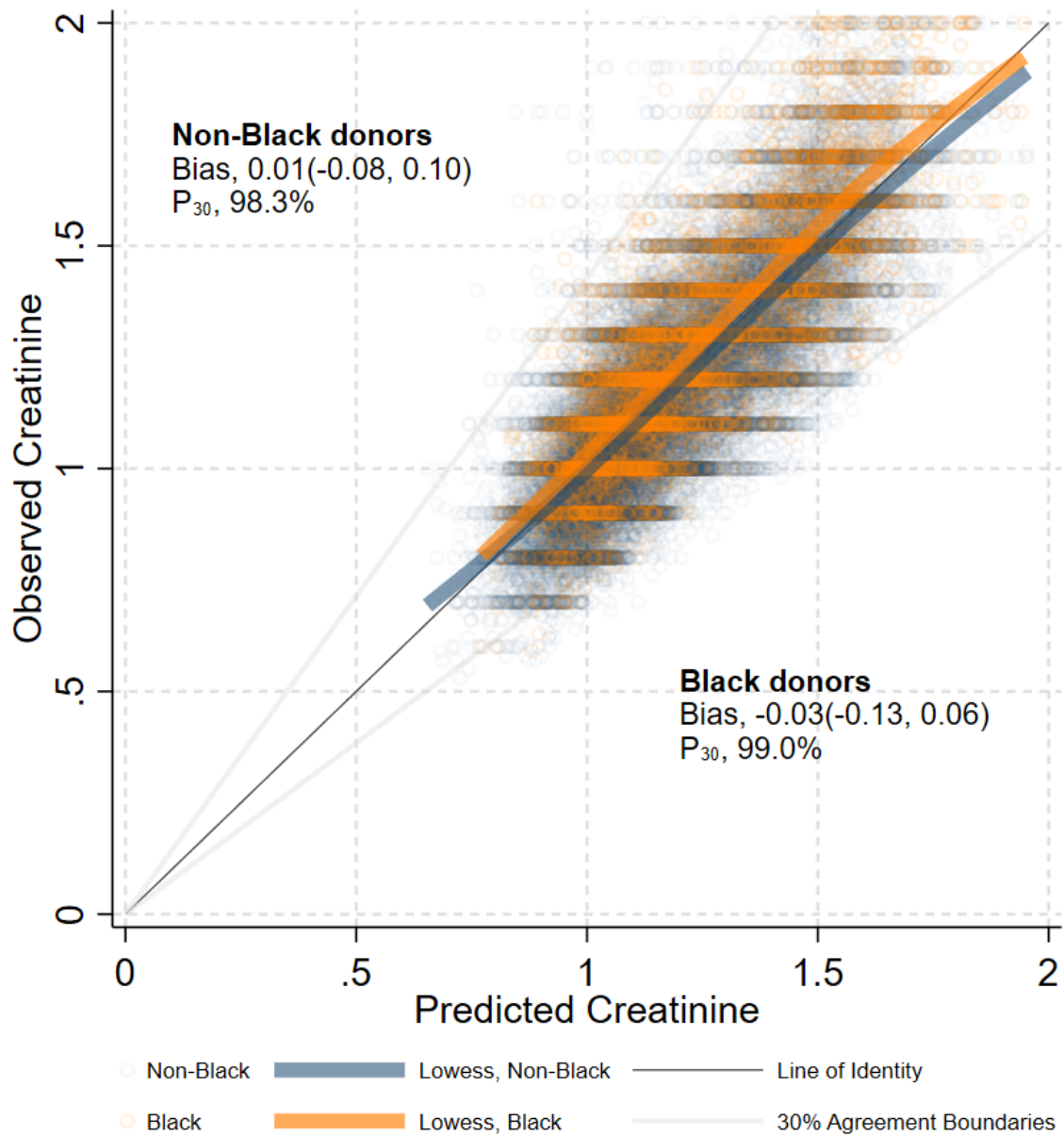
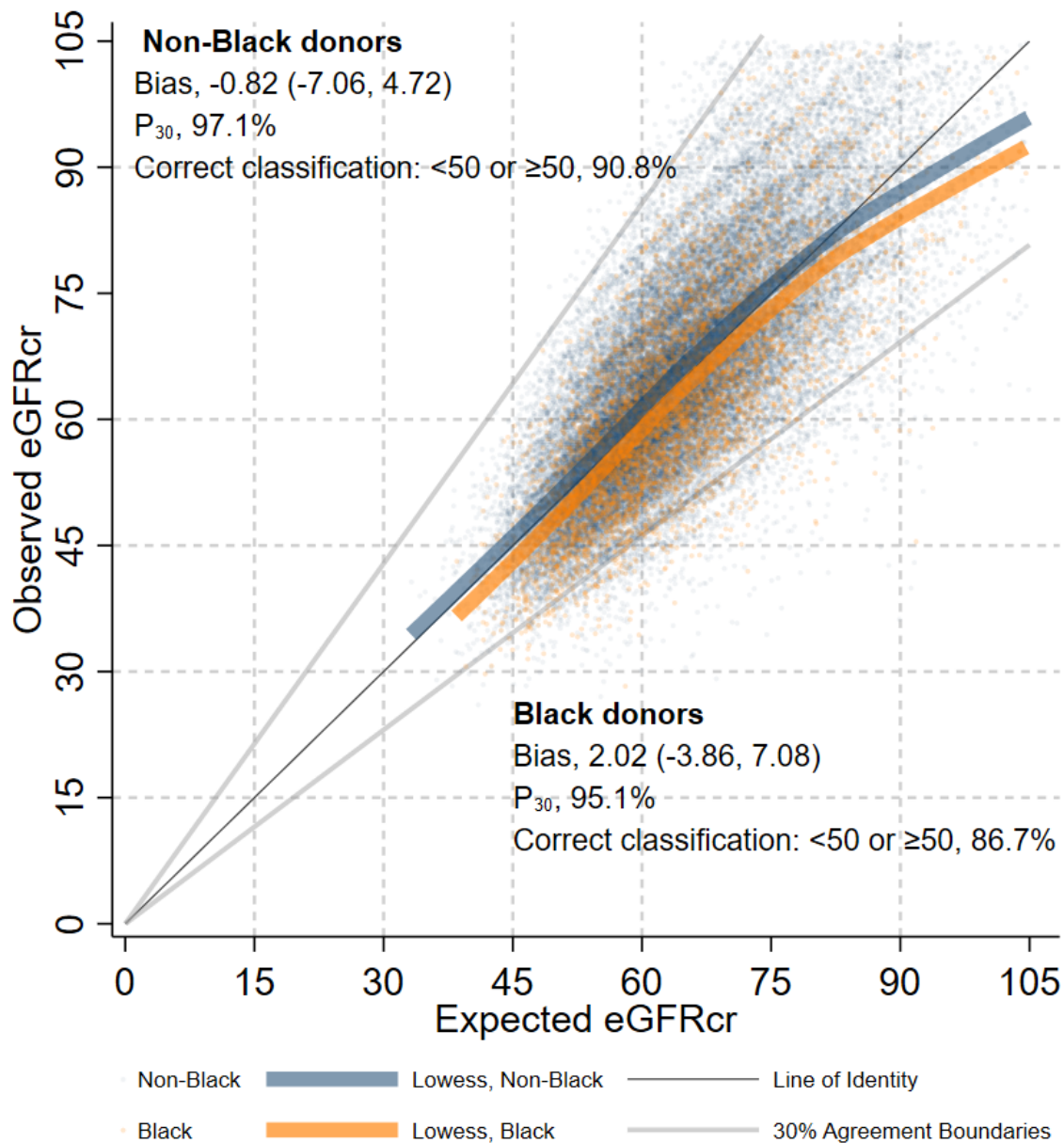
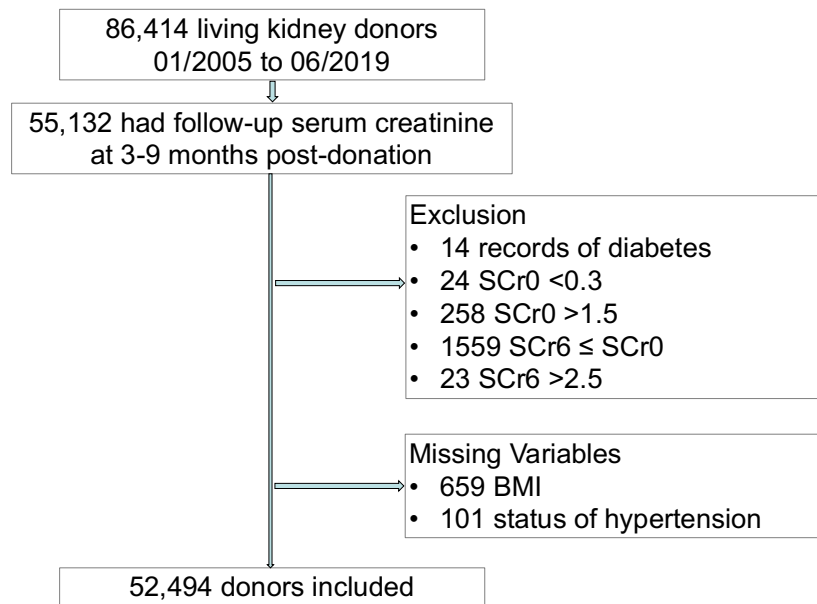


Figure 2B. Observed versus expected 6-month post-donation eGFR stratified by donor race.

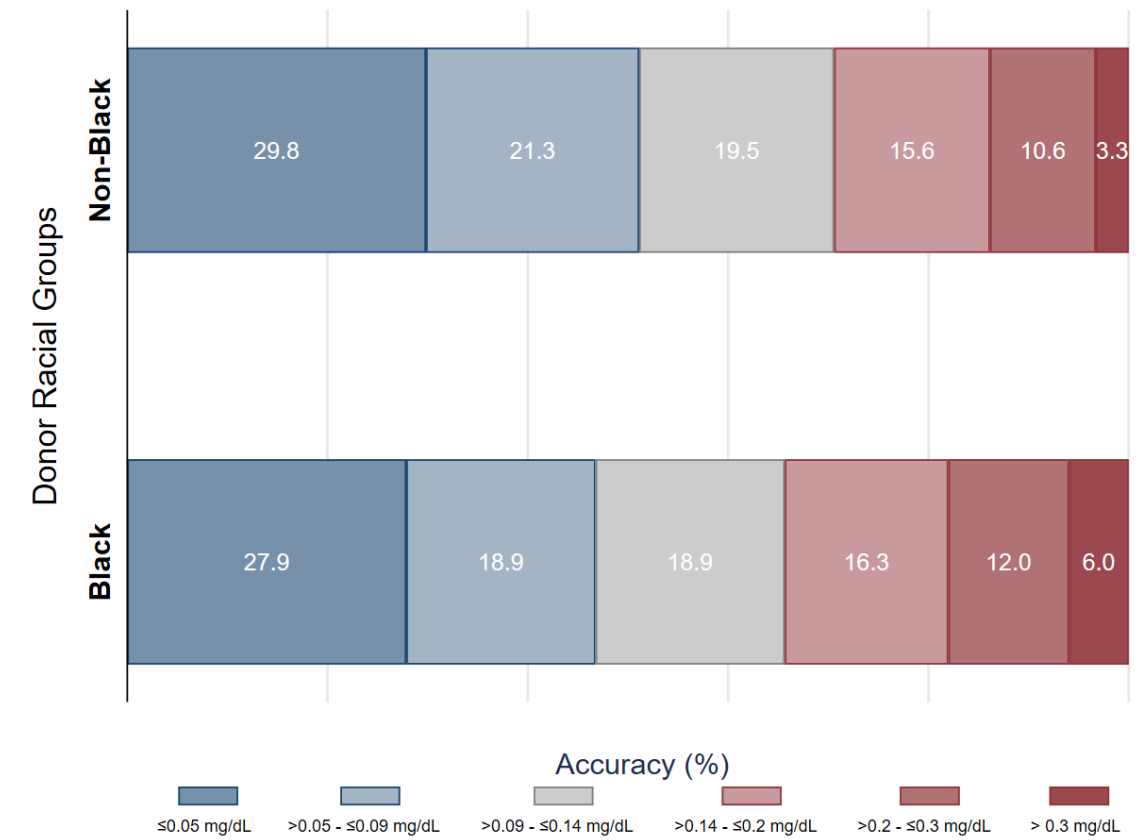


Calculated expected 6-month eGFRcr based on the predicted 6-month creatinine using the race-free equation CKD-EPI 2021; P_{30} , percentage of estimates within 30% of the observed values.

Supplementary Figure 1. Population Flow Chart



Supplementary Figure 2.



Percentage of predicted 6-month creatinine within a specific range of the absolute observed values: ≤ 0.05 , $>0.05 - \leq 0.09$, $>0.09 - \leq 0.14$, $>0.14 - \leq 0.2$, $>0.2 - \leq 0.3$, and >0.3 mg/dL.

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