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Creatinine clearance measured from 24-hour urine collection to predict trough plasma levels of direct oral anticoagulants in acute ischemic stroke patients with atrial fibrillation

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Research Article

Keywords: creatinine clearance, 24-hour urine collection, cardioembolic stroke, atrial fibrillation, trough plasma level, direct oral anticoagulant

Posted Date: May 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9612406/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Direct oral anticoagulants (DOACs) are excreted partly from the kidneys, and their doses should be adjusted to the renal function, with Cockcroft-Gault-formula being recommended to estimate the creatinine-clearance (eCrCl). Yet the accuracy of this estimation might be limited in the acute phase of stroke. A more reliable alternative might be direct measurement of creatinine-clearance using 24-hour-urine-collection (mCrCl). In this study, the two methods were compared regarding their applicability.

Methods

Acute ischemic stroke patients with atrial fibrillation under DOAC were enrolled. The trough plasma levels of DOAC were measured during steady state, i.e. 12 ± 1 hours for apixaban and dabigatran, and 24 ± 1 hours for edoxaban and rivaroxaban after the last intake, eCrCl and mCrCl were compared in terms of their ability to predict DOAC-levels using multivariate linear regression analyses and Pearson-tests with comparison using the Fisher's r-to-z transformation.

Results

224 patients (106 women, 77.9 ± 8.9 years old, median NIHSS 3) were enrolled. In 67% of cases, mCrCl was higher than eCrCL with mean differences of 10.9 ± 2.0 ml/min. Both eCrCl and mCrCl significantly correlated with the DOAC plasma levels (eCrCl: correlation coefficient=-0.303, $P < 0.001$; mCrCl: correlation coefficient=-0.294, $P < 0.001$) and the two correlation coefficients did not differ. High mCrCl was a predictor of extremely low DOAC plasma levels (OR 1.011, 95% CI 1.001–1.022).

Conclusions

The Cockcroft-Gault-formula seems to underestimate renal function among stroke patients, but differences were relatively low compared to mCrCl. Both mCrCl and eCrCl accurately predicted trough plasma levels of DOAC, still patients with extremely low values are more reliably identified by mCrCl.

Introduction

In ischemic stroke patients with atrial fibrillation, secondary prevention with anticoagulation is recommended with a preference for Direct Oral Anticoagulants (DOAC) over Vitamin-K-Antagonists (VKA) (1), because DOACs are at least noninferior or even superior than Vitamin-K-Antagonists in reducing the risk of ischemic stroke, and cause similar or less bleeding (2–5). As all currently four available DOACs are eliminated partly from the kidneys (6), doses of DOAC should be adjusted to renal function (1, 7–9). In all the four phase 3 DOAC clinical trials (2–5, 10–13), the Cockcroft-Gault formula

was used to estimate the creatinine clearance (eCrCl) and is currently recommended by the European Society of Cardiology to assess renal function in order to adjust the DOAC doses (1, 8).

Compared to VKA, no routine coagulation monitoring is considered needed in patients treated with DOAC (7). However, there is increasing evidence supporting that high trough plasma levels of DOAC were associated with increased risk of bleeding events, while low trough plasma levels of DOAC were associated with increased risk of ischemic stroke (14, 15).

In our previous study of 397 patients with ischemic stroke and atrial fibrillation, we found that a higher eCrCl estimated from the Cockcroft-Gault formula was an independent predictor of lower trough plasma levels of DOAC (16), which was associated with ischemic stroke recurrence (16). However, due to the inherent inaccuracy of all estimated values, the Cockcroft-Gault formula has its limitations and may not be suitable for certain patient groups. This includes the elderly, those suffering from frailty or exceptionally low or high body weight (17). We hypothesize the CrCl measured from the 24-hour urine collection (mCrCl) might more precisely reflect the renal function and therefore better predict the trough plasma levels of DOAC. In this study, we therefore aimed to assess and compare the associations of mCrCl and eCrCL with trough plasma levels of DOAC including the extremely low or high values in ischemic stroke patients with atrial fibrillation.

Patients and Methods

Study Population

This is a single-center observational study based on the data from the Erlangen Registry of Patients on Anticoagulation (ER-NOAC) (18–20). This study was conducted with the approval of the ethics committee, the study has been approved by the Ethics Committee of the University of Erlangen-Nuremberg (approval number377_17 Bc). Patients with acute ischemic stroke (AIS) and atrial fibrillation (AF) admitted to the Department of Neurology, University of Erlangen-Nuremberg were consecutively enrolled to our study. The diagnosis of AIS was established by clinical evaluation by specialists in neurology and confirmed with neuroimaging (Computed tomography and/or Magnetic Resonance Imaging). The current study cohort abstracted patients enrolled in this registry from April 2016 to December 2019.

Baseline demographic and clinical data

We collected demographic and clinical data including age, gender, body weight, height, body mass index (BMI), and pre-stroke modified Rankin scale (mRS) (21–23). Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) (24). CHA2DS2-VASc scores were calculated. Data on vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, current smoking, alcohol consumption), concomitant diseases (history of previous stroke or transient ischemic attack, heart

failure, coronary heart disease, etc.), large-vessel occlusion, intravenous thrombolysis, endovascular mechanical recanalization, as well as oral anticoagulation after stroke were collected.

Measured and estimated CrCl

The 24-hour urine collection was performed by dedicated study nurses at our Stroke Unit. For stroke patients with urinary incontinence or severe neurological deficits, the urine was collected by means of Foley catheter with connected drainage collection bag. For stroke patients with mild or moderate deficits, the urine was collected with urinals or bedside commodes. The obtained urine was first stored in a refrigerator. After finishing the 24-hour urine collection, the urine volume was measured, and a urine sample was sent to the central laboratory to measure the urine creatine concentration. Blood was drawn in the fasting state on the same day of urine collection to measure the serum creatine concentration. The mCrCl was calculated using the following formula: (urine creatinine concentration × urine volume] / (serum creatinine concentration × 1440) [ml/min]. The eCrCl was calculated using the Cockcroft-Gault formula: [(140 - Age) / (Serum creatinine)] × (Weight / 72) × 0.85 (if women) [ml/min] (25).

Measurement of trough plasma levels of DOAC

The plasma levels of DOAC were measured at the steady state, defined as after five or more regular intakes of DOAC (16, 26–28). The trough plasma levels were tested just before the next intake, i.e., 12 hours after intake for apixaban and dabigatran, 24 hours after intake for edoxaban and rivaroxaban (16, 26–28).

Plasma levels of apixaban, edoxaban, and rivaroxaban were measured using anti-Xa based chromogenic assays (STA-Liquid Anti-Xa, Diagnostica STAGO S.A.S., France) with anticoagulant-specific calibration (Diagnostica STAGO S.A.S., France) (16, 18). Plasma levels of dabigatran were determined using the Hemoclot direct thrombin inhibitor assay (HYPHEN BioMed, France), based on international recommendations (16, 18). The trough plasma levels of DOAC were categorized into low (< 50 ng/ml), intermediate (50–100 ng/ml), or high (> 100 ng/ml) (18). Moreover, we assessed the percentage of patients with extremely high and extremely low trough plasma levels of DOAC, defined as below or above the expected lower and upper ranges of trough plasma levels of DOAC respectively based on literature (supplementary table 1) (7, 14, 29–33).

Statistical Analyses

We used the Kolmogorov-Smirnov test to assess the normal distribution of the data, normally distributed data were expressed as mean ± standard deviation (SD), not normally distributed data were expressed as median with interquartile range (IQR), and categorical data were expressed as counts (percentages). The associations between trough plasma levels of DOAC and CrCl as well as other clinical factors (age, body weight, BMI, pre-stroke-mRS, CHA2DS2-VASc-Score and NIHSS) were assessed using the linear

regression analysis. Factors with a trend towards significance (P < 0.2) were included in the multiple linear regression analysis. The correlations between the trough plasma levels of DOAC and eCrCl as well as mCrCl were assessed using Pearson's correlation analysis and compared by means of Fisher's r-to-z transformation. Moreover, we used the multivariate binary regression analysis to assess the independent factors for predicting extremely high or low plasma levels of DOAC, defined as below or above the expected lower and upper ranges of trough plasma levels of DOAC respectively based on literature (7, 14, 29–33). We performed statistical analyses using the IBM SPSS Statistics Version 25 (Armonk, NY, USA), significance was set at $P < 0.05$.

Results

A total of 224 acute ischemic stroke patients with atrial fibrillation were included, there were 118 men and 106 women, the mean age was 77.9 ± 8.9 years, median NIHSS-score was 3 (IQR 1-7.75), and the median CHA2DS2-VASc-Score was 6 (IQR 5–7). 81 patients received DOAC before stroke-onset, while 143 patients were naive to DOAC. After the stroke event, 140 patients were on apixaban (113 patients with full dose and 27 patients with reduced dose), 53 patients were on dabigatran (38 patients with full dose and 15 patients with lower dose), 24 patients were on edoxaban (20 patients with full dose and 4 patients with reduced dose), 7 patients were on rivaroxaban (all with full dose). The median interval between the stroke-onset and DOAC-intake was 3 days (IQR 1–4 days).

The median interval between DOAC-intake and measurement of trough plasma levels of DOAC was 3 days (IQR 2–5 days). The median trough plasma level of DOAC was 82.2 ng/ml (IQR 53.9-126.8 ng/ml); 50 patients had low trough plasma levels of DOAC (< 50 ng/ml), 87 patients had intermediate (50–100 ng/ml) and 87 patients had high values (> 100 ng/ml). 23 patients (10.3%) had extremely high trough plasma levels of DOAC (median value 170.6 ng/ml, IQR 103.3-257.3 ng/ml), and 29 patients (12.9%) had extremely low trough plasma levels of DOAC (median value 1 ng/ml, IQR 0-29.5 ng/ml), while the remaining 172 patients (76.8%) showed trough plasma levels of DOAC in the expected range (median value 86.9 ng/ml, IQR 63.4-124.5 ng/ml).

In 67% of cases, the measured CrCl was higher than the estimated value. The mean difference was 10.9 ± 2.0 ml/min. The measured CrCl was significantly higher than the estimated CrCl (84.7 ± 43.5 vs. 73.8 ± 32.6 ml/min, P < 0.001).

In all 224 patients, both the eCrCl and the mCrCl significantly correlated negatively with trough DOAC levels (eCrCl: correlation coefficient = -0.303, P < 0.001; mCrCl: correlation coefficient = -0.294, P < 0.001; Fig. 1). According to the Fisher's r-to-z transformation, the two correlation coefficients did not differ (z statistic = 0.1039, P = 0.9173). The eCrCl significantly positively correlated with mCrCl (correlation coefficient = 0.735, P < 0.001; Fig. 2). The Delta CrCl (mCrCl-eCrCl) correlated positively with mCrCl (correlation coefficient = 0.660, P < 0.001, Fig. 3).

There was also a positive correlation between mCrCl and body weight (correlation coefficient = 0.386, P < 0.001), and a significant negative correlation between mCrCl and age (correlation coefficient = 0.461, P

< 0.001). In the multivariate linear regression analysis, both mCrCl and eCrCl significantly negatively correlated with the trough plasma levels of DOAC (Table 1). Age, body weight, BMI, pre-stroke-mRS, CHA2DS2-VASc-Score, and NIHSS did not significantly correlate with trough plasma levels of DOAC (Table 1).

Table 1
Linear regression analysis between trough plasma levels of DOAC and mCrCl, eCrCl, as well as other clinical factors (age, gender, body weight, BMI, pre-stroke-mRS, CHA2DS2-VASc-Score and NIHSS).

Parameters	**Univariate linear regression analysis**			**Multivariate linear regression analysis**		
	Standardized Regression Coefficient	**t-value**	**P-Value**	**Standardized Regression Coefficient**	**t-value**	**P-Value**
Age	0.279	4.328	**< 0.001**	0.136	1.567	0.119
Gender (men)	-0.051	-0.766	0.445	N.A.	N.A.	N.A.
Body weight	-0.071	-1.064	0.288	N.A.	N.A.	N.A.
BMI	0.009	0.132	0.895	N.A.	N.A.	N.A.
Pre-stroke mRS	0.238	3.646	< 0.001	0.086	1.151	0.251
CHA2DS2-VASc-Score	0.221	3.379	0.001	0.010	0.120	0.904
NIHSS on admission	-0.006	-0.092	0.927	N.A.	N.A.	N.A.
mCrCl	**-0.288**	-4.475	**< 0.001**	**-0.188**	-2.526	**0.012**
eCrCl	**-0.303**	-4.731	**< 0.001**	**-0.194**	-2.443	**0.015**

Abbreviations: CrCl, creatinine clearance; mCrCl, measured CrCl from the 24-hour urine collection; eCrCl, estimated CrCl from the Cockcroft-Gault formula; BMI, body mass index; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale. N.A., not applicable.

In the univariate binary regression analysis, increasing values of age and pre-stroke-mRS, decreasing values of mCrCl and eCrCl were significantly associated with extremely high trough plasma levels of DOAC (Table 2). In the multivariate binary regression analysis, there showed only a tendency of association between decreasing eCrCl and extremely high trough plasma levels of DOAC (Table 2).

Table 2

Binary logistic regression analysis between extremely high or low trough plasma levels of DOAC and mCrCl, eCrCl, as well as other clinical factors (age, gender, body weight, BMI, pre-stroke-mRS, CHA2DS2-VASc-Score and NIHSS).

	Extreme high trough plasma levels of DOAC				**Extreme low trough plasma levels of DOAC**			
	Univariate analysis		**Multivariate analysis**		**Univariate analysis**		**Multivariate analysis**	
	OR (95% CI)	P	95% CI	P	95% CI	P	OR 95% CI	P
Age	**1.075 (1.014–1.140)**	**0.016**	1.039 (0.966–1.118)	0.298	**0.925 (0.886–0.965)**	**< 0.001**	0.963 (0.902–1.028)	0.263
Gender (men)	0.805 (0.339–1.910)	0.623	N.A.	N.A.	2.200 (0.954–5.071)	0.064	1.292 (0.457–3.652)	0.629
Body weight	0.981 (0.954–1.009)	0.176	0.997 (0.968–1.027)	0.842	**1.022 (1.000-1.044)**	**0.048**	0.998 (0.969–1.028)	0.881
BMI	0.971 (0.883–1.068)	0.542	N.A.	N.A.	1.028 (0.950–1.112)	0.492	N.A.	N.A.
Pre-stroke mRS	**1.457 (1.081–1.965)**	**0.014**	1.208 (0.842–1.733)	0.305	**0.665 (0.453–0.976)**	**0.037**	0.971 (0.626–1.507)	0.971
CHA2DS2-VASc-Score	1.362 (0.988–1.877)	0.059	1.020 (0.680–1.258)	0.925	**0.608 (0.455–0.813)**	**0.001**	0.868 (0.561–1.342)	0.524
NIHSS on admission	0.951 (0.869–1.040)	0.270	N.A.	N.A.	0.967 (0.898–1.042)	0.376	N.A.	N.A.
mCrCl	**0.986 (0.972–0.999)**	**0.034**	0.993 (0.978–1.008)	0.375	**1.017 (1.008–1.026)**	**< 0.001**	**1.011 (1.001–1.022)**	**0.029**
eCrCl	**0.970 (0.950–0.990)**	**0.004**	0.972 (0.944-1.000)	0.052	**1.021 (1.010–1.032)**	**< 0.001**	1.015 (1.000-1.030)	0.051

Abbreviations: CrCl, creatinine clearance; mCrCl, measured CrCl from the 24-hour urine collection; eCrCl, estimated CrCl from the Cockcroft-Gault formula; BMI, body mass index; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale. N.A., not applicable.

On the contrary, decreasing values of age, pre-stroke-mRS and CHA2DS2-VASc-Score, increasing values of body weight, mCrCl and eCrCl were significantly associated with extremely low trough plasma levels of DOAC (Table 2). In the multivariate binary regression analysis, increasing values of mCrCl were the

only significant predictor of extremely low trough levels of DOAC (OR 1.011, 95% CI 1.001–1.022, P = 0.029, Table 2), also there showed a tendency of association between increasing eCrCl and extremely low trough plasma levels of DOAC (OR 1.015, 95% CI 1.000-1.0230, P = 0.057, Table 2).

Discussion

To the best of our knowledge, this is the first study using the creatinine clearance measured from the 24-hour urine collection to predict the trough plasma levels of DOAC in patients with acute ischemic stroke and atrial fibrillation. Our study yielded the following major findings. Firstly, both the measured CrCl from the 24-hour urine collection and the estimated CrCl using the Cockcroft-Gault formula significantly negatively correlated with trough plasma levels of DOAC, and the two correlation coefficients did not differ significantly between mCrCl and eCrCl. Secondly, the negative correlations between mCrCl or eCrCl with trough plasma levels of DOAC remained significant after multivariate linear regression analysis, implying that increasing values of mCrCl or eCrCl were independent predictors of low trough plasma levels of DOAC. Thirdly, trough plasma levels of DOAC were in the expected ranges in around 80% of the patients, while approximately 10% of the patients had either extremely low or high trough plasma levels of DOAC respectively. Fourthly, mCrCl might be more reliable than eCrCl to predict the extremely low trough plasma levels of DOAC, while patients with increasing values of mCrCl were more likely to have extremely low trough levels of DOAC.

The Cockcroft-Gault formula was initially developed by two Canadian physicians Cockcroft (pneumologist) and Gault (nephrologist) and published in 1976 for estimating CrCl based from 24-hour urine collection results in 249 male patients aged 18–92 years (25); serum creatinine, age, gender and body weight were considered in the formula. The Cockcroft-Gault formula was used to assess kidney function in all the four Phase 3 clinical trials leading to final approval of the four DOACs (2–5). Currently, it has been recommended by the European Heart Rhythm Association as the method of choice to assess renal function and adjust the doses of DOACs (7). Our current study also revealed good correlations between eCrCl and mCrCl, the correlation coefficient of 0.74 in our study was quite close to the original study from Cockcroft and Gault which was 0.83 (25). Still, our data suggests that the Cockcroft-Gault-formula might underestimate kidney function among patients with acute ischemic stroke.

In consistency with our previous study (16), we found that increasing mCrCl was significantly associated with decreasing trough plasma levels of DOAC. Similarly, in another study of 511 participants with atrial fibrillation but no acute stroke, Lin et al. investigated the impact of renal function on DOAC levels, the authors also reported negative correlations between the values of eCrCl estimated using the Cockcroft-Gault formula and trough plasma levels of DOAC (34). Recently, based on 90 patients with atrial fibrillation taking DOACs, Russo et al. also reported that increased creatinine clearance was one of the independent predictors of DOAC plasma levels below the reference range (35).

In our study, the trough plasma levels of DOAC were in the expected range in around 80% of the patients, extremely high or low in 10% of the patients respectively. The findings were similar to a Dutch study of

597 patients with DOAC measurement, 489 patients (81.9%) had DOAC plasma levels within range while 108 patients (18.1%) had DOAC plasma levels outside expected ranges (36). Moreover, the current study revealed that increasing mCrCl was an independent predictor of extremely low trough plasma levels of DOAC.

In conclusion, our study shows that the creatinine clearance - either measured based on the 24-hour urine collection or estimated from the Cockcroft-Gault formula - similarly predicts the trough plasma levels of DOAC. Still patients with extremely low values are more reliably identified by direct measurements.

Declarations

Acknowledgements: we thank all the study participants for their support and Mr. Stephan Kadur for helping collect the data.

Competing Interests: The authors have no conflicts of interest to declare.

Data availability statement: Data are available from the corresponding author upon reasonable request.

Human Ethics and Consent to Participate declarations: This study was conducted with the approval of the ethics committee, the study has been approved by the Ethics Committee of the University of Erlangen-Nuremberg (approval number377_17 Bc).

Funding Declaration: no Funding was received to this study.

Consent for publication: All authors have reviewed and approved the final manuscript for publication.

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Figures

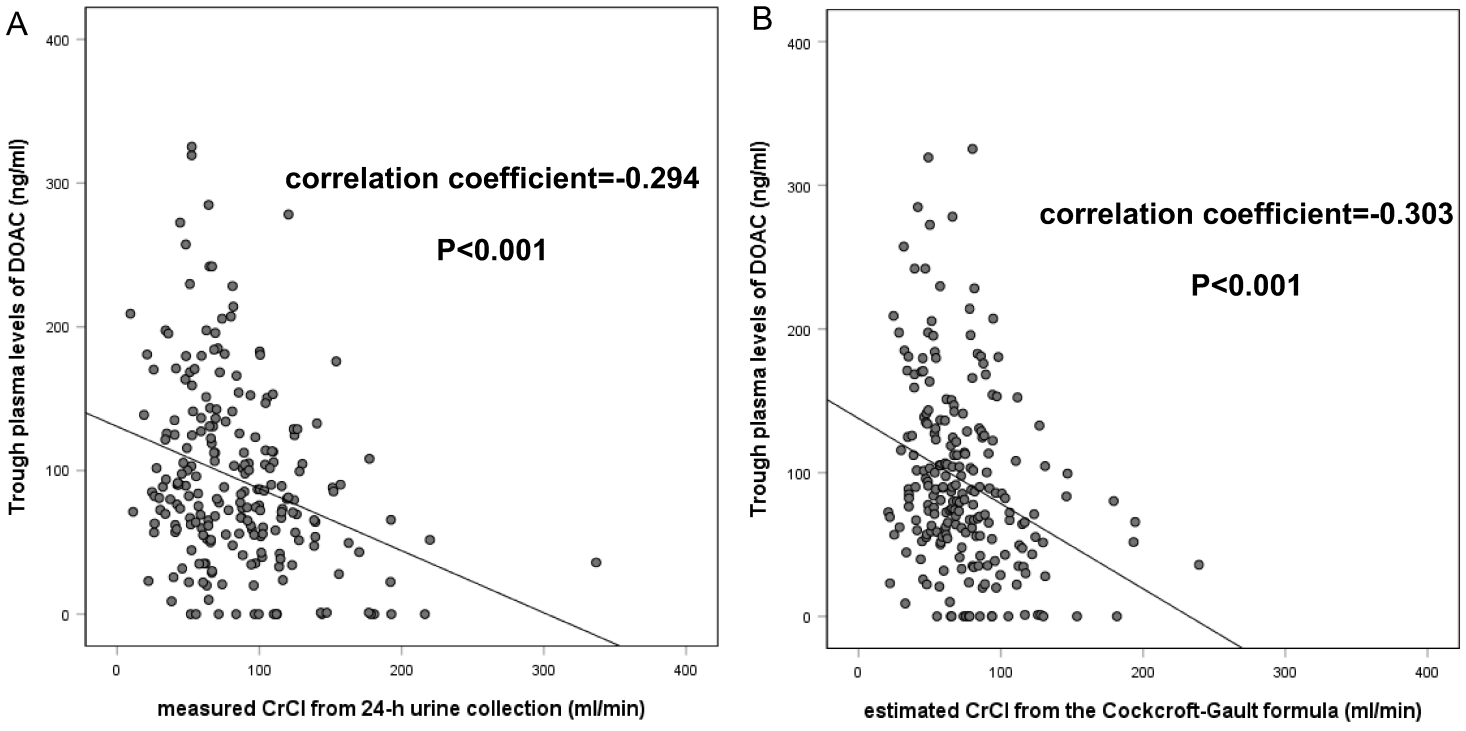


Figure 1

Negative correlations between trough plasma levels of DOAC and creatine clearance.

Significant negative correlations between the measured CrCl from the 24-hour urine collection and the trough plasma levels of DOAC (correlation coefficient= -0.294, P < 0.001), significant correlations between the estimated CrCl form the Cockcroft-Gault formula and the trough plasma levels of DOAC (correlation coefficient= -0.303, P < 0.001). DOAC = direct oral anticoagulants. CrCl = creatinine clearance.

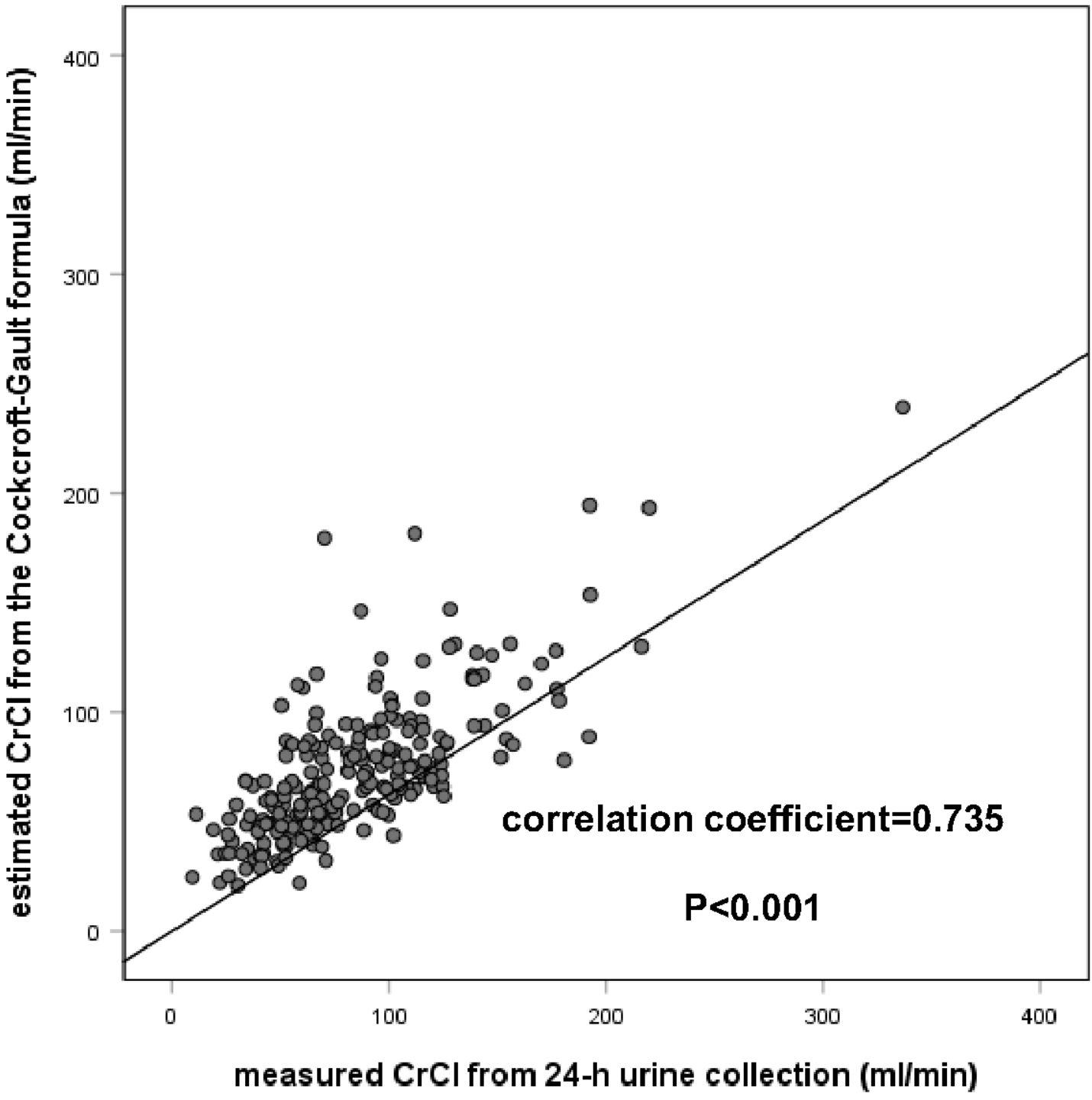


Figure 2

Positive correlation between measured and estimate creatine clearance.

Significant positive correlation between the measured CrCl from the 24-hour urine collection and the estimated CrCl form the Cockcroft-Gault formula (correlation coefficient= 0.735, P < 0.001). CrCl = creatinine clearance.

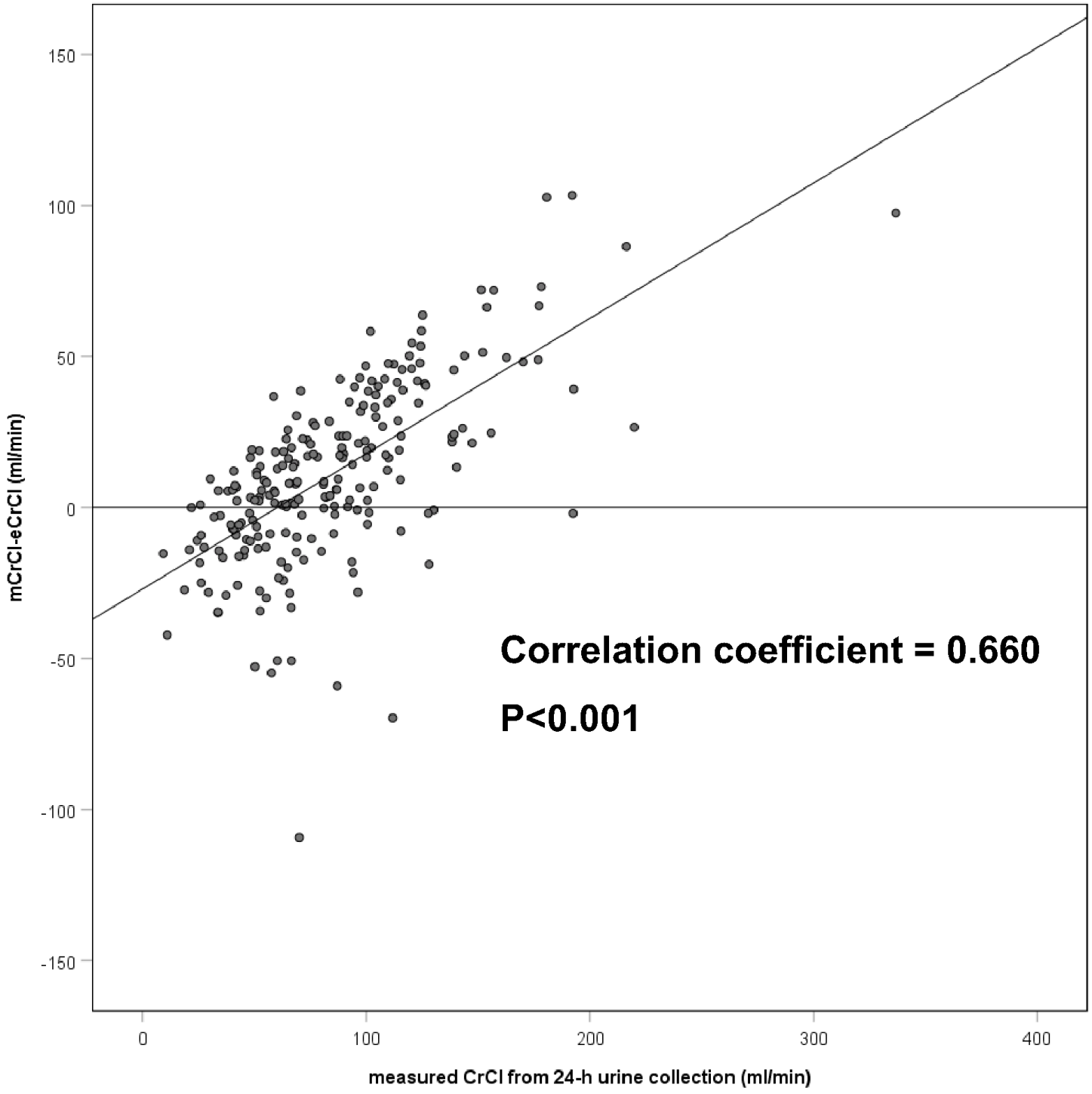


Figure 3

Positive correlation between Delta-CrCl (mCrCl-eCrCl) and mCrCl.

The Delta-CrCl (mCrCl-eCrCl) correlated positively with mCrCl (correlation coefficient = 0.660, P<0.001)

Supplementary Files

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- SupplementaryTable1.docx