

A joint pharmacometric model of iohexol and creatinine administered through a meat meal to assess GFR and renal OCT2/MATE activity

Zhendong Chen, Qian Dong, Charalambos Dokos, Jana Boland, Uwe Fuhr, Max Taubert

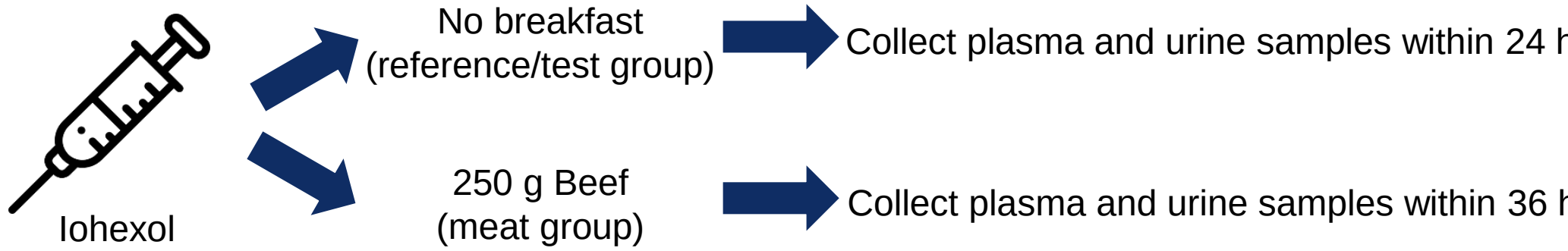
Department I of Pharmacology, Center for Pharmacology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Gleueler Straße 24, Cologne, 50931, Germany.

zhendong.chen@uk-koeln.de

Introduction

Accurately assessing glomerular filtration rate (GFR) from plasma creatinine concentrations is challenging in patients with unstable renal function. Compartmental nonlinear mixed-effects modelling offers a feasible method to more accurately assess unstable creatinine clearance (CrCL) and account for measurement errors[1-3]. A proposed creatinine population pharmacokinetic (popPK) model effectively described renal function changes and outperformed standard methods[4]. However, a further evaluation of this model by an independent assessment of GFR is desirable before application. Additionally, this study assumed a creatinine volume of distribution (V_d) of 60% of total body weight (TBW)[4], which neglected variability and may result in biased estimates of other kinetic parameters. Beyond glomerular filtration of creatinine, the net creatinine tubular secretion (nCTS) also accounts for 10-40% of its renal excretion[5]. The transport pathway responsible for creatinine secretion has been identified as basolateral organic cation transporter 2 (OCT2) and apical multidrug and toxin extrusion proteins (MATEs) through both in vitro experiments and clinical studies[6]. Therefore, creatinine might also serve as an endogenous marker of transporter activity.

Clinical study



Population	14 healthy participants
Blood sampling	Blood samples were collected at -0:15 hours (pre-dose); 10, 20, 30, 45, 60, and 90 minutes; and at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose during the non-meat period. Additional samples were taken at 45 and 75 minutes, as well as at 28, 32, and 36 hours post-dose during the meat period.
Urine sampling	Every 2 hours following iohexol administration until 16 hours post-dose, and every 4 hours from 16 hours until the end of hospitalization.
Measurement	LC-MS/MS methods
Data analysis software	NONMEM

Table 1 Demographics and baseline characteristics for enrolled participants

Demographics/Characteristic	Male	Female	All	
	Mean (SD)	Mean (SD)	Mean (SD)	Range
Number	9	5	14	-
Age (years)	31 (6)	37 (8)	33 (8)	23 – 48
Height (cm)	183 (6)	169 (6)	178 (9)	163 – 196
Total body weight (kg)	86.2 (7.1)	64.5 (4.7)	78.5 (12.2)	59.1 – 95.8
Body mass index (kg/m ²)	25.9 (2.1)	22.6 (0.9)	24.7 (2.4)	21.2 – 28.9
Body surface area (m ²)	2.08 (0.10)	1.74 (0.09)	1.96 (0.19)	1.63 – 2.22
Plasma albumin (g/L)	45.7 (1.6)	45.4 (3.6)	45.6 (2.5)	40.0 – 50.0
Plasma creatinine concentration (mg/dL) ^a	1.00 (0.08)	0.73 (0.09)	0.90 (0.15)	0.60 – 1.17
Estimated creatinine generation rate (mg/h)	78.4 (7.2)	48.0 (4.9)	67.3 (16.3)	41.0 – 92.6
Estimated lean body mass (kg)	64.6 (3.7)	47.8 (3.7)	58.6 (8.9)	43.7 – 69.7
Estimated total body water (L)	48.1 (2.6)	31.9 (1.7)	42.3 (8.1)	29.9 – 52.5
Estimated GFR (mL/min/1.73 m ²)	101 (9)	104 (12)	102 (10)	80.0 – 116

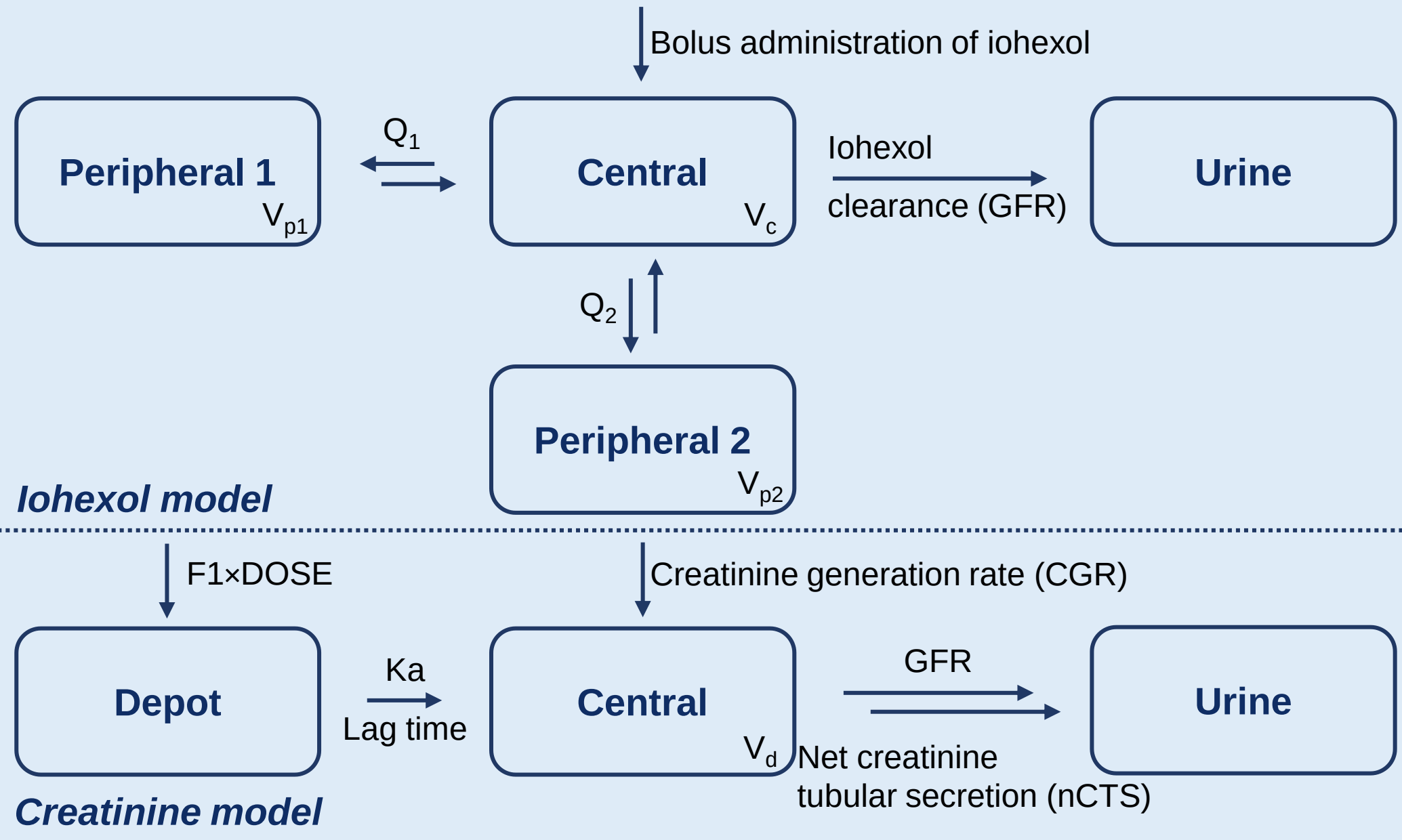
^aPlasma creatinine concentration was measured from a laboratory test at the screening visit.

Results & Discussion

- ✓ A **three-compartment** model for **iohexol** and a **one-compartment** model for **creatinine** fitted the data well;
- ✓ Final estimates for **GFR (IoCL)** and **CrCL (GFR plus nCTS)**, scaled to the mean weight of 78.5 kg, were **94.8 mL/min** and **138 mL/min**, respectively;
- ✓ The estimated nCTS in this study accounts for approximately **31% of the total CrCL**, which falls within the range of 10% to 40%;
- ✓ Creatinine **V_d** was estimated at **28.9 L**, accounting for **41.3% of body weight** in the investigated population;
- ✓ **Body weight** and **estimates of Cockcroft-Gault equation**, included as covariates improved the model fit;
- ✓ **Sex** was identified as a significant covariate on nCTS, potentially due to a higher abundance and expression of transporters in males compared to females;

Population pharmacokinetic analysis

Figure 1 Schematic diagram of the joint model of iohexol and creatinine.



Following bolus administration to the central compartment (volume V_c), iohexol is distributed into two peripheral compartments (volumes V_{p1} and V_{p2}) in parallel, with inter-compartment clearances (Q_{p1} and Q_{p2}). It is eliminated from the central compartment via glomerular filtration rate (GFR). Creatinine, derived from the meat meal, enters the central compartment (volume V_d) via first-order absorption (K_a) with bioavailability (F1). Simultaneously, creatinine is continuously produced at a constant rate (CGR) within the central compartment and is eliminated through both GFR and the net creatinine tubular secretion (nCTS), reflecting the difference between active secretion and re-absorption.

The circadian rhythm of both GFR and nCTS was described based on following equation: $CL = CL_{TV} \times (1 + \sin(\text{time}/\text{interval})) \times \theta_{\text{day/night}}$ where CL represents GFR or nCTS, CL_{TV} is the typical value of GFR or nCTS, "time" was adjusted to start as 0, and "interval" is 14 hours for daytime and 10 hours for night.

For covariate relationships, continuous covariates were modeled with mean-centered power models and categorical covariates were modeled with conditional effects.

Figure 2 Limited sampling strategy using a single plasma sample at 5 hours and a urine sample from 0–5 hours after low-dose (259 mg) iohexol administration.

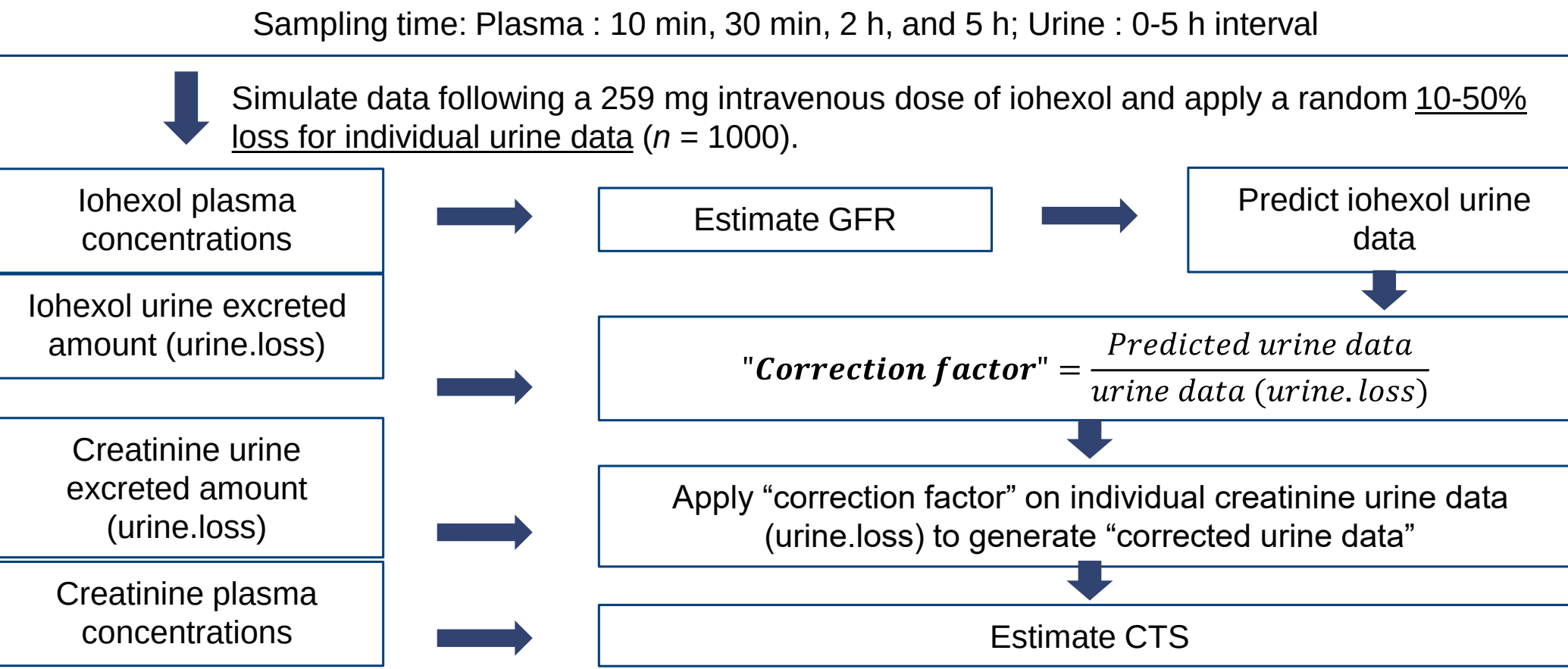
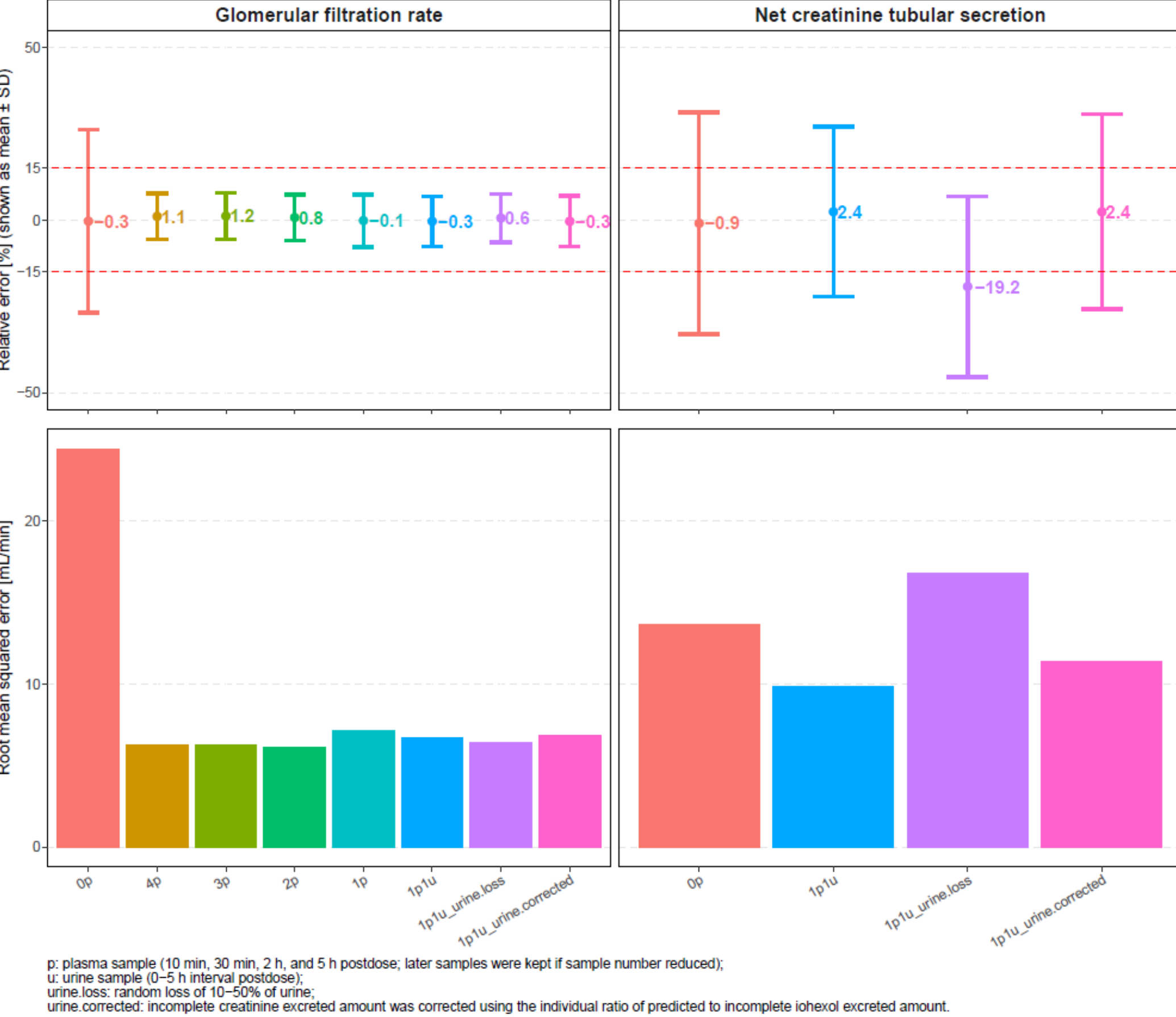


Figure 3 Comparison of prediction accuracy for GFR and nCTS between models using different numbers of plasma concentrations with or without urine data.

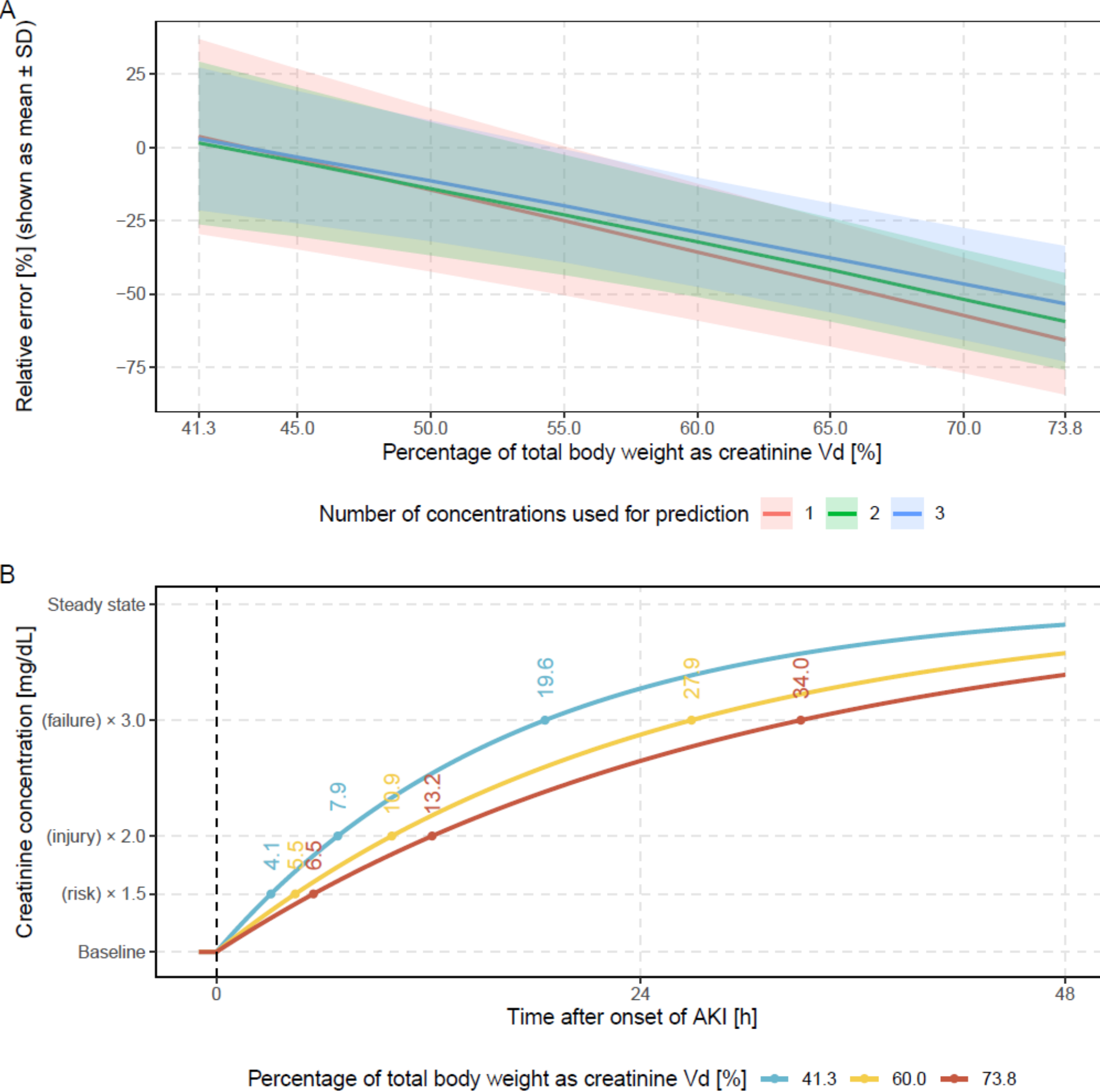


p: plasma sample (10 min, 30 min, 2 h, and 5 h postdose; later samples were kept if sample number reduced); u: urine sample (0–5 h interval postdose); urine loss: random loss of 10–50% of urine; urine corrected: incomplete creatinine excreted amount was corrected using the individual ratio of predicted to incomplete iohexol excreted amount.

Table 2 Parameter estimates and bootstrap ($n = 1000$) results.

Parameters	Estimate	RSE (%)	95% CI	CV (%)	SHR (%)
Fixed effect					
Iohexol					
GFR (mL/min)	87.0	3.4	(81.0, 92.7)	-	-
V_c (L)	8.69	4.7	(7.91, 9.54)	-	-
Q_{p1} (L/h)	0.131	9.2	(0.107, 0.163)	-	-
V_{p1} (L)	1.15	5.2	(1.05, 1.33)	-	-
Q_{p2} (L/h)	4.01	8.0	(3.37, 4.78)	-	-
V_{p2} (L)	4.22	3.1	(3.93, 4.53)	-	-
Creatinine					
K_a (1/h)	1.71	13.3	(1.35, 2.19)	-	-
nCTS (mL/min)	39.7	10.2	(31.2, 46.8)	-	-
V_d (L)	28.9	6.5	(25.6, 33.4)	-	-
F1 (%)	52.3	5.2	(47.7, 58.4)	-	-
Lag time (h)	0.291	3.0	(0.277, 0.308)	-	-
CGR (mg/h)	(140-age) $\times$ body weight/72 $\times$ 0.85(if female) $\times$ 60/100	-	-	-	-
Covariates					
Circadian rhythm during daytime (%)	3.70	21.0	(2.12, 5.72)	-	-
Circadian rhythm during nighttime (%)	8.42	17.7	(5.10, 11.1)	-	-
Sex (female) on nCTS ^a	0.627	15.0	(0.455, 0.857)	-	-
Weight on GFR, Q_{p1} , Q_{p2} , and nCTS	0.75 FIX	-	-	-	-
Weight on V_c and V_d	1 FIX	-	-	-	-
Random effect (inter-individual variability)					
Iohexol					
GFR	0.0226	43.6	(0.00379, 0.0246)	11.9	0.1
V_c	0.0211	38.2	(0.00585, 0.0390)	14.6	18.8
Q_{p1}	0.0121	63.9	(0.00164, 0.0259)	11.0	6.2
V_{p2}	0.0113	33.8	(0.00304, 0.0187)	10.7	9.7
Creatinine					
nCTS	0.0506	56.7	(0.00333, 0.102)	23.1	10.6
V_d	0.0211	40.7	(0.00284, 0.0375)	15.1	2.3
CGR	0.0163	31.2	(0.00710, 0.0278)	12.7	0.7
F1	0.00810	53.5	(0.00145, 0.0205)	10.4	22.8
Random effect (residual variability)					
Iohexol					
Plasma concentration	0.0171	18.4	(0.0118, 0.0240)	13.3	2.6
Excreted amount in urine	0.0617	27.2	(0.0330, 0.0970)	25.2	0.7
Creatinine					
Plasma concentration	0.00255	7.3	(0.00221, 0.00291)	5.1	1.8
Excreted amount in urine	0.0413	41.4	(0.0142, 0.0770)	20.5	1.2

Figure 4 Simulations for AKI diagnosis using different values for creatinine volume of distribution (V_d). A) prediction accuracy of changed GFR after onset of AKI comparing models with different number of concentrations. B) concentration-time curves following a 75% reduction in both GFR and nCTS and the timing to diagnose AKI risk, injury, and failure based on RIFLE criteria.



Conclusion

The joint model of iohexol and creatinine can serve as an effective tool for estimating unstable GFR and nCTS, with nCTS as a potential marker for assessing renal OCT2/MATE activity. Simulations revealed significant differences in predicting GFR changes after AKI based on varying creatinine V_d , emphasizing the importance of careful selection.

References

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