

Population pharmacokinetics and limited sampling of iohexol as a renal function marker

Aims

- To develop a population pharmacokinetic model for iohexol, an exogenous renal function marker.
- To develop limited sampling schedules to ensure optimal clinical feasibility of this approach.
- To provide an approach for reliable renal function evaluation for clinical situations in which conventional methods are not accurate enough or not feasible.

Background

- Current techniques for renal function evaluation in certain clinical situations are not accurate enough for clinical decision making or show limited clinical feasibility.¹
- Iohexol plasma clearance (IPC) shows excellent resemblance with the glomerular filtration rate (GFR).^{1,2}
- Current IPC-based methods require one or multiple blood late samples, up to 8 h after iohexol administration.^{1,2}
- A population pharmacokinetic model and limited sampling schedule (LSS) early after iohexol administration could drastically improve the clinical feasibility of this technique.

Methods

- Routine IPC-based GFR estimation for renal transplant donor candidates and renal transplant recipients was performed at Leiden University Medical Center.
- All individuals received a single intravenous injection of 5 ml of 647 mg iohexol per ml. PK sampling took place at 5 min, 30 min, 1 h, 2 h, 2.5 h, 3 h, 3.5 h and 4 h postdose.
- Iohexol plasma concentrations were quantified using a newly developed high performance liquid chromatography assay combined with ultraviolet detection (HPLC-UV).
- Population pharmacokinetic modelling was performed using NONMEM® 7.3.0 (Icon Development Solutions, Ellicott City, USA), with PsN Toolkit 4.8.1³ and Piraña 2.9.7⁴ as modelling environment. Data preparation, data visualization and statistics were performed with R 3.5.1 and Rstudio 1.1456.
- FOCE-I was applied throughout the model-building process. Model selection was based on a statistical significant change in the OFV ($\Delta\text{OFV} > -6.63$) between a candidate model and its precursor ($p < 0.01$, $df = 1$, assuming Chi-squared distribution).
- Internal evaluation of candidate models and the final model was performed using standard diagnostic plots with LOESS regression, prediction corrected visual predictive checks (VPC) (n=500) and bootstrap analysis (n=1000).
- LSS were developed based on the individual predicted IPC-based GFR for 1, 2, 3 and 4 sample-based sampling schedules within 3 h after iohexol administration.
- LSS performance was evaluated against the full dataset, using Pearson R², MPE, RMSE and the percentage of GFR_{ISS} exceeding the 5%-20% margins around the GFR_{full}.

Demographics

| Parameter | Model development cohort | | |
|---|--------------------------|------------|-------------|
| | Mean | 95% CI | Range |
| N | 49 | | |
| Gender (male; female) | 16; 33 | | |
| Age (years) | 58.2 | 55.4; 61.0 | 28.6; 73.1 |
| Weight (kg) | 71.8 | 68.4; 75.3 | 50.0; 99.0 |
| BMI (kg m ⁻²) | 24.9 | 23.8; 25.9 | 17.5; 33.5 |
| BSA (m ²) | 1.82 | 1.78; 1.87 | 1.49; 2.16 |
| eGFR (ml min ⁻¹ 1.73 ⁻²) | 68.0 | 61.7; 74.2 | 16.9; 109.1 |

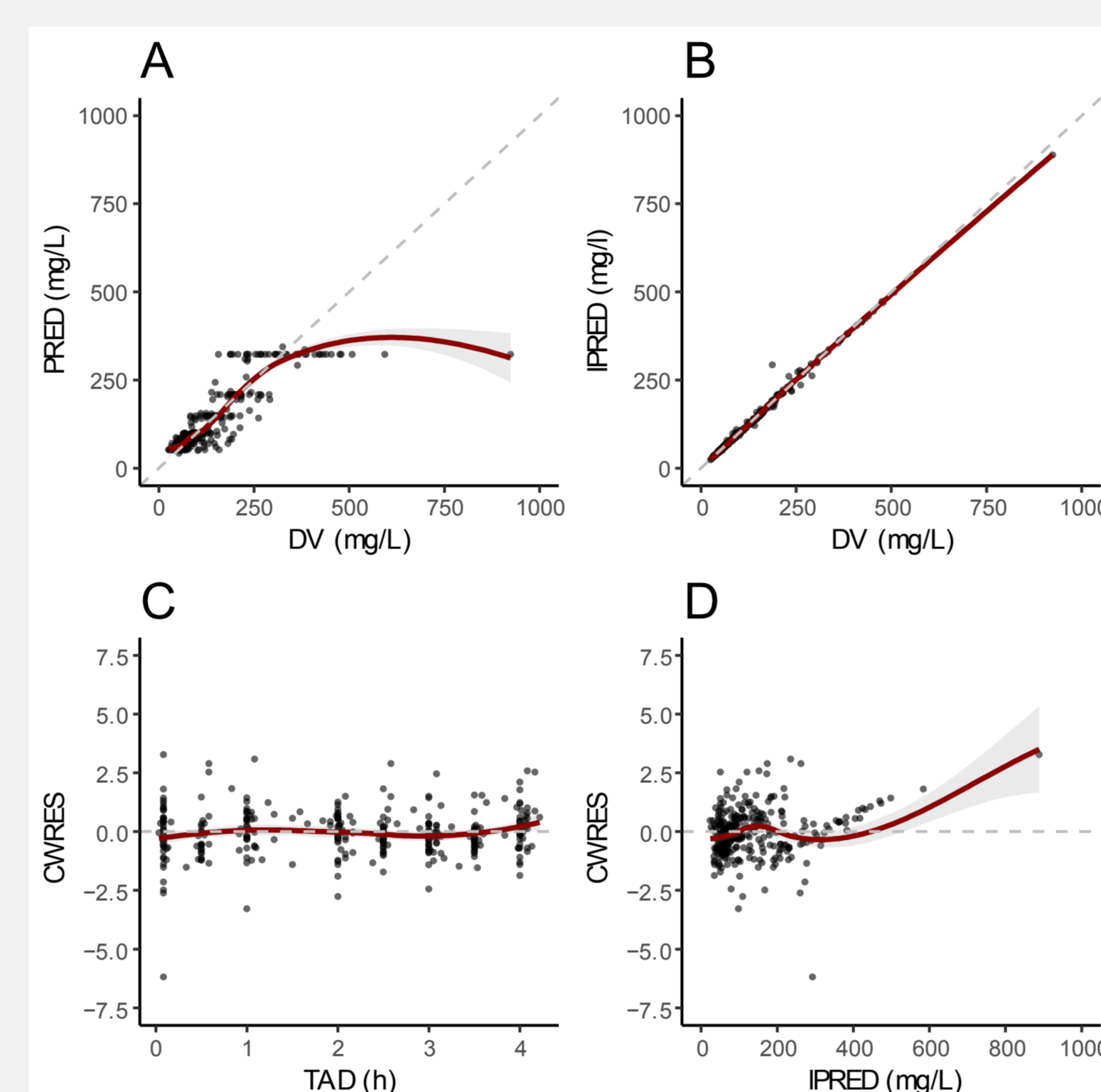
Population pharmacokinetic parameters

| Parameter | Final model | | | Bootstrap analysis | |
|--------------------------|-------------|---------|---------------|--------------------|-------------|
| | Estimate | RSE (%) | Shrinkage (%) | Median | 95% CI |
| CL (L h ⁻¹) | 4.89 | 6 | | 4.87 | 4.40; 5.38 |
| Q (L h ⁻¹) | 7.26 | 25 | | 7.33 | 4.78; 9.86 |
| V _c (L) | 9.20 | 6 | | 9.13 | 8.13; 10.26 |
| V _p (L) | 5.48 | 14 | | 5.65 | 4.44; 6.50 |
| IIV CL (CV%) | 34.4 | 14 | 0 | 33.6 | 22.2; 43.1 |
| IIV Q (CV%) | 86.2 | 18 | 11 | 85.4 | 29.9; 118.4 |
| IIV V _c (CV%) | 35.2 | 12 | 6 | 34.5 | 23.2; 44.1 |
| IIV V _p (CV%) | 41.7 | 44 | 9 | 40.0 | -18.1; 62.5 |
| Proportional error (CV%) | 5.4 | 42 | 25 | 5.3 | 2.4; 7.3 |

Evaluation of the final model

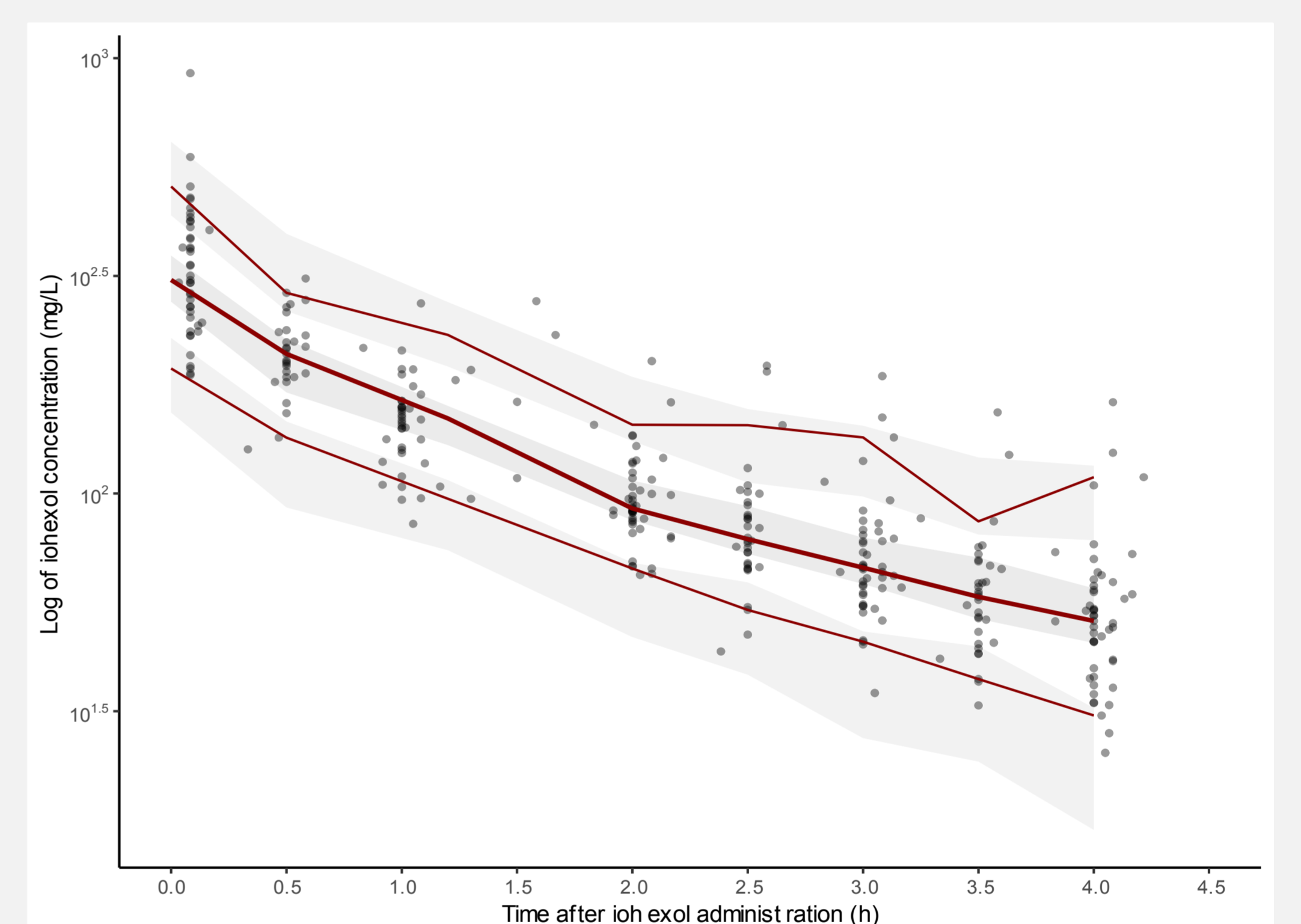
Diagnostic plots

DV vs PRED (A) and IPRED (B),
CWRES vs TAD (C) and IPRED (D)



Prediction corrected VPC

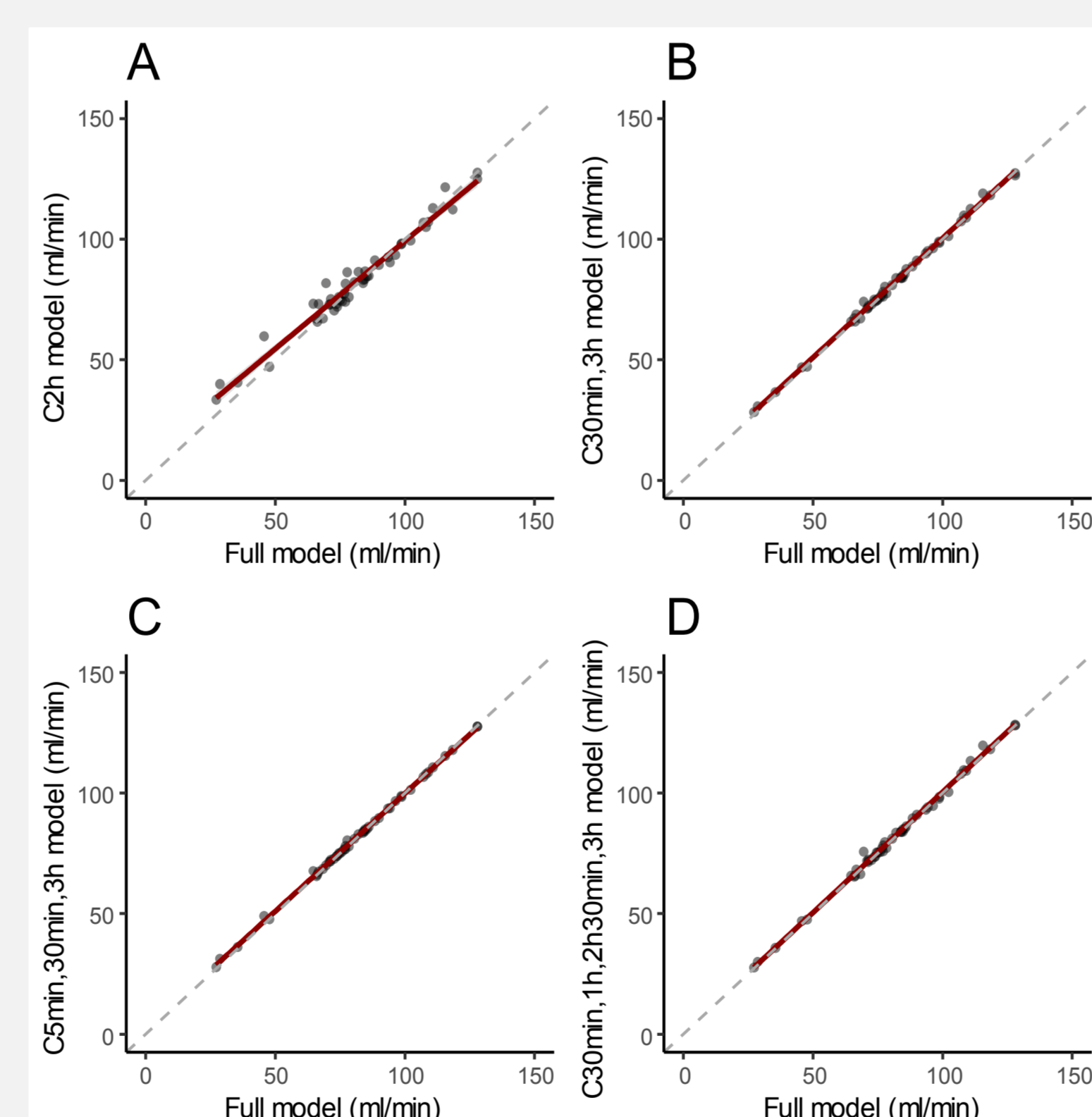
Log-normal median, 10th and 90th percentiles of predicted (grey shading) and observed iohexol concentrations (red solid lines)



Development of clinically feasible sampling schedules

Predictive performance (graphical)

Comparison of GFR estimated by the best one (A), two (B), three (C) and four (D) sample-based LSS models vs the full model



Predictive performance (numerical)

Comparison of GFR estimations from the best one, two, three and four sample-based LSS models vs GFR estimations from the full model

| | R ² | MPE (%) | RMSE (%) | Percentage of GFR _{ISS} within 5% of GFR _{full} | Percentage of GFR _{ISS} within 10% of GFR _{full} | Percentage of GFR _{ISS} within 15% of GFR _{full} | Percentage of GFR _{ISS} within 20% of GFR _{full} |
|----------------------|----------------|---------|----------|---|--|--|--|
| One sample | | | | | | | |
| 2h | 0.968 | 3.04 | 2.52 | 73.47 | 85.71 | 91.84 | 93.88 |
| Two samples | | | | | | | |
| 30 min, 3h | 0.997 | 0.97 | 0.77 | 95.92 | 100.0 | 100.0 | 100.0 |
| Three samples | | | | | | | |
| 5min, 30min, 3h | 0.999 | 0.67 | 0.41 | 95.92 | 100.0 | 100.0 | 100.0 |
| Four samples | | | | | | | |
| 30min, 1h, 2.5h, 3h | 0.996 | 0.62 | 0.60 | 97.96 | 100.0 | 100.0 | 100.0 |

References, COI, Funding

- Porrini *et al.* Nat Rev Nephrol. 2019.
 - Delanaye *et al.* Clin Kidney J. 2016.
 - Lindbom *et al.* Comput Methods Programs Biomed. 2005.
 - Keizer *et al.* Comput Methods Programs Biomed. 2011.
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Discussion

- CWRES vs IPRED indicated a slight misspecification at concentrations >400 mg/L, while the VPC did not.
- Iohexol shows minor (<5%) non-renal clearance, this was not taken into account or corrected for in this study.
- An external validation is warranted to provide additional confirmation of the validity of the final model and LSS.

Conclusions

- Iohexol pharmacokinetics were best described with a two-compartmental population pharmacokinetic model with linear elimination.
- Limited sampling in the first 3 h after iohexol administration can be applied to enable clinically feasible IPC-based GFR estimation for renal function evaluation purposes.



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