Clinical pharmacometrics to optimize immunosuppressive therapy in kidney transplantation

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CHAPTER 5

Model-based estimation of iohexol plasma clearance for pragmatic renal function determination in the renal transplantation setting

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Clin Pharmacokinet 2021; 60(9): 1201-1215

ABSTRACT

Background: Iohexol plasma clearance-based glomerular filtration rate (GFR) determination provides an accurate method for renal function evaluation. This technique is increasingly advocated for clinical situations that dictate highly accurate renal function assessment, as an alternative to conventional serum creatinine-based methods with limited accuracy or poor feasibility. In the renal transplantation setting, this particularly applies to living renal transplant donor eligibility screening, renal transplant function monitoring, and research purposes. The dependency of current iohexol GFR estimation techniques on extensive sampling, however, has limited its clinical application. We developed a population pharmacokinetic (PK) model and limited sampling schedules (LSSs), implemented in the online InsightRX precision dosing platform, to facilitate pragmatic iohexol GFR assessment.

Methods: Iohexol concentrations (N=587) drawn 5 min to 4 h after administration were available from 67 renal transplant recipients and 41 living renal transplant donor candidates with measured iohexol GFRs of 27–117 mL/min/1.73 m^2. These were split in a model development (N=72) and internal validation (N=36) cohort. External validation was performed with 1040 iohexol concentrations from 268 renal transplant recipients drawn between 5 min to 4 h after administration, and extended iohexol curves up to 24 h from 11 random patients with impaired renal function. LSSs based on 1–4 blood draws within 4 h after iohexol administration were evaluated in terms of bias and imprecision, using the mean relative prediction error (MPE) and mean absolute relative prediction error (MAPE). The total deviation index (TDI) and percentage of LSS-based GFR predictions within ±10% of those of the full model (P_{10}) were assessed to aid interpretation.

Results: Iohexol PK were best described with a two-compartmental first-order elimination model, allometrically scaled to fat-free mass, with patient type as a covariate on clearance and the central distribution volume. Model validity was confirmed during the internal and external validation. Various LSSs based on 3-4 blood draws within 4 h showed excellent predictive performance (MPE within ±0.5%, MAPE <3.5%, TDI <5.5%, and P_{10} >97%). The best LSSs based on 3–4 blood draws within 3 h showed reduced predictive performance (MPE within ±0.75%, MAPE <5.5%, TDI <9.5%, and P_{10} ≥85%), but may be considered for their enhanced clinical feasibility when deemed justified.

Conclusions: Our online pharmacometric tool provides an accurate, pragmatic, and ready-to-use technique for measured GFR-based renal function evaluation for clinical situations where conventional methods lack accuracy or show limited feasibility. Additional adaptation and validation of our model and LSS for renal transplant recipients with GFRs below 30 mL/min is warranted before considering this technique in these patients.

INTRODUCTION

Unequivocal renal function determination is pivotal in many clinical situations. In the renal transplantation setting, this is particularly true for living renal transplant donor eligibility screening and renal transplant function monitoring, as well as for research purposes.

Initial screening of living renal transplant donor candidates and routine monitoring of renal transplant recipients is typically performed with 24 h urinary creatinine clearance or by estimation of the glomerular filtration rate using serum creatinine and an estimation formula ($eGFR_{cr}$) [1, 2]. Although $eGFR_{cr}$ has provided a convenient renal function marker for decades, it shows poor agreement with measured GFR (mGFR) techniques, which are considered to correspond best with the true GFR [3, 4]. However, 24 h urinary creatinine clearance assessment, is considered cumbersome due to the challenge of collecting and transporting the timed urine collection [1]. In donor candidate screening, this poses a challenge when determining the eligibility of donor candidates with borderline 24 h urinary creatinine clearance or $eGFR_{cr}$ typically within the 60–90 mL/min/1.73 m^2 range [1, 3]. In recipients, it may render $eGFR_{cr}$ to be of limited informative value to monitor transplant function over time [2, 3]. International guidelines on donor screening and recipient care acknowledge the limited reliability of $eGFR_{cr}$ for these purposes and identify mGFR techniques, which utilize urinary or plasma clearance of exogenous filtration markers, superior in terms of accuracy [1-4]. Although mGFR techniques are generally considered the gold standard for renal function assessment, these can prove burdensome because of their dependency on extensive sampling [3, 5]. This limits the clinical feasibility of mGFR and has hampered its widespread use in routine clinical practice. In recent years, mGFR based on single-dose iohexol plasma clearance has, nonetheless, gained particular clinical interest and is advocated as an alternative for routine renal function evaluation [3-5].

In conventional iohexol mGFR methods, iohexol is administered via a single intravenous bolus injection [6, 7]. Iohexol plasma clearance is then quantified from the full area under the concentration-time curve (AUC), determined by either extensive sampling or sparse sampling during the terminal log-linear elimination phase with subsequent extrapolation to the full AUC using the Brøchner-Mortensen or Jacobsson equation [7-9]. Whereas these methods provide clinically feasible approaches for iohexol GFR determination, they are based on estimations guided by the terminal elimination phase exclusively [6]. Furthermore, these methods continue to rely on extensive sampling or late samples drawn up to 8 h after iohexol administration [6, 7], which still encompasses a large patient burden.

A pharmacometric approach could likely provide a more accurate and robust iohexol GFR estimation, as this technique can capture its entire pharmacokinetic (PK) profile. Moreover, it facilitates the development of limited sampling schedules (LSSs) drawn early after iohexol administration to aid clinical application. Indeed, a previously published pharmacometric model showed adequate GFR predictive abilities, utilizing Bayesian forecasting with four blood samples drawn within 5 h after iohexol administration [10]. Notably, sampling up to 5 h was required for adequate estimation reliability for GFRs below 30 mL/min [10]. As renal transplant recipients and particularly donor candidates typically show GFRs exceeding 30 mL/min, this likely allows for application of shorter sampling schemes in this population to further increase the clinical feasibility of iohexol mGFR determination.

Here, we aim to develop a population PK model and LSSs for iohexol to provide a pragmatic tool for iohexol GFR determination in the renal transplantation setting. Additionally, we incorporate the model in an online precision dosing platform to further aid its clinical application.

METHODS

Software

Data handling, visualization, and statistics were performed in R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio 1.2.5019 (RStudio Inc., Boston, USA). The pharmacometric analysis was performed with nonlinear mixed-effects modelling software NONMEM® 7.4 (Icon Development Solutions, Ellicott City, USA), using Piraña 2.9.8 and Perl-speaks-NONMEM (PsN) Toolkit 5.0.0 as modelling environment [11, 12].

Pharmacokinetic data

The study was based on pooled iohexol PK profiles from 335 renal transplant recipients and 41 living renal transplant donor candidates. These included recipients who participated in the multicentre REPAIR trial (ISRCTN30083294; N=320, of which 52 were treated at Leiden University Medical Center; LUMC) [13] or a phase I study conducted at LUMC (NCT00734396; N=15) [14], and donor candidates who underwent routine eligibility screening at LUMC (N=41). The ISRCTN30083294 participants received a single intravenous injection of Omnipaque 240 (2590 mg iohexol) or Omnipague 300 (3235 mg iohexol) with sampling at 5 min, 2 h, 3 h, and 4 h after administration, whereas the NCT00734396 participants received Omnipaque 300 with sampling at 5 min, 1 h, 2 h, 3 h, and 4 h. Donor candidates received Omnipaque 300 for renal function confirmation purposes, with sampling at 5 min, 30 min, 1 h, 2 h, 2.5 h, 3 h, 3.5 h, and 4 h. Sex, age, weight, height, and the iohexol GFR as determined using the slope-intercept method with the Brøchner-Mortensen correction (GFR_{bm}) [8], were available.

All renal transplant recipients (N=67) and donor candidates (N=41) treated at LUMC were pooled and then split to create a model development and internal validation cohort, using automated block-randomized assignment of recipients and donor candidates to the development and internal validation cohort in a 2:1 manner. Renal transplant recipients who participated in ISRCTN30083294 but were not treated at LUMC (N=268) were pooled in an external validation cohort.

All data originated from studies with previous medical ethical approval or were collected retrospectively from routine clinical care. Hence, this study by Dutch Law is considered research not subjected to the Medical Research Involving Human Subjects Act. A statement of non-objection was issued by the scientific committee of the Department of Internal Medicine of LUMC (W2019.033). All donor candidates gave written informed consent for the retrospective collection of their relevant medical records, in accordance with the European General Data Protection Regulation (GDPR; Regulation (EU) 2016/679),

Bioanalytics

A novel high-performance liquid chromatography assay combined with ultraviolet detection (HPLC-UV) was developed for quantification of iohexol in plasma for NCT00734396 and routine donor eligibility screening, based on two previous assays [15, 16]. Details on the technical aspects and analytical validation are provided in the Supplementary Material.

Iohexol quantification for ISRCTN30083294 was performed at Evelina London Children's Hospital (London, UK) using a previously validated HPLC tandem mass spectrometry (HPLC-MS/MS) assay [17]. No substantial divergence between the iohexol results from LUMC and Evelina London Children's Hospital were expected, as these assays have a similar analytical set-up and both centres participate in interlaboratory proficiency testing (Equalis AB, Uppsala, Sweden) for their iohexol assays. For thoroughness, 24 randomly selected NCT00734396 samples were re-analysed at LUMC. All but one (95.8%) of the iohexol concentrations quantified at LUMC were within ±15% of those of Evelina London Children's Hospital, and 21/24 (87.5%) within ±10%. These findings confirmed that the iohexol data from both centers could be applied interchangeably. Further details are provided in the Supplementary Material.

Pharmacometric modelling

Model development

Iohexol PK were estimated from the concentration-time data of the model development cohort using a population PK model. The first-order conditional estimation method with interaction (FOCE-I) was applied throughout the analysis. Model selection was based primarily on a statistically significant change in the objective function value (ΔOFV) between a modified model and its precursor, with ΔOFV below -6.64 ($p<0.01$, degrees of freedom = 1, assuming Chi-squared distribution) resulting in selection of the modified model, provided proper model convergence, appropriate visual diagnostics, and acceptable extents of parameter estimate uncertainty and shrinkage (<30%) [18]. During the base model development, one-, two-, and three-compartmental model structures with zero- and first-order elimination were explored and additive, proportional, and combined residual error model structures were evaluated.

A covariate analysis was performed to explore options to optimize the individual predictive performance of the model. Allometric scaling of the parameters to account for between-subject variability (BSV) in body composition was considered likely to improve model performance [19]. Accordingly, we evaluated a covariate model in which all flow and volume parameters were allometrically scaled to a fat-free mass (FFM) of 57.18 kg, corresponding with a male with a height of 1.80 m and total body weight of 70 kg. The FFM was predicted from sex, total bodyweight, and height using standard equations [20]. All flow parameters in this model were exponentiated by 0.75, whereas linear proportionality was assumed for volume parameters [21]. In addition, a discrepancy between the typical renal function of renal transplant donor candidates and recipients is apparent. Hence, accounting for this divergence by addition of patient type ('recipient' or 'donor candidate') as a covariate was considered likely to improve model performance. Characterization of the final covariate model was guided by biological plausibility, reduction of the random variability, improvement of visual diagnostics, model stability, and the ΔOFV.

Graphical model evaluation was performed using standard diagnostic plots [22] and prediction-corrected visual predictive checks (pcVPCs; N=1000) [23]. As the model was intended primarily for individual clearance estimation from PK measurements using maximum *a posteriori* Bayesian estimation (MAP-BE), most emphasis was laid on the individual predictive performance of the model. Evaluation of the robustness of the final parameter estimates was performed using the bootstrap procedure in PsN (N=1000) [24], stratified to patient type to ensure an even distribution of recipients and donor candidates in the resampling datasets.

Model validation

The final model was validated on the internal and external validation cohorts using a two-step approach. First, a model run with the parameter re-estimation option enabled and a bootstrap analysis (N=1000) were performed on the internal validation cohort to evaluate parameter estimate robustness. Second, we evaluated the performance of the model using pcVPCs (N=1000) and individual prediction diagnostics on the internal and external validation cohorts. For the latter analysis, all model parameters were fixed to the median population values of the final model.

Additionally, we compared the model-predicted individual iohexol clearances to the GFR_{bm} to assess whether its ability to describe individual iohexol concentrations coincided with reliable GFR predictions. A complicating factor for this comparison, however, was that the model was expected to outperform GFR_{bm}. Namely, the GFR_{bm} assumes a terminal log-linear elimination phase for every patient from 2 h after administration. Moreover, the mathematical extrapolation to time zero is highly dependent of a correct characterisation of the log-linear regression slope. Furthermore, and most importantly, the Brøchner-Mortensen equation encompasses a correction factor tailored to the iohexol distribution profile of the typical patient, whereas this profile varies across GFRs. Albeit helpful to provide a GFR estimate when characterisation of the non-linear portion of the curve is impossible or infeasible, these intrinsic dependencies and assumptions render the GFR_{bm} error prone for individual GFR determination. Alternatively, an appropriate population PK model enables characterisation of the entire individual iohexol curve utilizing all available PK information, likely yielding more accurate and more precise GFR estimates. Comparison between our model-predicted GFRs and the GFR_{bm}, however, still is informative. For this purpose, a virtual patient population (N=1000) was created in which FFM and patient type were sampled randomly from a univariate distribution and a binomial distribution with equal probabilities, respectively. The final model with residual error was then applied to simulate 5 h iohexol curves. The simulated iohexol concentrations at 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min were then used as PK input data to derive model-predicted individual iohexol clearances. The GFR_{bm} was calculated following standard practice; the iohexol dose was divided by the area under the log-linear regression curve of the iohexol concentrations at either 120, 180, and 240 min (3-point GFR_{bm}), 120, 150, 180, 210, and 240 min (5-point GFR_{bm}), or 120, 150, 180, 210, 240, 270, and 300 min (7-point GFR_{bm}) extrapolated to the concentration at time zero, corrected for the early distribution phase using the Brøchner-Mortensen formula, assuming a terminal log-linear elimination phase [6, 8].

Finally, we evaluated the ability of the model to fit iohexol curves beyond 4 h after administration using standard individual plots. Whereas the 0-4 h window captures most of the iohexol

AUC for most renal transplant recipients and donor candidates, it is important to evaluate whether the model is also able to adequately capture the remainder of the curve. Iohexol curves up to 24 h after Omnipaque 300 administration from 11 random subjects (N=108) with GFRs below 40 mL/min who participated in the study by Åsberg et al. [10] were kindly provided by Oslo University Hospital. This hospital also participates in the Equalis interlaboratory proficiency testing program, ensuring iohexol data interchangeability.

Limited sampling schedule selection

Various LSSs based on 1-4 blood draws within the first 4 h after iohexol administration were evaluated. Herein, an optimal LSS would require as few samples as possible, drawn as early after administration as possible, while ensuring highly accurate and precise iohexol GFR estimation.

The LSS analysis was performed on the virtual patient population created during the model validation. This dataset included model-predicted individual iohexol clearances, estimated from concentrations at 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min. These individual iohexol clearance estimates were considered the reference GFR values (GFR_{ref}). For each LSS, the dataset was subsetted to include only the PK data obtained at the time instances included in that particular LSS. Subsequently, the individual iohexol clearance estimates for each LSS (GFR_{lss}) were derived from estimation of the PK curve up to 240 min using MAP-BE. The GFR_{ref} and GFR_{lss} were then compared to evaluate the predictive performance of the model for each LSS.

Herein, the predictive performance was expressed with the mean relative prediction error (MPE) for bias, and the mean relative absolute prediction error (MAPE) for imprecision [25]. In addition, the root mean squared percentage prediction error (RMSE), Pearson correlation coefficient (R^2), total deviation index (TDI) [26], concordance correlation coefficient (CCC) [27], and the percentages of the GFR_{lss} within ±5% to ±20% of the GFR_{ref} (P_5-P_{20}) were assessed to aid interpretation [3].

Implementation in the InsightRX framework

To provide a certified, robust, ready-to-use, and end-user friendly tool for applying our model, the final model was incorporated in the InsightRX Nova framework (InsightRX, San Francisco, CA, USA). Via a license agreement, InsightRX Nova (www.insight-rx.com) is accessible as an online web-application, built around the open-source PKPDsim simulation library for R (www.pkpdsim-docs.com). Based on collected PK measurements and additional patient characteristics, the platform applies MAP-BE for derivation of the individual estimates for the population model parameters. The platform relies on local electronic medical record (EMR) software integration, or, when this is not operable, manual input of patient characteristics, dosing information and collected PK measurements. No modelling knowledge or experience is required to operate the tool. Our final population PK model was implemented in an InsightRX Nova dosing module for iohexol. InsightRX Nova adheres to ISO13485 (Quality Management for Medical Devices) and its quality procedures require verification of model implementation for numerical accuracy and robustness. Numerical verification against NONMEM was performed for the simulation of iohexol concentration data based on PK parameters, covariates, and dosing regimens, as well as for the calculation of individual estimates using MAP-BE based on simulated input data.

RESULTS

Pharmacokinetic data

A total of 394 PK observations from 72 subjects were available for the model development. Internal and external validation were performed with 193 and 1044 observations from 36 and 268 subjects, respectively. The demographics of these cohorts are summarized in Table 5.1.

Table 5.1: Characteristics of the model development and internal and external validation cohorts

	Development cohort			**Internal validation cohort**			**External validation cohort**		
Characteristic	N	Median	Range	N	Median	Range	N	Median	Range
Total number of patients	72			36			268		
Patient type (recipient; donor)	45; 27			22; 14			268; 0		
Sex (male; female)	32; 40			17; 19			193; 75		
Age (years)		58.0	19.9; 78.3		58.3	24.8; 72.5		47.2	19.1; 77.0
Weight (kg)		72.8	45.0; 124		73.8	50.0; 99.0		80.0	38.5; 133
Height (cm)		171	148; 204		170	156; 186		175	147; 196
mGFR (mL/min/1.73 m^2)		67.0	27.0; 117		73.0	28.8; 113		58.9	16.6; 104

mGFR measured glomerular filtration rate as derived from iohexol plasma clearance, calculated using the slope-intercept method with Brøchner-Mortensen correction.

Pharmacometric modelling

Model development

Iohexol PK were best described by a two-compartmental model with first-order elimination, with BSV on clearance (CL), intercompartmental clearance (Q), and the central (V_c) and peripheral distribution volumes (V_p), and a proportional error model. Efforts to fit the model with a full variance-covariance matrix of random effects showed slight model instability, which was resolved after parametrization of the matrix to include only the covariance between the BSV in CL, V_c, and Q, but not V_p. A one-compartmental model showed a clear misspecification in the early distribution phase, whereas efforts to fit a three-compartmental model resulted in overparameterization. Allometric scaling of all flow and volume parameters to FFM yielded a ΔOFV of -19.6, whereas addition of patient type as a covariate on CL and V_c yielded a ΔOFV of -14.1. Combining both in the final covariate model yielded a ΔOFV of -45.7, with reduction of the random variabilities in CL (34.1% → 29.8%), V_c (42.2% → 40.4%), Q (67.7% → 61.7%), and V_p (28.2% → 23.5%). The parameter estimates of the base and final model on the development cohort are summarized in Table 5.2. The NONMEM code for the final model is provided in the Supplementary Material.

The goodness-of-fit plots for the final model are depicted in Figure 5.1. The individual predicted and observed iohexol concentrations showed excellent agreement across the concentration range (Figure 5.1a) with a RMSE of 3.37%. The conditional weighted residuals (CWRES) showed an even distribution over the individual predicted iohexol concentrations (Figure 5.1b) and GFRs (Figure S5.3) within acceptable ranges. The population prediction diagnostics indicated adequate model appropriateness (Figure 5.1c-e).

The results of the bootstrap analysis of the final covariate model on the development cohort are presented in Table 5.2. Convergence was successful in 83.0% of the bootstrap runs. All median parameter estimates from the bootstrap analysis were within 5% of the parameter estimates of the final model, indicating good parameter estimate reliability.

Model validation

The final model was validated successfully on the internal and external validation cohorts. The results of the parameter re-estimation and bootstrap analysis of the final model on the internal validation cohort are presented in Table 5.2. Convergence was successful in 89.2% of the bootstrap runs. The parameters, as re-estimated on the validation cohort, generally showed adequate concordance with those estimated on the development cohort. The estimates of the primary model parameters, CL, V_c, Q, and V_p, and the covariate relationships were within the

Table 5.2: Population pharmacokinetic parameter estimates from the base model, final model, and bootstrap analysis of the final model on the development and internal validation cohort

	Development cohort			**Internal validation cohort**	
	Base model Estimate (RSE; shrinkage)	*Final model* Estimate (RSE; shrinkage)	*Bootstrap analysis* Median estimate [95% CI]	*Final model* Estimate (RSE; shrinkage)	*Bootstrap analysis* Median estimate [95% CI]
Parameter					
CL (L/h)	4.19 (5%)	4.07 (5%)	4.06 [3.65; 4.48]	4.32 (6%)	4.32 [3.76; 4.81]
V_c (L)	8.15 (6%)	8.36 (9%)	8.30 [7.27; 9.60]	8.05 (6%)	8.17 [7.16; 9.17]
Q (L/h)	6.50 (12%)	7.71 (9%)	7.83 [6.05; 10.1]	9.56 (8%)	9.54 [7.18; 11.3]
V_p (L)	6.07 (5%)	6.88 (5%)	6.94 [6.22; 7.62]	7.11 (6%)	7.13 [6.37; 8.15]
Covariate relationships					
Patient type on CL		0.483 (21%)	0.487 [0.312; 0.692]	0.463 (24%)	0.469 [0.270; 0.730]
Patient type on V_c		0.342 (38%)	0.336 [0.100; 0.609]	0.351 (34%)	0.314 [0.081; 0.595]
Between-subject variability					
CL (CV%)	34.1 (8%; 3%)	29.8 (11%; 4%)	29.1 [22.6; 36.3]	22.6 (17%; 2%)	22.1 [14.2; 30.0]
V_c (CV%)	42.2 (8%; 5%)	40.4 (8%; 5%)	39.7 [33.1; 46.3]	24.1 (11%; 9%)	23.1 [17.1; 30.7]
Q (CV%)	67.7 (10%; 25%)	61.7 (12%; 27%)	59.8 [31.7; 76.4]	14.8 (51%; 8%)	16.4 [3.57; 56.0]
V_p (CV%)	28.2 (23%; 27%)	23.5 (18%; 30%)	23.6 [12.9; 32.6]	28.4 (19%; 14%)	27.1 [13.3; 37.3]
Random residual variability					
Proportional error (CV%)	5.27 (13%; 31%)	5.23 (14%; 30%)	5.16 [3.84; 6.55]	5.19 (21%; 26%)	5.05 [3.45; 7.38]
Additive error (CV%)	0 (FIX)	0 (FIX)	0 (FIX)	0 (FIX)	0 (FIX)

95% CI 95% confidence interval; *CL* total body clearance; *CV%* coefficient of variation; *FIX* fixed; *Q* intercompartmental clearance; *RSE* relative standard error; V_c volume of distribution of the central compartment; V_p volume of distribution of the peripheral compartment.

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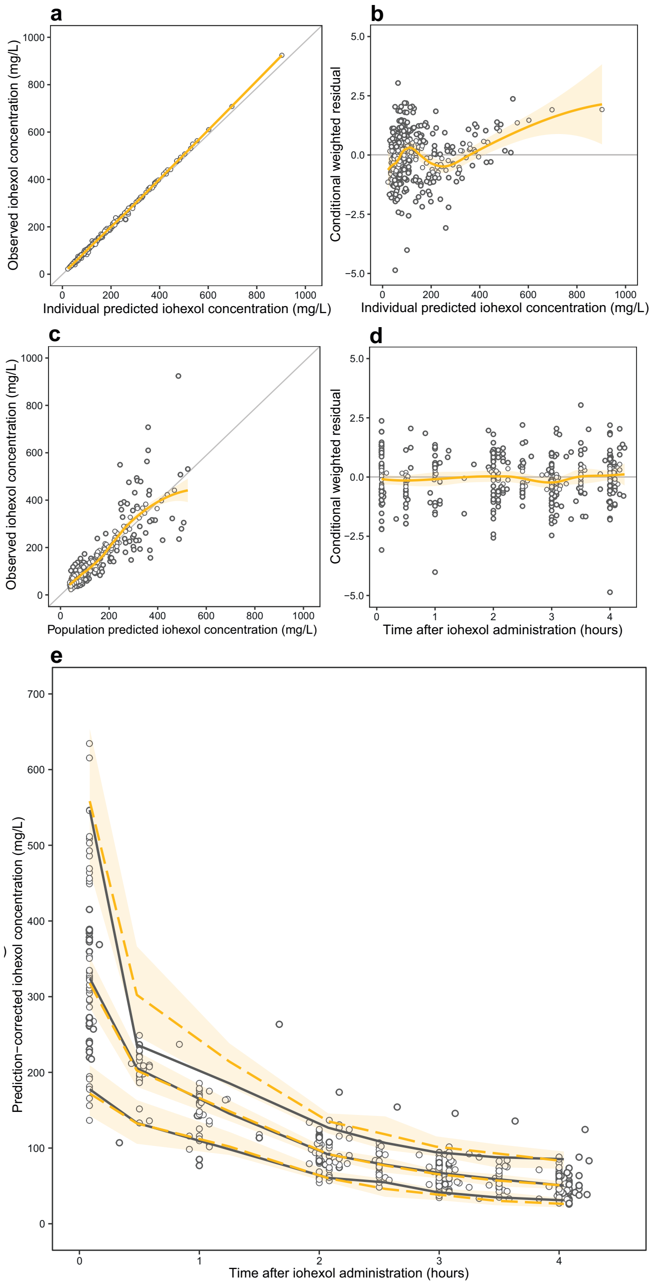

Figure 5.1: Diagnostic plots for the final population pharmacokinetic model on the development cohort. a) Observed *vs.* individual predicted iohexol concentrations. b) Conditional weighted residuals *vs.* individual predicted iohexol concentrations. c) Observed *vs.* population predicted iohexol concentrations. d) Conditional weighted residuals *vs.* time after iohexol administration. The solid gold lines and gold-shaded areas in a-d represent the loess regression fit and its standard error. e) Prediction-corrected visual predictive check, in which the solid black lines represent the 5th, 50th and 95th percentiles of the observed iohexol concentrations and the dashed gold lines and gold-shaded areas depict the 5th, 50th and 95th percentiles of the model-simulated iohexol concentrations and their respective 95% confidence intervals.

95% confidence intervals of those estimated on the development cohort. For the BSV on V_c and Q, however, some divergence between the estimates on the development and validation cohorts was apparent. The pcVPC on the internal validation cohort showed adequate overlap for the median iohexol concentrations, but slight BSV overprediction (Figure 5.2a). However, this was deemed acceptable as these deviations did not exceed the 95% confidence intervals of the 5^{th} and 95^{th} percentiles of the predicted data. Moreover, the individual prediction diagnostics showed excellent model performance with an RMSE of 2.68% between the observed

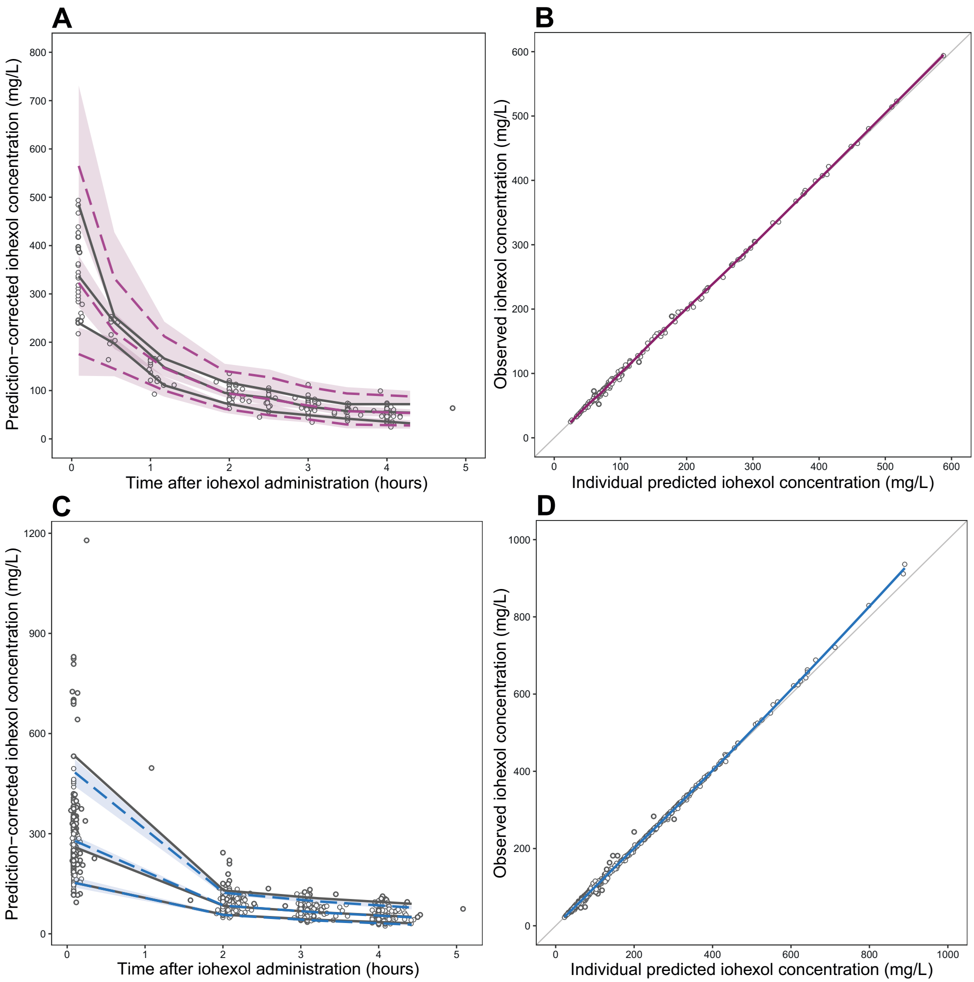

Figure 5.2: Prediction-corrected visual predictive checks and individual prediction diagnostic plots for the a-b) internal validation cohort and c-d) external validation cohort. The solid black lines in a and c represent the 5^{th}, 50^{th}, and 95^{th} percentiles of the observed iohexol concentrations and the dashed purple and blue lines and purple- and blue-shaded areas depict the 5^{th}, 50^{th}, and 95^{th} percentiles of the model-simulated iohexol concentrations and their respective 95% confidence intervals. The solid purple and blue lines and purple- and blue-shaded areas in b and d represent the loess regression fit and its standard error.

and individual predicted iohexol concentrations (Figure 5.2b) and an even distribution of the CWRES over the individual predicted iohexol GFRs (Figure S5.3). Similarly, the pcVPC on the external validation cohort showed adequate model appropriateness (Figure 5.2c), adequate individual prediction diagnostics with a RMSE of 3.79% (Figure 5.2d), and an even distribution of the CWRES over the individual predicted iohexol GFRs (Figure S5.3). Additionally, although limited data were available for this analysis, the model was able to adequately capture iohexol curves up to 24 h after administration in patients with impaired renal function (Figure S5.4). These findings confirmed that the model is fit for purpose.

Comparison of the model-predicted individual iohexol GFR estimates to the 3- , 5-, and 7-point GFR_{bm} indicated moderate method agreement, with TDIs of 18.2% to 18.7% and P_{10} values of 65.0% to 69.2% (Figure S5.5 and Table S5.2). The slightly improved method agreement with increasingly informed GFR_{bm}, however, did indicate a trend towards our model-based GFR estimates. Furthermore, the GFR_{bm} is known to incrementally underpredict the GFR beyond approximately 90 mL/min [6, 28], consistent with its observed incremental underprediction of our model-based GFR predictions beyond 90 mL/min. Indeed, the GFR_{bm} demonstrated considerably higher method agreement for GFRs up to 90 mL/min, with TDIs of 9.47% to 9.95% and P_{10} values of 75.5% to 79.9% (Figure S5.5 and Table S5.2), indicating acceptable method agreement within the reliable GFR_{bm} range. Albeit speculative as the true GFR remains unknown, the residual method disagreement likely provides an estimation of the potential benefit of our model-based approach over the GFR_{bm}.

Limited sampling schedule selection

The predictive performance of all LSSs in terms of bias and precision are depicted in Figure 5.3a and Figure 5.3b, respectively. Numerical details are provided in the Table S5.3.

LSSs based on 3-4 blood draws within 4 h after iohexol administration, including one or more early samples and one or more late samples, showed optimal predictive performance with TDIs below 7.5% and P_{10} values exceeding 95%. LSSs based on 3-4 blood draws within 3 h after iohexol administration generally showed lower predictive performance. Nevertheless, several of these LSSs still showed a TDI <10% and P_{10} >85%. The best LSSs based on 3-4 samples within 3 h to 4 h after iohexol administration are highlighted in Table 5.3, Figure 5.4a and Figure 5.4b. Two additional LSSs; $LSS_{5\text{-}120\text{-}180}$ and $LSS_{5\text{-}60\text{-}120\text{-}180}$, are highlighted because of clinical interest. These LSSs could provide options for blood draw alignment with tacrolimus and mycophenolate pharmacometric model-based exposure monitoring in renal transplant recipients, which rely on blood draws just before and at 1 h (mycophenolate), 2 h and 3 h after intake [29]. The $LSS_{5\text{-}60\text{-}120\text{-}180}$ (TDI: 11.5%±0.74%; P_{10}: 81.9%) and $LSS_{5\text{-}120\text{-}180}$ (TDI: 13.8%±0.74%;

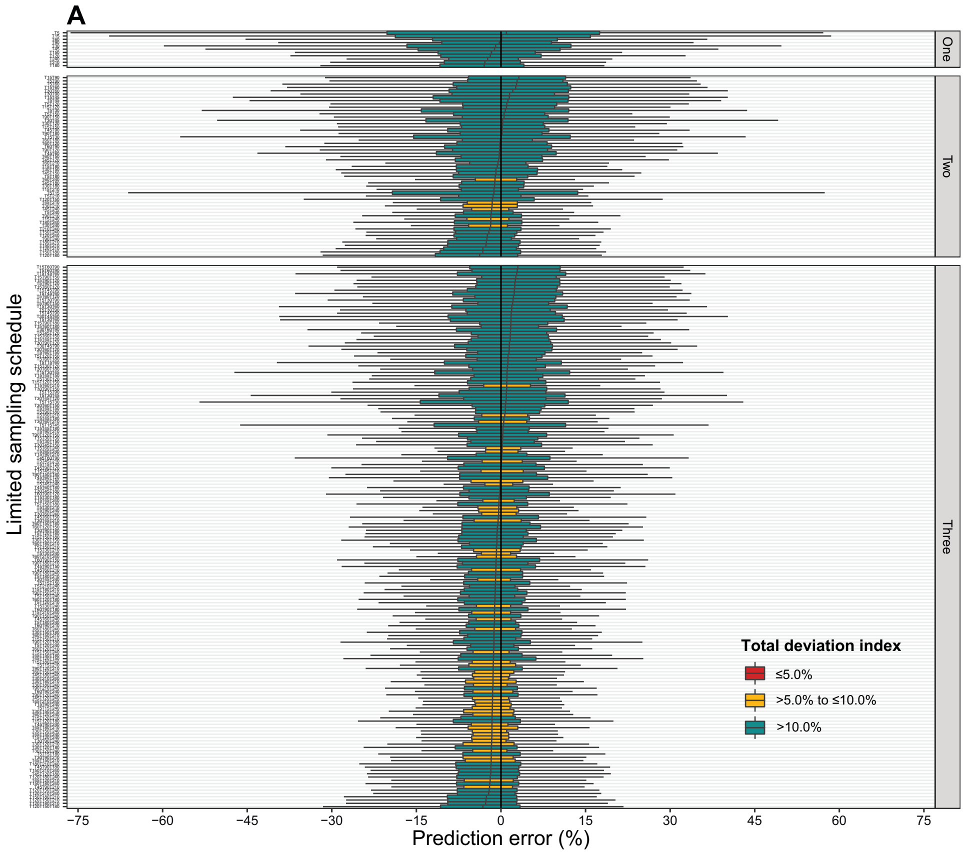

Figure 5.3: Limited sampling schedule selection. a) Individual iohexol clearance prediction bias of all limited sampling schedules, sorted according to the median bias and the number of sampling instances. b) Individual iohexol clearance prediction imprecision, sorted according to the median imprecision and the number of sampling instances. Each boxplot represents the data of a 1000 simulated individuals. Limited sampling schedules that showed a total deviation index (TDI) below 10% and below 5%, indicating good and excellent predictive performance, are highlighted in gold and red, respectively. *Figure 5.3 continues on the next pages.*

P_{10}: 71.9%) LSSs showed slightly lower predictive performance as compared to the best LSSs within 3 h after iohexol administration. Also, a previously published LSS with blood draws at 10, 30, 120, and 300 min [10], was evaluated to investigate any potential benefit of sampling up to 5 h in our population. This LSS showed similar predictive performance as our best LSSs with blood draws up to 4 h, with TDI and P_{10} values of 5.2% and 97.1%, respectively.

Additionally, albeit beyond their intended application, the performances of the best applicable LSSs were evaluated in 11 patients with impaired renal function, using individual plots with the iohexol GFR as determined by Åsberg et al. [10] as reference (Figure S5.4). This confirmed that, although our model adequately captures these curves when provided

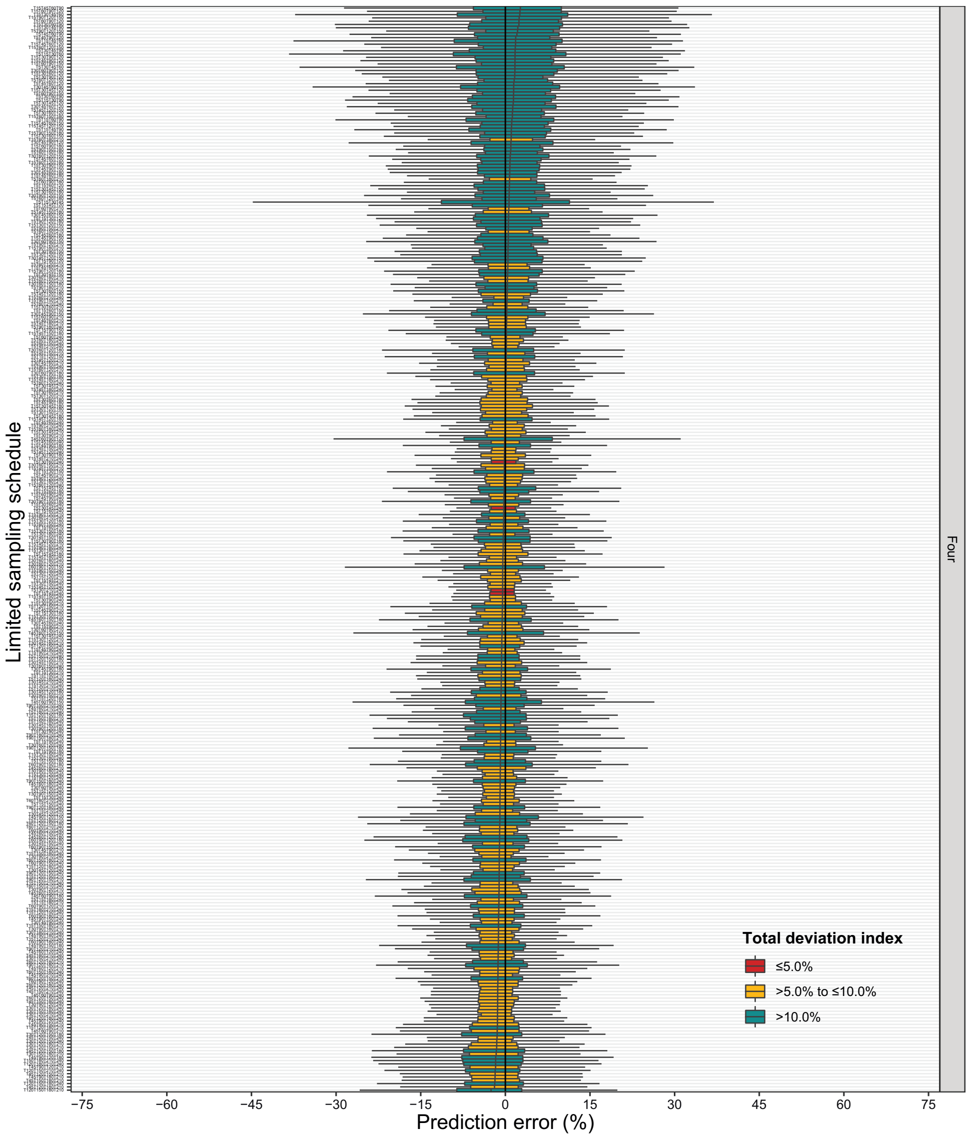

Figure 5.3: *Continued.*

extensive PK information, it yields biased estimates in patients with GFRs below 30 mL/min when relying on limited PK information. Also, these results stress the need for the application of 4-point LSSs up to 4 h in patients with GFRs in the range of 30-40 mL/min.

Finally, as MAP-BE is guided predominantly by PK input, exclusion of covariate information can be considered to enhance clinical feasibility. When relying on limited PK input, however, this may impair the predictive performance of the model. Hence, three reduced versions of

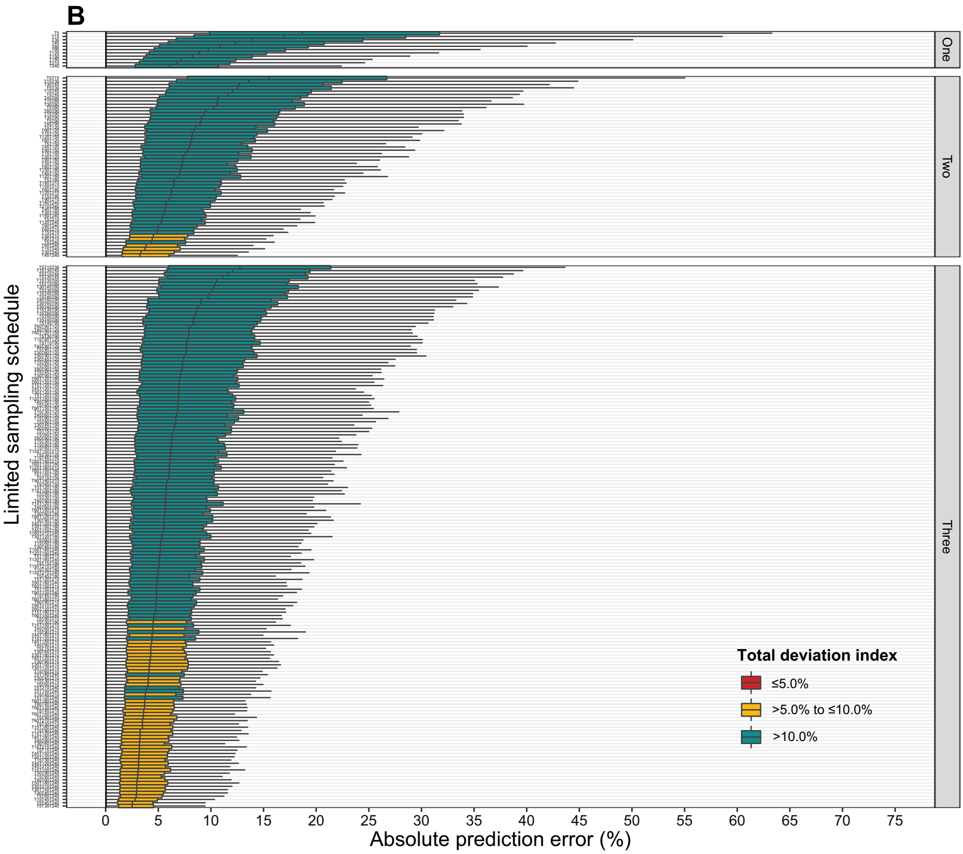

Figure 5.3: *Continued.*

the final model were created to assess whether FFM (Model 2), patient type (Model 3), or both (Model 4) could be excluded from the final model (Model 1). The NONMEM codes for these models are provided in the Supplementary Material. Models 2-4 were fitted to the development dataset for parameter re-estimation (Table S5.4), fixed, applied to the LSS dataset with the four best LSSs, and evaluated for their predictive performance (Table S5.5). Models 2-4 showed reduced predictive performance for all four LSSs, with 0.03-1.02% higher TDI and 0.20-5.60% lower P_{10} as compared to Model 1. Covariate information thus is essential to ensure adequate LSS performance.

Implementation in the InsightRX platform

The final model was implemented successfully in the InsightRX Nova platform. Using simulated data for a virtual patient population, all simulated concentration data and all estimated indi-

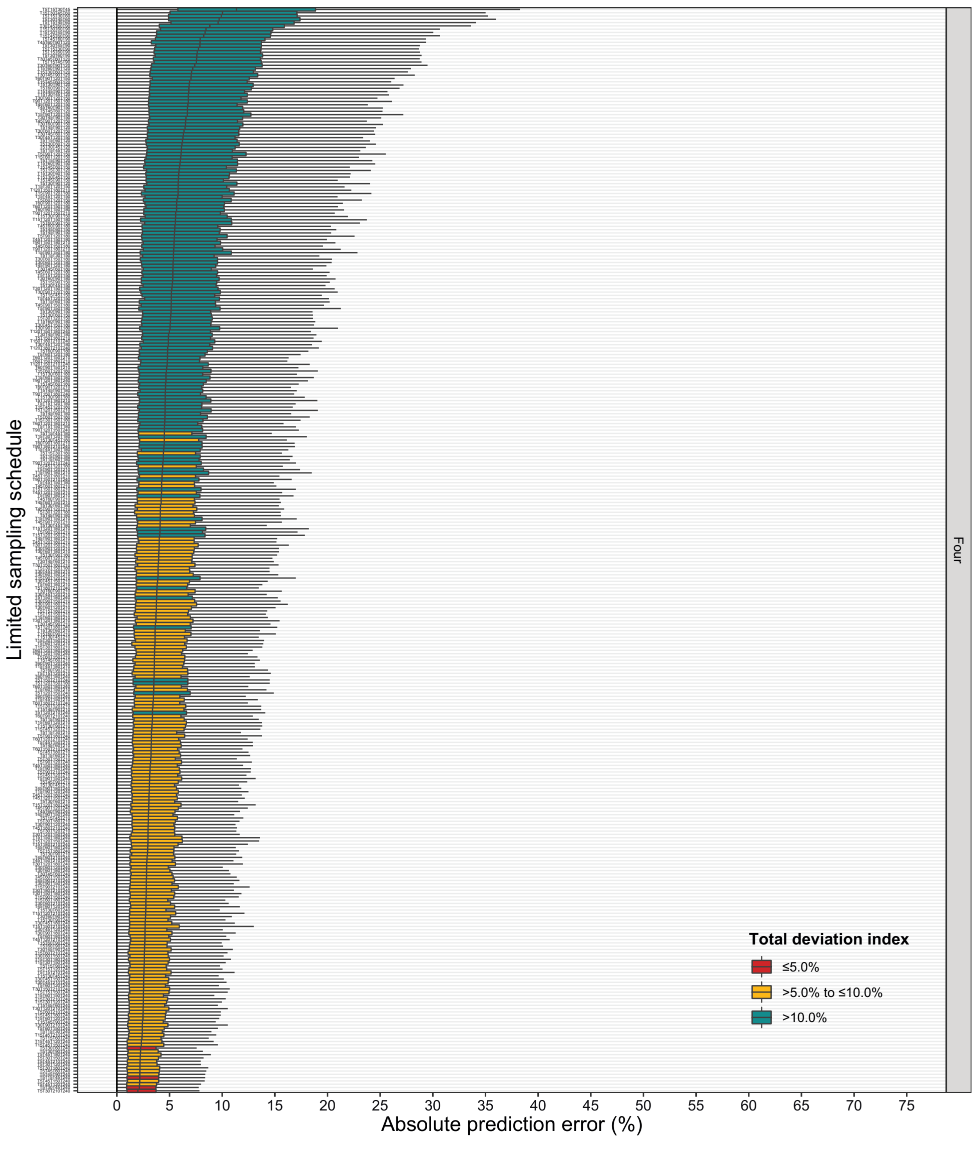

Figure 5.3: *Continued.*

vidual PK parameters were within 1% and 5% of those estimated by NONMEM, respectively. All essential PK parameters, in this case iohexol clearance, were within 1% of those estimated by NONMEM. The iohexol dosing module was made available in the InsightRX Nova platform. The verification report and user interface are provided in the Supplementary Material.

Table 5.3: Predictive performance of the best limited sampling schedules based on 3-4 samples within 3-4 h and two additional limited sampling schedules that were of particular clinical interest

Range	N	LSS	R^2	MPE (%) [95% CI]	MAPE (%) [95% CI]	RMSE (%) [95% CI]	CCC [95% CI]	TDI (%) [95% CI]	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
3 h	3	5-30-180	0.984	-0.72 [-1.15; -0.28]	5.43 [5.15; 5.71]	6.52 [6.51; 6.53]	0.98 [0.98; 0.99]	9.48 [8.97; 9.98]	54.4	85.0	96.4	98.9
	3	5-120-180[a]	0.967	-1.79 [-2.44; -1.14]	7.72 [7.27; 8.16]	9.51 [9.49; 9.52]	0.97 [0.96; 0.97]	13.8 [13.1; 14.6]	44.8	71.9	87.4	93.8
	4	5-30-150-180	0.987	-0.28 [-0.69; 0.13]	5.00 [4.73; 5.27]	6.06 [6.05; 6.07]	0.99 [0.98; 0.99]	8.81 [8.31; 9.29]	59.4	87.8	96.6	99.0
	4	5-60-120-180[a]	0.977	0.64 [0.14; 1.14]	6.10 [5.77; 6.43]	7.91 [7.89; 7.92]	0.98 [0.97; 0.98]	11.5 [10.8; 12.2]	51.2	81.9	93.1	98.0
4 h	3	5-45-240	0.995	-0.33 [-0.58; -0.07]	3.14 [2.98; 3.31]	3.76 [3.75; 3.76]	0.99 [0.99; 1.00]	5.46 [5.17; 5.73]	79.0	97.2	99.8	100.0
	4	5-30-45-240	0.996	-0.44 [-0.65; -0.22]	2.64 [2.50; 2.79]	3.15 [3.15; 3.16]	1.00 [1.00; 1.00]	4.58 [4.32; 4.84]	87.7	98.9	99.9	100.0

95% CI 95% confidence interval; *CCC* concordance correlation coefficient; *LSS* limited sampling schedule; *MAPE* mean absolute prediction error; *MPE* mean prediction error; *N* number of sampling instances; P_5-P_{20} percentages of individual iohexol clearance predictions within 5% to 20% of the reference individual iohexol clearance; R^2 Pearson's correlation coefficient; *RMSE* root mean squared prediction error; *TDI* total deviation index. *a* These limited sampling schedules were of particular clinical interest, given their potential for blood draw alignment with immunosuppressant monitoring in renal transplant recipients.

5

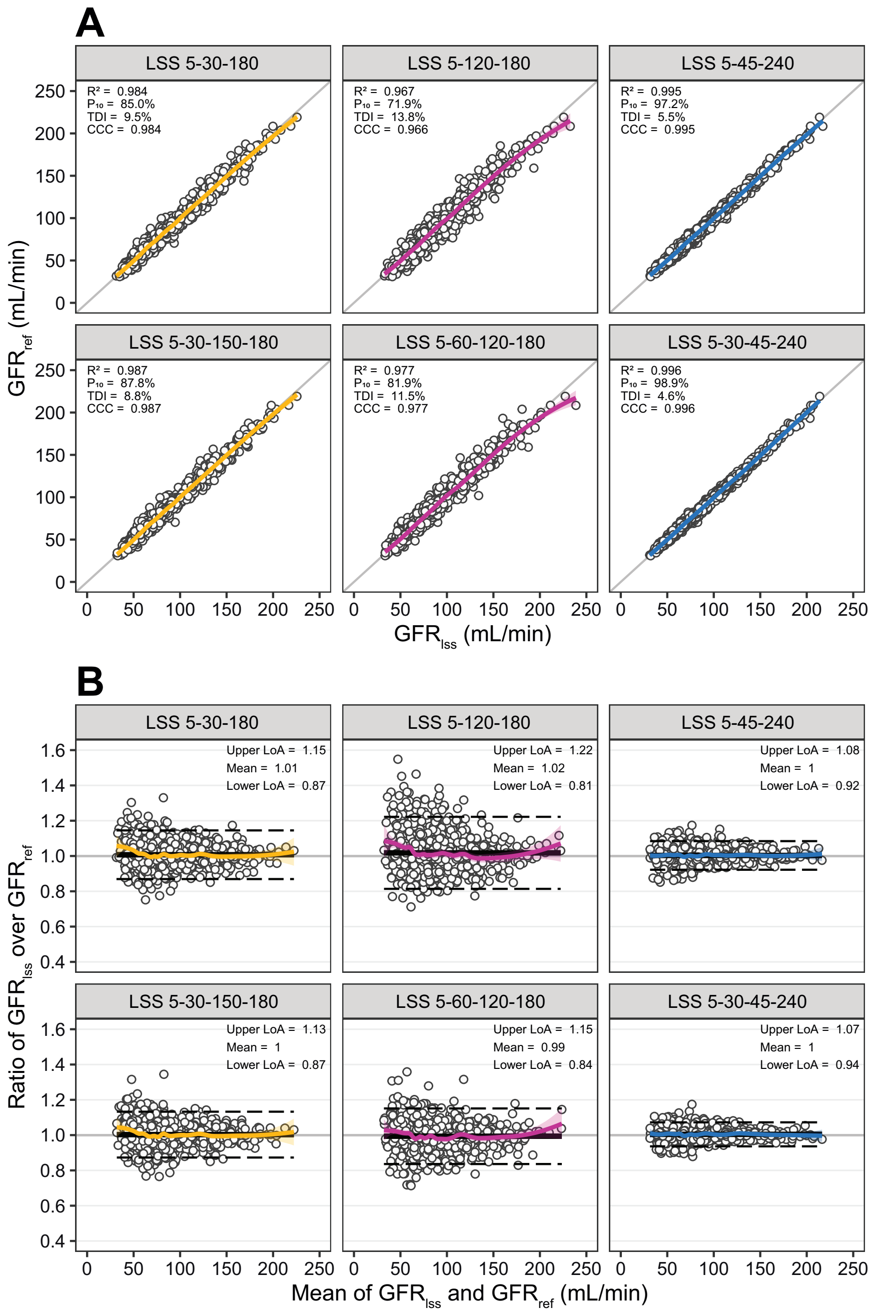

Figure 5.4: Predictive performance of selected limited sampling schedules (LSSs). a) Scatter and b) Bland-Altman ratio plots of the reference (GFR_{ref}) and predicted iohexol clearance (GFR_{lss}). The best LSSs based on 3-4 samples within 3 h are depicted in gold, whereas the two LSSs with particular clinical interest are depicted in purple. The best LSSs based on 3-4 samples within 4 h are indicated in blue. Solid gold, purple, and blue lines and gold-, purple- and blue-shaded areas represent the loess regression fits and their standard errors. The solid and upper and lower dashed black lines represent the mean ratios, upper limits of agreement (LoA) and lower LoA. Solid grey lines represent the lines of equality.

DISCUSSION

A population PK model and LSSs for iohexol mGFR estimation in renal transplant recipients and living renal transplant donor candidates were developed. Our approach enables pragmatic mGFR determination for donor candidate eligibility screening and renal transplant function monitoring for clinical and research purposes. This is the first study to describe the population PK of iohexol in donor candidates and the third for recipients [30, 31]. Furthermore, the study provides clinically feasible LSSs based on 3-4 blood draws within 3-4 h after iohexol administration, whereas previous studies reported LSSs which relied on sampling up to 4.5 h to 5 h [10, 31]. Finally, we implemented our model in a validated point-of-care precision dosing platform which facilitates its application in clinical practice, especially when integrated with local EMR software.

A two-compartmental model adequately captured the concentration-time data, showing a good resemblance between individual predicted and measured iohexol concentrations in the development and validation cohorts. Allometric scaling of all flow and volume parameters to FFM and inclusion of patient type as a covariate on CL and V_c improved the model and its individual predictions. During the internal validation, some divergence regarding the BSVs of Q and V_c, was apparent. The individual predictive performance combined with adequate stability of CL and V_c did, however, provide reassurance that the model is fit for purpose, which was confirmed in the external validation. Comparison of our model-predicted GFR against the GFR_{bm} showed adequate method agreement in the 30-90 mL/min range. Agreement in the higher GFR range was moderate, likely explained by incremental GFR underprediction of the GFR_{bm} at higher GFRs [6, 28].

Previously published population PK models for iohexol comprised one-compartmental [30], two-compartmental [10, 31, 32], and three-compartmental model structures [33]. Taubert et al. showed that their initial two-compartmental population model based on data from 570 elderly patients, displayed underprediction in the early distribution phase, which was resolved in a three-compartmental model [33]. Efforts to fit a three-compartmental model to our data, however, resulted in overparameterization. Benz-de Bretagne et al. developed an one-compartmental model in 95 renal transplant recipients, but this model described only the terminal log-linear elimination phase and still relied on Brøchner-Mortensen extrapolation [30]. Riff et al. developed a model in 151 renal transplant recipients with PK data up to 4.5 h after administration, and developed 3-point LSSs based on data from 8-22 patients [31]. Notably, their LSSs were not validated for patients with GFRs below 30 mL/min [31]. Moreover, the limited number of patients complicates interpretation of their overall validity [31]. Åsberg et al. developed their model in 219 patients with PK data up to 24 h [10]. Their 4-point LSS within 5 h showed excellent predictive performance for GFRs of 14-149 mL/min, whereas a 3 h LSS showed unacceptable extents of bias and imprecision in the lower GFR range [10]. Application of their 5 h LSS with our model yielded similar predictive performance as observed for our 4 h LSSs, confirming that deprecated sampling up to 4 h is possible without impairing LSS performance in our population with GFRs exceeding 30 mL/min. Ultimately, selection of an appropriate model and LSS should be guided by the tradeoff between clinical pragmatism and LSS predictive performance, on which considerations may vary across clinical situations and centers.

Our study showed some limitations. First, most PK data originated from subjects with estimated GFRs between 30-150 mL/min, drawn up to 4 h after iohexol administration. Whereas most of the iohexol AUC is captured within this 4 h time frame for most of these patients, the model would ideally have been based on full iohexol PK profiles from subjects with GFRs across the entire GFR range. Unfortunately, limited data from patients with GFRs below 30 mL/min were available, thwarting model and LSS development for this GFR range. This warrants adaptation and validation of our model and LSS for renal transplant recipients with a GFR <30 mL/min before considering this technique for these patients, which could be particularly valuable to inform clinical decisions concerning dialysis and medication and dose adaptation. By contrast, the model and LSSs were successfully developed and validated for GFRs between 30-150 mL/min, which captures most renal transplant recipients and living renal transplant donor candidates. Moreover, the majority of donor eligibility decisions and longitudinal renal transplantation research, and part of renal function-guided clinical decisions regarding medication and dose adaptation, for which mGFR determination shows particular added value over conventional eGFR assessment, occur in subjects with GFRs exceeding 30 mL/min. This limitation thus only slightly narrows the added value of our technique. Second, our approach assumes iohexol to be fully cleared renally, whereas a small portion of iohexol (<5%) undergoes non-renal excretion [4]. Additional validation against, for example, urinary inulin clearance could have provided additional insight into the accuracy of our approach. Third, small deviations between the prescribed iohexol doses and the actually administered doses may have occurred, as the syringes were not weighed before and after administration as suggested previously [10]. This may have contributed to the residual error of our model, although the contributions of measurement errors and small sampling time reporting deviations, especially early after iohexol administration, are likely more important. Fourth, part of our study was based on simulations beyond 4 h after iohexol administration. As the model was developed and thoroughly validated using PK data up to 4 h exclusively, simulations beyond 4 h may be associated with additional uncertainty. This uncertainty, however, is likely limited provided the rather standard terminal log-linear clearance of iohexol, and the demonstrated ability of the model to adequately fit PK data beyond 4 h. Fifth, the InsightRX platform is only accessible with a license, which may pose a hurdle for applying our tool in comparison with open-source solutions.

By contrast, such a professional platform guarantees a certified and validated tool with sustained end-user support, adequate maintenance, data safety, and flexibility to adapt to local situations, whereas open-source solutions are not seldomly short-lived owing to insufficient maintenance, limited end-user support, and low flexibility. Moreover, clinical laboratory accreditation requirements demand such dosing tools to be certified and validated, which poses an important hurdle for realizing open-source solutions. Last, it is important to acknowledge that mGFR, including urinary inulin clearance, also introduces bias in comparison to the true GFR and that outcomes may vary across markers and laboratory sites [34].

Additional possibilities to aid the clinical application of iohexol mGFR in renal transplant recipients include microsampling. We have previously developed a volumetric dried blood spot method for remote tacrolimus and mycophenolic acid exposure monitoring [29]. As tacrolimus and mycophenolate exposure are estimated using the trough, 1, 2 and 3 h concentrations [29], the iohexol $LSS_{5-60-120-180}$ could allow for blood draw alignment. Incorporation of iohexol in the multiplex immunosuppressant assay could then allow for simultaneous (partially) remote renal function and immunosuppressant monitoring. This may provide options for further reducing patient burden and costs, as patients would only have to come to the outpatient clinic for iohexol administration and the first sample and perform the remaining samples remotely. Also, remote microsampling may enable pragmatic extended iohexol sampling for patients with impaired renal function.

Lastly, our approach could be interesting for application in other populations. As living renal transplant donor candidates are mostly healthy individuals across the adult age range, it seems valid to apply the model and LSSs for renal evaluation in healthy volunteers as these generally show similar renal functions. This could particularly be valuable for research purposes [4]. Healthy volunteer populations, however, usually show an overrepresentation of young males, which may warrant external model validation.

CONCLUSIONS

The developed pharmacometric tool and LSSs based on 3-4 blood draws within 3-4 h after iohexol administration provide an accurate, robust, and pragmatic approach for iohexol mGFR assessment in the renal transplantation setting. This technique can be readily implemented in routine clinical care and fills a clear gap for clinical situations in which conventional renal function evaluation methods lack accuracy or show limited feasibility. Additional adaptation and validation of our model and LSSs for renal transplant recipients with GFRs <30 mL/min is warranted before considering this technique in these patients.

REFERENCES

1. Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberú J, Bakr MA, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation*. 2017; 101(8S): S1-S109.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009; 9(3): S1-S155.
3. Porrini E, Ruggenenti P, Luis-Lima S, Carrara F, Jiménez A, de Vries APJ, et al. Estimated GFR: time for a critical appraisal. *Nat Rev Nephrol*. 2019; 15(3): 177-90.
4. Delanaye P, Melsom T, Ebert N, Bäck SE, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: Why to measure glomerular filtration rate with iohexol? *Clin Kidney J*. 2016; 9(5): 700-4.
5. Soveri I, Berg UB, Björk J, Elinder CG, Grubb A, Mejare I, et al. Measuring GFR: a systematic review. *Am J Kidney Dis*. 2014; 64(3): 411-24.
6. Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: How to measure glomerular filtration rate with iohexol? *Clin Kidney J*. 2016; 9(5): 682-99.
7. Carrara F, Gaspari F. GFR measured by iohexol: the best choice from a laboratory perspective. *J Lab Precis Med*. 2018; 3(77).
8. Brøchner-Mortensen J. A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest*. 1972; 30(3): 271-4.
9. Jacobsson L. A method for the calculation of renal clearance based on a single plasma sample. *Clin Physiol*. 1983; 3(4): 297-305.
10. Åsberg A, Bjerre A, Almaas R, Luis-Lima S, Robertsen I, Salvador CL, et al. Measured GFR by utilizing population pharmacokinetic methods to determine iohexol clearance. *Kidney Int Rep*. 2020; 5(2): 189-98.
11. Keizer RJ, van Benten M, Beijnen JH, Schellens JH, Huitema AD. Pirana and PCluster: a modeling environment and cluster infrastructure for NONMEM. *Comput Methods Programs Biomed*. 2011; 101(1): 72-9.
12. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed*. 2005; 79(3): 241-57.
13. MacAllister R, Clayton T, Knight R, Robertson S, Nicholas J, Motwani M, et al. Remote preconditioning for protection against ischaemia-reperfusion in renal transplantation (REPAIR): a multicentre, multinational, double-blind, factorial designed randomised controlled trial. Southampton (UK): NIHR Journals Library. 2015.
14. Reinders ME, de Fijter JW, Roelofs H, Bajema IM, de Vries DK, Schaapherder AF, et al. Autologous bone marrow-derived mesenchymal stromal cells for the treatment of allograft rejection after renal transplantation: results of a phase I study. *Stem Cells Transl Med*. 2013; 2(2): 107-11.
15. Gaspari F, Perico N, Ruggenenti P, Mosconi L, Amuchastegui CS, Guerini E, et al. Plasma clearance of nonradio-active iohexol as a measure of glomerular filtration rate. *J Am Soc Nephrol*. 1995; 6(2): 257-63.
16. Gaspari F, Guerini E, Perico N, Mosconi L, Ruggenenti P, Remuzzi G. Glomerular filtration rate determined from a single plasma sample after intravenous iohexol injection: is it reliable? *J Am Soc Nephrol*. 1996; 7(12): 2689-93.
17. Dixon JJ, Lane K, Dalton RN, Turner C, MacPhee IAM, Chis Ster I, et al. Continuous infusion of low-dose iohexol measures changing glomerular filtration rate in critically ill patients. *Crit Care Med*. 2018; 46(3): e190-e7.
18. Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. *AAPS J*. 2009; 11(3): 558-69.
19. Holford NHG, Anderson BJ. Allometric size: the scientific theory and extension to normal fat mass. *Eur J Pharm Sci*. 2017; 109s: s59-s64.
20. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. *Clin Pharmacokinet*. 2005; 44(10): 1051-65.
21. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science*. 1997; 276(5309): 122-6.

22. Nguyen TH, Mouksassi MS, Holford N, Al-Huniti N, Freedman I, Hooker AC, et al. Model evaluation of continuous data pharmacometric models: metrics and graphics. *CPT Pharmacometrics Syst Pharmacol*. 2017; 6(2): 87-109.
23. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J*. 2011; 13(2): 143-51.
24. Yafune A, Ishiguro M. Bootstrap approach for constructing confidence intervals for population pharmacokinetic parameters. I: A use of bootstrap standard error. *Stat Med*. 1999; 18(5): 581-99.
25. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm*. 1981; 9(4): 503-12.
26. Lin LI. Total deviation index for measuring individual agreement with applications in laboratory performance and bioequivalence. *Stat Med*. 2000; 19(2): 255-70.
27. Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*. 1989; 45(1): 255-68.
28. De Sadeleer C, Piepsz A, Ham HR. How good is the slope on the second exponential for estimating 51Cr-EDTA renal clearance? A Monte Carlo simulation. *Nucl Med Commun*. 2000; 21(5): 455-8.
29. Zwart TC, Gokoel SRM, van der Boog PJM, de Fijter JW, Kweekel DM, Swen JJ, et al. Therapeutic drug monitoring of tacrolimus and mycophenolic acid in outpatient renal transplant recipients using a volumetric dried blood spot sampling device. *Br J Clin Pharmacol*. 2018; 84(12): 2889-902.
30. Benz-de Bretagne I, Le Guellec C, Halimi JM, Gatault P, Barbet C, Alnajjar A, et al. New sampling strategy using a Bayesian approach to assess iohexol clearance in kidney transplant recipients. *Ther Drug Monit*. 2012; 34(3): 289-97.
31. Riff C, Besombes J, Gatault P, Barbet C, Buchler M, Blasco H, et al. Assessment of the glomerular filtration rate (GFR) in kidney transplant recipients using Bayesian estimation of the iohexol clearance. *Clin Chem Lab Med*. 2020; 58(4): 577-87.
32. Friedman AN, Strother M, Quinney SK, Hall S, Perkins SM, Brizendine EJ, et al. Measuring the glomerular filtration rate in obese individuals without overt kidney disease. *Nephron Clin Pract*. 2010; 116(3): C224-34.
33. Taubert M, Ebert N, Martus P, van der Giet M, Fuhr U, Schaeffner E. Using a three-compartment model improves the estimation of iohexol clearance to assess glomerular filtration rate. *Sci Rep*. 2018; 8(1): 17723.
34. Levey AS, Inker LA. GFR as the "gold standard": estimated, measured, and true. *Am J Kidney Dis*. 2016; 67(1): 9-12.

SUPPLEMENTARY MATERIAL

Supplementary information

Development of HPLC-UV assay for iohexol quantification in plasma

Chemical and materials

Iohexol (Omnipaque 300) was purchased from GE Healthcare BV (Eindhoven, the Netherlands) and internal standard 1,3-dimethyluric acid from Sigma-Aldrich (Zwijndrecht, the Netherlands). Analytical grade phosphate buffered saline (PBS) was purchased from Braun (Oss, the Netherlands), perchloric acid (70%) from VWR (Amsterdam, the Netherlands) and acetonitrile and phosphoric acid (85%) from Merck (Darmstadt, Germany). Ultrapure water was produced on-site using a PURELAB® Flex purification system from ELGA LabWater (Lane End, UK).

Sample preparation

After collection, patient samples were transferred to the Leiden University Medical Center (LUMC) laboratory and stored at 4–8°C until analysis. All samples were analyzed within one week after collection. Iohexol high and low quality controls (QCs) and calibration standards were produced on-site by spiking blank serum with iohexol, which were then homogenized on a tube roller bench for 15 min at 60 rpm and stored at -20°C. From each QC, calibration standard and patient sample, 200 µL was transferred to an Eppendorf tube and combined with 50 µL of a solution of 0.2 mg/mL 1,3-dimethyluric acid in PBS and 250 µL 0.8 M perchloric acid. Subsequently, the mixture was vortex-mixed (VWR, Amsterdam, The Netherlands) for 5 s and centrifuged (ThermoFisher Scientific, Bleiswijk, The Netherlands) for 5 min at 13000 rpm, respectively. The supernatant was then transferred to an autosampler vial of which 20 µL was injected onto the HPLC-UV system.

HLPC-UV assay

Patient samples, QCs, and calibration standards were analyzed on an HPLC-UV system, consisting of an UltiMate 3000 series UHPLC system connected to an UltiMate 3000 rapid separation (RS) diode array detector (DAD-3000RS), all from ThermoFisher Scientific. The HPLC system consisted of a WPS-3000RS autosampler and ISO-3100SD isocratic pump. Chromatographic separation was achieved using an Inertsil® ODS-2 (150 × 4.6 mm ID, particle size 5 µm) C18 column (Alltech, Ridderkerk, the Netherlands), protected by a SecurityGuard® C18 pre-column (4 × 3 mm ID) (Phenomenex, Utrecht, the Netherlands). Elution was performed with a mobile phase consisting of a mixture of 0.025% phosphoric acid and 4% acetonitrile in water.

A constant flow rate of 1.2 mL/min and pressure of 120 bar were applied at room temperature. The injection volume was set at 20 µL and the detection wavelength at 245 nm. The total run time was 12.0 min. Data were acquired and processed using ThermoFisher Scientific Chromeleon software v7.2.

Analytical validation

The assay was validated according to the European Medicines Agency (EMA) guidelines on bioanalytical method validation, including selectivity, linearity, accuracy, precision, recovery, matrix effects, measurement error, cross validation and stability. The maximum tolerated validation limits were set as follows: linearity correlation coefficient >99%; accuracy 90–110%; within-run precision <10%CV; between-run precision <15%CV; LLQ imprecision <20%CV; ULQ imprecision <15%CV; stability content loss <10%; cross-validation correlation coefficient ≥99% with a slope of 0.9–1.1 at ≤15% divergence (≤20% for LLQ); and measurement error <15%. Linearity was first established over a concentration range of 25.9 to 129.5 mg/L. In addition, the lower and upper limits of quantification were established at 10 mg/L and 500 mg/L, respectively. Accuracy was evaluated on two separate days in six-fold (day 1) and eight-fold (day 2) at QC_{low} (25.9 mg/L) and QC_{high} (129.5 mg/L), resulting in an average accuracy of 98% for QC_{low} and 106% for QC_{high}, showing adequate accuracy. The within-run precision was assessed in six-fold for both the QC_{low} and QC_{high}, resulting in a within-run precision of 3.0%CV for QC_{low} and 2.7%CV for QC_{high}. The between-run precision was evaluated in seven-fold for QC_{low} and in eight-fold for QC_{high}, resulting in a between-run precision of 3.9%CV and 3.8%CV for QC_{low} and QC_{high}, respectively. The recovery was assessed in six-fold for QC_{low} and QC_{high}, resulting in an average recovery of 101% (2.8%CV) for iohexol and 95% (1.3%CV) for 1,3-dimethyluric acid, showing adequate and reproducible recovery. Differences between the matrix effects in plasma as compared to those in serum were negligible. The measurement error was established at 11.8% and 9.8% for QC_{low} and QC_{high}, respectively. Any differences observed during cross-validation did not exceed 10%, showing no clinically relevant divergence. The sample stability was determined in two-fold at six time points at room temperature, in the refrigerator (4–8°C), and in the freezer (-20°C), with the maximum tolerable decrease in iohexol content set at <15%. The sample stability at room temperature, in the refrigerator and in the freezer were established up to 7 days, 14 days, and 6 months, respectively. Calibration standards and QCs stored in the freezer were stable for a year and stock and working solutions for 14 days.

Cross-validation of the iohexol data from LUMC (HPLC-UV) and ELCH (HPLC-MS/MS)

Cross-validation PK data

A total of 24 samples from NCT00734396 were re-analyzed at Leiden University Medical Center (LUMC) for the purpose of cross-validation. The iohexol concentrations in these samples as quantified at Evelina London Children's Hospital (ELCH) and re-quantified at LUMC are summarized in Table S5.1.

Agreement between the iohexol data from LUMC and ELCH

Agreement between the iohexol data from both centers was compared in terms of linearity and bias, using Passing-Bablok regression and Bland-Altman plots. The Passing-Bablok regression fit is depicted in Figure S5.1, showing a clear linear relationship between the iohexol concentrations quantified at ELCH and LUMC, with a slope of 0.93 [95% CI: 0.89; 0.98] and intercept of 4.66 [0.19; 8.92]. The Bland-Altman relative difference plot is depicted in Figure S5.2, showing that the differences between the iohexol concentrations quantified at ELCH and LUMC were evenly spread around the line of equality across the iohexol concentration range, with a mean bias of -1.24% [-4.81%; 2.34%] and 95% lower and upper limits of agreement of -17.8% [-24.0%; -11.6%] and 15.3% [9.15%; 21.5%], respectively. All but one (95.8%) of the iohexol concentrations re-quantified at LUMC fell within ±15% of the corresponding iohexol concentrations quantified at ELCH, and 21/24 (87.5%) within ±10%.

Conclusion

The findings of the cross-validation indicated good agreement between both iohexol assays, and provided reassurance that iohexol measurements from both assays could be used interchangeably within this study.

NONMEM code for the final model

```
$SUBROUTINES ADVAN3 TRANS4

$PK
; --- FAT FREE MASS CALCULATION -
IF (SEX.EQ.0) WHSMAX=42.92           ; MEN
IF (SEX.EQ.0) WHS50=30.93            ; MEN
IF (SEX.EQ.1) WHSMAX=37.99           ; WOMEN
IF (SEX.EQ.1) WHS50=35.98            ; WOMEN
HGT=HEIGHT/100
FFM=(WHSMAX*(HGT**2)*WEIGHT)/(WHS50*(HGT**2)+WEIGHT)

; --- ALLOMETRY SCALED TO 1.80M MAN OF 70 KG
ALLOCL=(FFM/57.18)**0.75
```

```
ALLOV=(FFM/57.18)

; --- PATIENT TYPE ON V1 AND CL
IF(TX.EQ.0) CLTX = 1
IF(TX.EQ.1) CLTX = (1 + THETA(7))
CLCOV=CLTX
IF(TX.EQ.0) V1TX = 1
IF(TX.EQ.1) V1TX = (1 + THETA(8))
V1COV=V1TX

; --- IOHEXOL PK
CL = THETA(1) * ALLOCL * CLCOV * EXP(ETA(1))
V1 = THETA(2) * ALLOV * V1COV * EXP(ETA(2))
Q = THETA(3) * ALLOCL * EXP(ETA(3))
V2 = THETA(4) * ALLOV * EXP(ETA(4))
S1 = V1

$ERROR
IPRED = F
W = SQRT(THETA(5)**2*IPRED**2 + THETA(6)**2)
Y = IPRED + W*EPS(1)
IRES = DV-IPRED
IWRES = IRES/W

$THETA
(0, 4.07) ; CL
(0, 8.36) ; V1
(0, 7.71) ; Q
(0, 6.88) ; V2
(0, 0.0523,1) ; Prop.RE (sd)
(0) FIX ; Add.RE (sd)
(-5, 0.483,5) ; CLCOV
(-5, 0.342,5) ; V1COV

$OMEGA BLOCK(3)
0.0891 ; IIV CL
0.038 0.163 ; IIV V1
0.0642 -0.0706 0.381 ; IIV Q

$OMEGA
0.0554 ; IIV V2

$SIGMA
1 FIX ; prop error
```

NONMEM code for Model 2

```
$SUBROUTINES ADVAN3 TRANS4

$PK
```

```
; --- PATTYPE ON V1 AND CL
IF(TX.EQ.0) CLTX = 1 ; Most common
IF(TX.EQ.1) CLTX = (1 + THETA(7))
CLCOV=CLTX
IF(TX.EQ.0) V1TX = 1 ; Most common
IF(TX.EQ.1) V1TX = (1 + THETA(8))
V1COV=V1TX

CL = THETA(1) * CLCOV * EXP(ETA(1))
V1 = THETA(2) * V1COV * EXP(ETA(2))
Q = THETA(3) * EXP(ETA(3))
V2 = THETA(4) * EXP(ETA(4))
S1 = V1

$ERROR
IPRED = F
    W = SQRT(THETA(5)**2*IPRED**2 + THETA(6)**2)
    Y = IPRED + W*EPS(1)
 IRES = DV-IPRED
IWRES = IRES/W

$THETA
3.76 FIX ; CL
7.66 FIX ; V1
6.52 FIX ; Q
6.05 FIX ; V2
0.0525 FIX ; Prop.RE (sd)
0 FIX ; Add.RE (sd)
0.344 FIX ; CLCOV
0.18 FIX ; V1COV

$OMEGA BLOCK(3)
 0.102 ; IIV CL
 0.0475 0.167 ; IIV V1
 0.101 -0.0407 0.462 ; IIV Q
$OMEGA
 0.0855 FIX ; IIV V2

$SIGMA
 1 FIX ; prop error

$EST METHOD=1 INTER MAXEVAL=0 NOABORT SIG=3 PRINT=1 POSTHOC
```

NONMEM code for Model 3

```
$SUBROUTINES ADVAN3 TRANS4

$PK
; --- ALLOMETRY SCALED TO 1.80M MAN OF 70 KG
ALLOCL=(FFM/57.18)**0.75
```

```
ALLOV=(FFM/57.18)

CL = THETA(1) * ALLOCL * EXP(ETA(1))
V1 = THETA(2) * ALLOV * EXP(ETA(2))
Q = THETA(3) * ALLOCL * EXP(ETA(3))
V2 = THETA(4) * ALLOV * EXP(ETA(4))
S1 = V1

$ERROR
IPRED = F
    W = SQRT(THETA(5)**2*IPRED**2 + THETA(6)**2)
    Y = IPRED + W*EPS(1)
 IRES = DV-IPRED
IWRES = IRES/W

$THETA
(0, 4.73) FIX ; CL
(0, 9.32) FIX ; V1
(0, 7.89) FIX ; Q
(0, 6.9) FIX ; V2
(0, 0.0524,1) FIX ; Prop.RE (sd)
(0) FIX ; Add.RE (sd)

$OMEGA BLOCK(3)
 0.119 ; IIV CL
 0.0657 0.188 ; IIV V1
 0.0347 -0.0896 0.368 ; IIV Q

$OMEGA
 0.0537 FIX ; IIV V2

$SIGMA
 1 FIX ; prop error

$EST METHOD=1 INTER MAXEVAL=0 NOABORT SIG=3 PRINT=1 POSTHOC
```

NONMEM code for Model 4

```
$SUBROUTINES ADVAN3 TRANS4

$PK
CL = THETA(1) * EXP(ETA(1))
V1 = THETA(2) * EXP(ETA(2))
Q = THETA(3) * EXP(ETA(3))
V2 = THETA(4) * EXP(ETA(4))
S1 = V1

$ERROR
IPRED = F
    W = SQRT(THETA(5)**2*IPRED**2 + THETA(6)**2)
```

```
    Y = IPRED + W*EPS(1)
 IRES = DV-IPRED
IWRES = IRES/W

$THETA
(0, 4.19) FIX ; CL
(0, 8.15) FIX ; V1
(0, 6.5) FIX ; Q
(0, 6.07) FIX ; V2
(0, 0.0527,1) FIX ; Prop.RE (sd)
(0) FIX ; Add.RE (sd)

$OMEGA BLOCK(3)
  0.116 ; IIV CL
  0.059 0.178 ; IIV V1
  0.0766 -0.0583 0.459 ; IIV Q

$OMEGA
  0.0793 FIX ; IIV V2

$SIGMA
  1 FIX ; prop error

$EST METHOD=1 INTER MAXEVAL=0 NOABORT SIG=3 PRINT=1 POSTHOC
```

InsightRX model verification

Introduction

The InsightRX platform is a clinical decision support tool for selecting optimal drug regimens by optimizing on pharmacokinetic and pharmacodynamic characteristics of individual patients. Since it is essential that the core numeric functionality of the InsightRX platform is accurate and precise, many validation and verification tests are applied before any PK/PD modules are released on the InsightRX platform. In this report, the simulation and individual estimation algorithms are documented:

- Simulation: any model that is simulated within the platform should provide the exact same results as other (gold standard) methods.
- Individual estimation: given a population PK model and some TDM data, the individual estimation algorithms in InsightRX should not differ relevantly from individual estimates obtained from commonly used gold standard softwares.

The tests included in this report are deployed in a continuous integration development workflow at InsightRX. This means that any potential disruptions of the numerical integrity of these models or the simulation or estimation algorithms will be caught and fixed before new versions are deployed to production environments.

Methods - simulation

For simulation, the platform relies on the R software package PKPDsim (http://github.com/InsightRX/PKPDsim), which is developed internally by InsightRX and released under an open source license. The package allows the numeric integration of ordinary differential equations (ODE), and is specifically designed for use in pharmacometrics. Any PK/PD model that can be written in ODEs or analytical equations can be simulated with this package. To ensure the numerical correctness of PKPDsim, predictions from the package are checked against a gold standard. As reference we use predictions from the same model implemented in NONMEM, which is considered a gold standard software in the field of pharmacometrics and used e.g. for most FDA new drug filings.

Methods - estimation

For fitting of models to drug concentration data, the platform relies on the PKPDmap R package (proprietary). This package allows estimation of individual parameters based on prior distributions from a population PK model and observed concentration data, using maximum a posteriori (MAP) Bayesian fitting. In our verification tests, individual empirical Bayes estimates (EBEs) from PKPDmap are compared to EBEs calculated in NONMEM based on simulated data in a prespecified number of patient. By default, NONMEM employs the same MAP methodology as PKPDmap — based on the BFGS-algorithm for finding the maximum likelihood — so estimates are expected to be highly similar.

Methods - comparison

Since exact numerical equivalence between test and reference results is not expected due to small differences in implementation of algorithms or internal rounding, we define equivalence thresholds, i.e. maximum allowed deviations from predicted concentrations or estimated parameters. The allowed deltas between test and reference values are shown in the diagram below. Due to the difference in orders of magnitude of expected concentrations for the various drugs, the allowed deltas in simulated concentrations are defined for each drug/model separately. This is done by defining a relevant limit of quantification (rLOQ), a value close or equal to the bioanalytical LOQ, or if that is unknown the lowest value commonly observed for that drug. For data below this rLOQ the allowed difference with the reference value is measured in absolute terms and is defined as 15% of the rLOQ. For data above the rLOQ the allowed delta is defined relative to the reference value, and is allowed to differ <1%. For parameter estimates,

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a distinction is made between primary and derived parameters. This is due to the fact that, especially with low amounts of data, the model is not always globally identifiable (the likelihood surface is very flat), and minute differences in the estimation algorithms can lead to noticeable differences in parameter estimates, and thus the set of reference parameter estimates is not necessarily the "optimal" solution. However, concentration predictions or other derived exposure estimates should still show near exact correspondence with the respective reference values. Therefore, to avoid false positive test results due to the issue of model identifiability, a derived parameter is defined, most commonly AUC for PK models, on which the test is run with a much lower allowed margin. The allowed deltas for model parameters and derived parameters are 10% and 1%, respectively.

Methods - simulated population

The distribution and correlation plots for the simulated population used in the simulation and estimation tests are depicted in Figure S5.7 and Figure S5.8, respectively. For discrete covariates, the possible values of the covariate are sampled discretely, with equal probability for each possible value. For continuous covariates, a realistic range is defined for each covariate and values are sampled uniformly to ensure proper coverage of the population.

PKPDsim model code

```
ODE definition:
CLi = CL * pow(FFM/57.18, 0.75) * (1 + 0.483*(TX == 1)) ;
Vi = V * (FFM/57.18) * (1 + 0.342*(TX == 1)) ;
Qi = Q * pow(FFM/57.18, 0.75) ;
V2i = V2 * (FFM/57.18) ;
dAdt[0] = -(CLi/Vi)*A[0] - (Qi/Vi)*A[0] + (Qi/V2i)*A[1] ;
dAdt[1] = + (Qi/Vi)*A[0] - (Qi/V2i)*A[1] ;
dAdt[2] = A[0]/Vi;
;
PK event code:
if(SEX == 0) {;
WHSMAX = 42.92;;
WHS50 = 30.93;;
} else { WHSMAX = 37.99;;
WHS50 = 35.98;;
};
FFM=(WHSMAX*(pow(HT/100.0, 2))*WT)/(WHS50*(pow(HT/100.0,2))+WT);
;
Required parameters: CL, V, Q, V2
Covariates: WT, HT, SEX, TX
Variables: CLi, Vi, Qi, V2i, FFM, WHSMAX, WHS50
Number of compartments: 3
Observation variable: NULL
```

```
Observation scaling: Vi
Lag time: noneIOV CV:
IOV bins: 1
Comments: -
```

Results

The results of the estimation tests are depicted in Figure S5.9, Figure S5.10, and Figure S5.11, whereas the results for the comparison tests are depicted in Figure S5.12 and S5.13.

Conclusion

The iohexol model was implemented successfully in the InsightRX Nova platform. All simulated concentration data and all estimated individual PK parameters were within 1% and 5% of those estimated by NONMEM, respectively. All essential PK parameters, in this case iohexol clearance, were within 1% of those estimated by NONMEM.

Supplementary Tables

Table S5.1: Iohexol concentrations as quantified at Evelina London Children's Hospital (ELCH) and re-quantified at Leiden University Medical Center (LUMC) for cross-validation

Sample	Iohexol concentration quantified at ELCH (mg/L)	Iohexol concentration quantified at LUMC (mg/L)
1	51.24	53.59
2	62.82	67.08
3	83.76	90.37
4	76.78	69.50
5	248.0	261.9
6	399.1	422.4
7	59.61	56.53
8	73.25	79.79
9	106.8	103.7
10	151.9	150.1
11	34.73	35.02
12	52.31	50.36
13	87.04	66.78
14	86.22	84.76
15	407.3	410.4
16	115.0	120.9
17	707.8	788.4[a]
18	77.93	74.39
19	76.69	78.81
20	36.95	40.27
21	47.79	45.36
22	523.1	607.5[a]
23	258.7	283.3
24	54.52	54.36

ELCH Evelina London Children's Hospital; *LUMC* Leiden University Medical Center.
a These samples initially exceeded the upper quantification limit for iohexol in plasma at LUMC (500 mg/L) and were, therefore, re-quantified after dilution.

Table S5.2: Agreement between the glomerular filtration rate (GFR) as estimated with the slope-intercept method with Brøchner-Mortensen correction (GFR_{bm}) and the model-predicted GFR

GFR_{bm} model	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95%CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
3-point	0.960	-3.10 [-3.77; -2.43]	8.72 [8.28; 9.16]	13.5 [13.4; 13.5]	0.93 [0.92; 0.93]	18.7 [17.3; 20.1]	36.4	65.0	84.0	93.0
3-point (≤90 ml/min)	0.908	1.51 [0.77; 2.24]	7.08 [6.60; 7.56]	8.95 [8.93; 8.98]	0.90 [0.89; 0.92]	9.95 [9.23; 10.7]	45.2	75.5	91.0	96.4
5-point	0.962	-2.63 [-3.27; -1.99]	8.33 [7.91; 8.74]	13.1 [13.1; 13.1]	0.93 [0.92; 0.94]	18.3 [16.9; 19.8]	38.7	66.3	86.2	93.9
5-point (≤90 ml/min)	0.917	2.00 [1.34; 2.67]	6.63 [6.21; 7.06]	8.54 [8.52; 8.56]	0.91 [0.90; 0.92]	9.53 [8.88; 10.3]	47.3	77.0	92.9	97.6
7-point	0.966	-2.53 [-3.16; -1.90]	8.02 [7.60; 8.43]	13.0 [12.9; 13.0]	0.93 [0.93; 0.94]	18.2 [16.8; 19.7]	42.5	69.2	85.2	93.7
7-point (≤90 ml/min)	0.923	1.96 [1.31; 2.61]	6.29 [5.86; 6.73]	8.48 [8.46; 8.50]	0.92 [0.90; 0.93]	9.47 [8.82; 10.1]	52.5	79.9	91.7	97.3

95% CI 95% confidence interval; *CCC* concordance correlation coefficient; GFR_{bm} slope-intercept method with Brøchner-Mortensen correction; *MAPE* mean absolute prediction error; *MPE* mean prediction error; P_5-P_{20} percentage of GFR_{bm} GFR predictions within 5-20% of model-based GFR predictions; R^2 Pearson's correlation coefficient; *RMSE* root mean squared prediction error; *TDI* total deviation index.

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Table S5.3: Numerical predictive performance of all evaluated limited sampling schedules (LSSs), sorted according to the number of sampling instances in the limited sampling schedule and the total deviation index (TDI)

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
One	210	0.957	-3.81 [-4.45; -3.17]	8.37 [7.93; 8.81]	11.06 [11.04; 11.07]	0.95 [0.95; 0.96]	16.07 [15.14; 17.08]	40.0	67.7	85.2	93.6
	240	0.956	-3.54 [-4.16; -2.92]	7.89 [7.45; 8.33]	11.07 [11.05; 11.09]	0.95 [0.95; 0.96]	16.09 [15.02; 17.11]	42.0	72.5	86.9	93.7
	180	0.954	-4.10 [-4.81; -3.40]	9.16 [8.67; 9.66]	11.39 [11.37; 11.41]	0.95 [0.94; 0.96]	16.55 [15.51; 17.64]	35.2	64.9	82.6	91.2
	150	0.945	-3.25 [-4.03; -2.48]	9.98 [9.47; 10.49]	12.21 [12.19; 12.22]	0.94 [0.94; 0.95]	17.74 [16.57; 19.11]	31.6	58.6	78.8	89.9
	120	0.934	-2.59 [-3.44; -1.75]	10.79 [10.25; 11.32]	13.28 [13.26; 13.30]	0.93 [0.92; 0.94]	19.29 [18.20; 20.39]	29.3	55.6	74.3	86.1
	90	0.910	-2.19 [-3.18; -1.19]	12.18 [11.52; 12.84]	15.61 [15.59; 15.63]	0.91 [0.90; 0.92]	22.68 [21.36; 24.11]	26.8	51.5	69.9	81.3
	60	0.873	-3.03 [-4.21; -1.85]	14.16 [13.34; 14.97]	18.18 [18.15; 18.21]	0.87 [0.85; 0.88]	26.42 [24.88; 27.91]	24.7	46.5	64.4	77.1
	45	0.833	-4.20 [-5.52; -2.87]	15.92 [14.99; 16.84]	20.47 [20.44; 20.50]	0.82 [0.80; 0.84]	29.75 [27.95; 31.39]	21.3	42.4	58.7	73.0
	30	0.782	-4.05 [-5.51; -2.58]	17.88 [16.89; 18.87]	23.16 [23.13; 23.19]	0.75 [0.72; 0.77]	33.65 [31.56; 35.73]	18.8	36.3	53.4	66.1
	15	0.697	-3.63 [-5.30; -1.96]	20.79 [19.70; 21.87]	26.77 [26.73; 26.80]	0.64 [0.60; 0.67]	38.89 [36.44; 41.23]	15.9	29.9	44.3	58.5
	5	0.634	-3.55 [-5.36; -1.75]	22.74 [21.59; 23.89]	28.92 [28.88; 28.96]	0.56 [0.53; 0.60]	42.02 [39.59; 44.49]	13.1	25.6	40.7	53.4
Two	45-240	0.991	-2.09 [-2.43; -1.75]	4.35 [4.11; 4.60]	5.42 [5.42; 5.43]	0.99 [0.99; 0.99]	7.88 [7.34; 8.41]	66.7	92.2	97.8	99.4
	30-240	0.990	-2.65 [-3.00; -2.29]	4.62 [4.35; 4.89]	5.77 [5.77; 5.78]	0.99 [0.99; 0.99]	8.39 [7.91; 8.86]	66.1	89.4	96.3	99.1
	60-240	0.986	-1.20 [-1.59; -0.81]	4.81 [4.56; 5.07]	6.39 [6.38; 6.40]	0.99 [0.98; 0.99]	9.29 [8.36; 10.42]	64.1	89.4	97.4	99.1
	45-210	0.985	-1.83 [-2.26; -1.41]	5.49 [5.21; 5.77]	6.48 [6.47; 6.49]	0.98 [0.98; 0.99]	9.41 [8.90; 9.93]	56.1	86.6	95.9	99.0
	30-210	0.986	-2.29 [-2.72; -1.87]	5.63 [5.35; 5.92]	6.48 [6.47; 6.49]	0.98 [0.98; 0.99]	9.42 [9.00; 9.85]	55.3	84.3	95.3	98.6
	15-240	0.986	-2.88 [-3.29; -2.47]	5.17 [4.86; 5.49]	6.76 [6.75; 6.77]	0.98 [0.98; 0.99]	9.83 [9.08; 10.69]	62.8	86.5	94.6	97.5
	60-210	0.980	-0.86 [-1.33; -0.39]	5.96 [5.66; 6.25]	7.36 [7.35; 7.37]	0.98 [0.98; 0.98]	10.69 [10.02; 11.57]	50.8	83.2	94.4	98.7
	15-210	0.981	-2.32 [-2.79; -1.84]	6.11 [5.79; 6.42]	7.40 [7.39; 7.41]	0.98 [0.98; 0.98]	10.75 [10.11; 11.54]	51.7	81.5	93.4	97.6
	5-240	0.982	-2.99 [-3.46; -2.52]	5.82 [5.47; 6.18]	7.49 [7.48; 7.50]	0.98 [0.98; 0.98]	10.89 [10.18; 11.65]	56.6	83.4	92.5	96.9
	30-180	0.980	-2.10 [-2.63; -1.56]	6.78 [6.43; 7.13]	7.55 [7.54; 7.56]	0.98 [0.98; 0.98]	10.97 [10.48; 11.47]	45.6	78.1	92.1	96.6
	45-180	0.978	-1.84 [-2.38; -1.30]	6.84 [6.49; 7.19]	7.83 [7.82; 7.84]	0.98 [0.97; 0.98]	11.38 [10.86; 11.95]	44.7	78.5	91.9	96.5
	15-180	0.976	-1.75 [-2.31; -1.19]	7.25 [6.90; 7.61]	8.17 [8.16; 8.19]	0.98 [0.97; 0.98]	11.88 [11.34; 12.40]	41.7	72.6	90.8	96.7
	5-210	0.976	-2.69 [-3.22; -2.16]	6.81 [6.44; 7.17]	8.25 [8.24; 8.27]	0.98 [0.97; 0.98]	12.00 [11.39; 12.58]	46.8	78.1	90.5	95.9
	90-240	0.977	-3.57 [-4.07; -3.07]	6.51 [6.14; 6.88]	8.42 [8.41; 8.43]	0.97 [0.97; 0.98]	12.24 [11.33; 13.15]	50.3	80.7	90.5	95.9
	60-180	0.971	-0.86 [-1.44; -0.27]	7.39 [7.02; 7.75]	8.84 [8.83; 8.86]	0.97 [0.97; 0.97]	12.85 [12.13; 13.58]	41.5	73.2	89.1	96.1
	5-180	0.969	-2.40 [-3.02; -1.77]	7.92 [7.51; 8.33]	9.29 [9.28; 9.30]	0.97 [0.96; 0.97]	13.50 [12.76; 14.25]	39.5	71.4	88.0	94.2
	30-150	0.968	-1.28 [-1.93; -0.63]	8.31 [7.91; 8.71]	9.36 [9.34; 9.37]	0.97 [0.96; 0.97]	13.59 [13.03; 14.17]	36.8	66.1	87.6	94.8

120-240	0.970	-3.60 [-4.14; -3.06]	6.99 [6.59; 7.38]	9.36 [9.35; 9.37]	0.97 [0.96; 0.97]	13.60 [12.55; 14.76]	47.9	77.7	89.6	95.5
90-210	0.968	-2.57 [-3.17; -1.96]	7.59 [7.19; 8.00]	9.46 [9.45; 9.48]	0.97 [0.96; 0.97]	13.75 [12.89; 14.64]	42.9	73.4	88.1	94.6
45-150	0.965	-1.38 [-2.04; -0.72]	8.31 [7.89; 8.73]	9.77 [9.76; 9.78]	0.96 [0.96; 0.97]	14.20 [13.47; 15.01]	38.1	67.8	86.1	94.0
15-150	0.964	-0.35 [-1.01; 0.31]	8.57 [8.18; 8.96]	9.93 [9.91; 9.94]	0.96 [0.96; 0.97]	14.42 [13.78; 15.05]	34.9	63.4	85.4	95.1
120-210	0.965	-4.37 [-4.99; -3.76]	8.07 [7.63; 8.51]	10.21 [10.20; 10.22]	0.96 [0.96; 0.97]	14.84 [13.80; 15.92]	41.5	70.7	85.1	93.3
180-240	0.961	-3.03 [-3.62; -2.45]	7.33 [6.92; 7.75]	10.35 [10.34; 10.37]	0.96 [0.95; 0.96]	15.04 [13.92; 16.33]	44.8	75.4	88.4	94.9
150-240	0.961	-3.16 [-3.75; -2.58]	7.18 [6.76; 7.61]	10.45 [10.44; 10.47]	0.96 [0.95; 0.96]	15.19 [13.63; 17.06]	47.3	77.0	89.0	94.6
180-210	0.961	-3.62 [-4.24; -3.00]	8.00 [7.57; 8.43]	10.57 [10.55; 10.58]	0.96 [0.95; 0.96]	15.35 [14.34; 16.33]	41.2	70.3	87.4	94.1
210-240	0.959	-3.04 [-3.63; -2.45]	7.44 [7.02; 7.85]	10.65 [10.64; 10.67]	0.96 [0.95; 0.96]	15.48 [14.41; 16.66]	45.1	75.5	87.9	94.7
5-150	0.958	-0.64 [-1.34; 0.06]	9.05 [8.63; 9.46]	10.69 [10.68; 10.70]	0.96 [0.95; 0.96]	15.53 [14.79; 16.19]	31.9	61.2	83.1	93.9
150-210	0.960	-3.91 [-4.54; -3.29]	8.01 [7.56; 8.46]	10.69 [10.67; 10.70]	0.96 [0.95; 0.96]	15.53 [14.18; 17.07]	42.0	71.4	86.6	93.5
60-150	0.957	-0.73 [-1.42; -0.03]	8.75 [8.31; 9.19]	10.80 [10.79; 10.82]	0.96 [0.95; 0.96]	15.69 [14.75; 16.80]	36.4	65.3	83.7	92.1
90-180	0.956	-0.22 [-0.92; 0.47]	8.76 [8.33; 9.19]	10.97 [10.96; 10.99]	0.96 [0.95; 0.96]	15.94 [15.04; 16.88]	36.5	64.6	81.5	92.6
150-180	0.956	-4.48 [-5.17; -3.78]	9.03 [8.53; 9.54]	11.23 [11.22; 11.25]	0.95 [0.95; 0.96]	16.32 [15.08; 17.53]	36.8	66.5	82.7	91.3
120-180	0.958	-5.46 [-6.17; -4.74]	9.41 [8.87; 9.94]	11.27 [11.26; 11.29]	0.95 [0.95; 0.96]	16.38 [15.31; 17.53]	37.6	64.9	80.4	89.2
30-120	0.948	-0.62 [-1.41; 0.16]	9.66 [9.15; 10.16]	11.90 [11.88; 11.91]	0.94 [0.94; 0.95]	17.29 [16.35; 18.12]	34.5	62.1	78.1	88.5
45-120	0.946	-1.19 [-1.98; -0.40]	9.72 [9.20; 10.24]	12.03 [12.02; 12.05]	0.94 [0.94; 0.95]	17.48 [16.56; 18.39]	34.5	61.4	79.2	88.4
15-120	0.947	0.89 [0.14; 1.64]	9.65 [9.19; 10.11]	12.21 [12.20; 12.23]	0.94 [0.93; 0.95]	17.75 [16.86; 18.66]	32.8	59.2	77.3	89.9
90-150	0.945	0.20 [-0.57; 0.97]	9.61 [9.13; 10.09]	12.25 [12.24; 12.27]	0.94 [0.94; 0.95]	17.80 [16.67; 18.90]	34.5	60.3	78.4	89.4
120-150	0.944	-2.98 [-3.77; -2.19]	10.14 [9.63; 10.66]	12.33 [12.31; 12.35]	0.94 [0.93; 0.95]	17.91 [16.94; 18.90]	32.3	59.6	77.7	88.5
5-120	0.944	1.08 [0.33; 1.83]	9.71 [9.26; 10.17]	12.50 [12.48; 12.51]	0.94 [0.93; 0.95]	18.16 [17.24; 19.13]	32.5	57.1	77.4	90.3
60-120	0.939	-0.84 [-1.67; -0.02]	10.14 [9.61; 10.68]	12.78 [12.76; 12.80]	0.94 [0.93; 0.95]	18.57 [17.46; 19.47]	33.2	59.6	77.4	88.1
90-120	0.928	-0.92 [-1.78; -0.05]	10.71 [10.16; 11.26]	13.92 [13.90; 13.94]	0.93 [0.92; 0.94]	20.23 [18.98; 21.53]	31.2	57.3	73.7	86.1
5-90	0.931	1.86 [1.01; 2.71]	10.80 [10.27; 11.34]	13.96 [13.94; 13.98]	0.92 [0.91; 0.93]	20.29 [19.20; 21.39]	29.2	54.4	72.7	86.1
15-90	0.929	2.09 [1.22; 2.97]	11.08 [10.53; 11.63]	14.25 [14.23; 14.27]	0.92 [0.91; 0.93]	20.71 [19.53; 21.75]	29.9	53.4	71.8	85.9
30-90	0.921	-0.57 [-1.53; 0.39]	11.56 [10.93; 12.20]	14.55 [14.53; 14.57]	0.91 [0.90; 0.92]	21.15 [20.01; 22.35]	29.6	53.6	71.9	83.9
45-90	0.919	-1.87 [-2.84; -0.90]	11.56 [10.89; 12.22]	14.62 [14.60; 14.64]	0.92 [0.91; 0.93]	21.25 [19.93; 22.49]	32.4	55.3	71.8	84.1
60-90	0.911	-2.00 [-3.00; -1.01]	11.95 [11.28; 12.63]	15.35 [15.32; 15.37]	0.91 [0.90; 0.92]	22.30 [20.96; 23.64]	30.2	52.7	71.4	82.9
5-60	0.908	0.78 [-0.21; 1.77]	12.47 [11.85; 13.10]	15.78 [15.76; 15.80]	0.90 [0.89; 0.91]	22.93 [21.79; 24.11]	26.5	49.3	67.1	79.9
15-60	0.904	0.83 [-0.18; 1.84]	12.61 [11.97; 13.24]	16.11 [16.08; 16.13]	0.90 [0.88; 0.91]	23.40 [22.15; 24.77]	26.0	48.0	66.8	80.5
30-60	0.887	-0.03 [-1.11; 1.06]	13.37 [12.67; 14.08]	17.28 [17.26; 17.31]	0.88 [0.87; 0.89]	25.11 [23.86; 26.56]	25.6	47.8	64.8	77.5
5-45	0.879	-1.05 [-2.17; 0.08]	14.01 [13.29; 14.73]	17.76 [17.73; 17.78]	0.87 [0.85; 0.88]	25.80 [24.52; 27.33]	22.2	44.2	61.9	77.4

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	45-60	0.878	-2.82 [-3.97; -1.66]	13.95 [13.17; 14.74]	17.80 [17.77; 17.82]	0.88 [0.86; 0.89]	25.86 [24.29; 27.27]	24.7	46.6	64.7	77.9
	15-45	0.870	-1.36 [-2.53; -0.19]	14.48 [13.73; 15.23]	18.32 [18.30; 18.35]	0.86 [0.84; 0.87]	26.62 [25.10; 28.10]	22.4	42.3	60.2	76.6
	30-45	0.841	-2.82 [-4.12; -1.53]	15.58 [14.70; 16.46]	20.06 [20.03; 20.08]	0.83 [0.81; 0.85]	29.14 [27.27; 30.86]	20.0	40.9	59.3	73.4
	5-30	0.835	-2.42 [-3.68; -1.16]	15.72 [14.91; 16.53]	20.42 [20.39; 20.45]	0.82 [0.80; 0.84]	29.67 [27.86; 31.63]	20.9	39.4	57.1	72.1
	15-30	0.821	-3.08 [-4.41; -1.75]	16.50 [15.63; 17.37]	21.16 [21.13; 21.19]	0.80 [0.78; 0.82]	30.74 [29.01; 32.62]	20.5	39.1	54.0	68.0
	5-15	0.742	-4.71 [-6.27; -3.14]	19.50 [18.47; 20.53]	24.87 [24.84; 24.91]	0.71 [0.69; 0.74]	36.14 [34.03; 38.35]	16.6	32.5	48.7	60.7
Three	5-45-240	0.995	-0.33 [-0.58; -0.07]	3.14 [2.98; 3.31]	3.76 [3.75; 3.76]	0.99 [0.99; 1.00]	5.46 [5.17; 5.73]	79.0	97.2	99.8	100.0
	5-30-240	0.994	-1.04 [-1.30; -0.78]	3.25 [3.08; 3.43]	4.10 [4.10; 4.11]	0.99 [0.99; 0.99]	5.96 [5.60; 6.34]	78.5	97.2	99.8	100.0
	15-45-240	0.993	-0.50 [-0.79; -0.21]	3.54 [3.34; 3.73]	4.32 [4.32; 4.33]	0.99 [0.99; 0.99]	6.28 [5.95; 6.65]	75.8	95.4	99.1	100.0
	30-45-240	0.992	-1.31 [-1.63; -0.99]	3.94 [3.71; 4.16]	4.78 [4.77; 4.78]	0.99 [0.99; 0.99]	6.94 [6.57; 7.34]	72.0	93.1	98.2	99.7
	15-60-240	0.992	0.59 [0.28; 0.91]	3.88 [3.67; 4.09]	4.83 [4.82; 4.84]	0.99 [0.99; 0.99]	7.02 [6.67; 7.41]	72.5	93.7	98.9	99.8
	5-60-240	0.992	0.33 [0.02; 0.64]	3.78 [3.58; 3.98]	4.86 [4.85; 4.87]	0.99 [0.99; 0.99]	7.06 [6.62; 7.56]	72.6	94.4	99.0	99.9
	30-60-240	0.991	-0.28 [-0.63; 0.06]	4.16 [3.93; 4.38]	5.10 [5.09; 5.11]	0.99 [0.99; 0.99]	7.41 [7.07; 7.78]	69.9	92.9	97.6	99.8
	5-30-210	0.991	-0.72 [-1.06; -0.38]	4.27 [4.05; 4.48]	5.10 [5.10; 5.11]	0.99 [0.99; 0.99]	7.42 [7.05; 7.75]	65.8	92.9	98.7	99.9
	45-210-240	0.991	-1.76 [-2.08; -1.44]	4.10 [3.88; 4.33]	5.10 [5.10; 5.11]	0.99 [0.99; 0.99]	7.42 [6.91; 7.95]	70.0	93.1	98.2	99.6
	15-30-240	0.991	-1.52 [-1.84; -1.20]	4.02 [3.80; 4.24]	5.15 [5.14; 5.15]	0.99 [0.99; 0.99]	7.48 [6.94; 8.10]	70.3	93.1	98.5	99.5
	30-210-240	0.992	-2.24 [-2.57; -1.91]	4.19 [3.94; 4.43]	5.16 [5.15; 5.17]	0.99 [0.99; 0.99]	7.50 [7.08; 7.88]	70.9	91.1	97.0	99.6
	30-180-240	0.992	-2.37 [-2.72; -2.02]	4.28 [4.02; 4.55]	5.20 [5.20; 5.21]	0.99 [0.99; 0.99]	7.56 [7.16; 7.96]	70.2	90.1	96.7	99.1
	45-60-240	0.991	-1.48 [-1.83; -1.14]	4.18 [3.93; 4.42]	5.27 [5.26; 5.28]	0.99 [0.99; 0.99]	7.66 [7.15; 8.21]	69.2	93.1	97.6	99.2
	30-150-240	0.991	-2.54 [-2.90; -2.18]	4.36 [4.08; 4.64]	5.34 [5.33; 5.35]	0.99 [0.99; 0.99]	7.76 [7.32; 8.18]	70.9	90.5	95.7	98.8
	5-45-210	0.990	0.03 [-0.32; 0.38]	4.40 [4.18; 4.63]	5.36 [5.35; 5.37]	0.99 [0.99; 0.99]	7.78 [7.43; 8.15]	64.4	92.4	98.9	99.8
	45-150-240	0.991	-2.19 [-2.53; -1.84]	4.29 [4.03; 4.54]	5.40 [5.40; 5.41]	0.99 [0.99; 0.99]	7.85 [7.33; 8.42]	69.4	91.6	97.3	99.1
	45-180-240	0.990	-1.94 [-2.28; -1.59]	4.30 [4.05; 4.56]	5.40 [5.39; 5.41]	0.99 [0.99; 0.99]	7.85 [7.28; 8.43]	67.2	92.1	97.4	99.2
	30-90-240	0.991	-2.79 [-3.15; -2.43]	4.44 [4.15; 4.73]	5.41 [5.40; 5.41]	0.99 [0.99; 0.99]	7.86 [7.40; 8.29]	70.6	89.1	95.1	98.8
	30-120-240	0.991	-2.72 [-3.09; -2.35]	4.51 [4.22; 4.80]	5.46 [5.45; 5.46]	0.99 [0.99; 0.99]	7.93 [7.45; 8.39]	71.0	89.3	95.1	98.5
	45-120-240	0.990	-2.33 [-2.69; -1.98]	4.36 [4.09; 4.63]	5.46 [5.46; 5.47]	0.99 [0.99; 0.99]	7.94 [7.40; 8.46]	68.4	91.4	96.9	98.8
	45-90-240	0.990	-2.49 [-2.84; -2.13]	4.47 [4.19; 4.74]	5.58 [5.58; 5.59]	0.99 [0.99; 0.99]	8.11 [7.56; 8.70]	67.5	90.3	96.7	98.8
	15-45-210	0.988	0.06 [-0.32; 0.44]	4.72 [4.47; 4.96]	5.71 [5.71; 5.72]	0.99 [0.99; 0.99]	8.30 [7.91; 8.70]	62.5	90.1	97.9	99.3

5-15-240	0.989	-2.14 [-2.49; -1.79]	4.41 [4.15; 4.66]	5.89 [5.88; 5.90]	0.99 [0.99; 0.99]	8.56 [7.79; 9.58]	68.5	90.4	96.8	99.2
15-210-240	0.989	-2.33 [-2.72; -1.95]	4.63 [4.34; 4.93]	5.95 [5.94; 5.96]	0.99 [0.99; 0.99]	8.64 [8.11; 9.18]	66.2	88.7	95.7	98.1
15-30-210	0.987	-1.03 [-1.42; -0.64]	5.02 [4.77; 5.26]	5.95 [5.94; 5.96]	0.99 [0.99; 0.99]	8.65 [8.23; 9.06]	60.1	88.1	97.1	99.6
15-90-240	0.988	-1.97 [-2.39; -1.55]	4.90 [4.58; 5.21]	5.96 [5.95; 5.97]	0.99 [0.99; 0.99]	8.66 [8.16; 9.13]	67.3	86.8	94.8	97.5
30-45-210	0.987	-0.85 [-1.26; -0.43]	5.12 [4.85; 5.39]	5.98 [5.98; 5.99]	0.99 [0.99; 0.99]	8.70 [8.25; 9.11]	58.7	87.8	96.5	98.9
15-180-240	0.988	-2.42 [-2.82; -2.02]	4.81 [4.51; 5.12]	6.04 [6.03; 6.05]	0.99 [0.99; 0.99]	8.78 [8.20; 9.33]	66.3	88.3	95.4	97.7
30-180-210	0.987	-2.14 [-2.55; -1.73]	5.40 [5.12; 5.67]	6.09 [6.08; 6.10]	0.99 [0.98; 0.99]	8.85 [8.44; 9.23]	57.6	85.2	95.9	98.9
60-210-240	0.987	-1.00 [-1.37; -0.63]	4.54 [4.30; 4.79]	6.14 [6.14; 6.15]	0.99 [0.98; 0.99]	8.93 [7.96; 10.17]	65.2	91.6	97.6	99.1
15-150-240	0.988	-2.58 [-2.99; -2.17]	4.80 [4.48; 5.13]	6.20 [6.20; 6.21]	0.99 [0.98; 0.99]	9.02 [8.42; 9.63]	68.3	86.5	95.2	97.5
60-180-240	0.987	-1.39 [-1.77; -1.01]	4.68 [4.42; 4.94]	6.22 [6.21; 6.22]	0.99 [0.98; 0.99]	9.03 [8.04; 10.26]	65.4	90.7	97.3	98.9
45-180-210	0.986	-1.75 [-2.17; -1.33]	5.39 [5.12; 5.66]	6.28 [6.27; 6.29]	0.99 [0.98; 0.99]	9.13 [8.64; 9.57]	56.1	86.7	96.3	99.0
15-60-210	0.986	1.25 [0.85; 1.66]	5.13 [4.87; 5.39]	6.28 [6.27; 6.29]	0.99 [0.98; 0.99]	9.13 [8.65; 9.58]	59.1	87.9	97.1	99.1
60-120-240	0.987	-1.82 [-2.21; -1.44]	4.79 [4.52; 5.06]	6.29 [6.28; 6.29]	0.99 [0.98; 0.99]	9.13 [8.23; 10.49]	64.3	89.7	96.6	98.5
5-60-210	0.986	0.73 [0.33; 1.13]	5.02 [4.76; 5.27]	6.34 [6.33; 6.35]	0.99 [0.98; 0.99]	9.21 [8.70; 9.75]	59.5	88.1	97.0	99.6
60-90-240	0.986	-1.89 [-2.28; -1.50]	4.80 [4.52; 5.07]	6.37 [6.36; 6.38]	0.99 [0.98; 0.99]	9.26 [8.33; 10.48]	65.6	88.5	96.4	98.8
5-15-210	0.986	-1.88 [-2.29; -1.48]	5.24 [4.97; 5.51]	6.39 [6.38; 6.39]	0.99 [0.98; 0.99]	9.28 [8.79; 9.76]	57.1	86.8	96.5	99.0
30-60-210	0.985	0.24 [-0.20; 0.67]	5.37 [5.09; 5.65]	6.39 [6.38; 6.40]	0.99 [0.98; 0.99]	9.29 [8.82; 9.74]	57.4	86.1	95.8	98.8
15-120-240	0.987	-2.88 [-3.31; -2.44]	5.08 [4.73; 5.42]	6.40 [6.39; 6.41]	0.99 [0.98; 0.99]	9.30 [8.75; 9.85]	67.5	85.6	93.6	96.6
30-150-210	0.986	-2.57 [-3.01; -2.13]	5.60 [5.29; 5.91]	6.41 [6.40; 6.42]	0.98 [0.98; 0.99]	9.31 [8.85; 9.76]	58.5	83.9	93.9	98.0
60-150-240	0.986	-1.73 [-2.11; -1.35]	4.69 [4.42; 4.95]	6.42 [6.42; 6.43]	0.99 [0.98; 0.99]	9.34 [8.02; 11.08]	66.1	90.5	96.5	98.7
45-60-210	0.985	-1.11 [-1.54; -0.68]	5.42 [5.14; 5.70]	6.48 [6.47; 6.49]	0.98 [0.98; 0.99]	9.42 [8.90; 9.95]	55.9	86.8	96.0	98.8
5-30-180	0.984	-0.72 [-1.15; -0.28]	5.43 [5.15; 5.71]	6.52 [6.51; 6.53]	0.98 [0.98; 0.99]	9.48 [8.97; 9.98]	54.4	85.0	96.4	98.9
5-90-240	0.984	-0.61 [-1.03; -0.19]	4.92 [4.63; 5.22]	6.55 [6.54; 6.56]	0.98 [0.98; 0.99]	9.52 [8.83; 10.25]	63.5	88.1	95.0	98.6
45-150-210	0.985	-2.17 [-2.60; -1.74]	5.54 [5.25; 5.84]	6.57 [6.56; 6.58]	0.98 [0.98; 0.99]	9.55 [9.03; 10.15]	56.3	85.8	94.9	98.5
30-120-210	0.986	-2.93 [-3.38; -2.48]	5.72 [5.39; 6.05]	6.59 [6.58; 6.60]	0.98 [0.98; 0.99]	9.58 [9.09; 10.04]	58.3	83.6	92.8	97.0
45-120-210	0.985	-2.56 [-3.00; -2.12]	5.61 [5.30; 5.92]	6.66 [6.65; 6.67]	0.98 [0.98; 0.99]	9.68 [9.17; 10.25]	56.1	86.4	94.3	97.7
30-90-210	0.985	-2.81 [-3.27; -2.34]	5.82 [5.48; 6.15]	6.78 [6.77; 6.79]	0.98 [0.98; 0.99]	9.86 [9.34; 10.35]	56.3	82.6	92.6	97.2
45-90-210	0.985	-2.80 [-3.25; -2.35]	5.73 [5.41; 6.05]	6.81 [6.80; 6.82]	0.98 [0.98; 0.98]	9.89 [9.34; 10.48]	55.3	84.7	94.2	97.3
15-180-210	0.983	-2.06 [-2.52; -1.61]	5.83 [5.53; 6.14]	6.98 [6.97; 6.99]	0.98 [0.98; 0.98]	10.14 [9.51; 10.79]	52.7	82.8	93.7	98.1
15-30-180	0.982	-0.79 [-1.27; -0.31]	6.04 [5.73; 6.35]	7.06 [7.05; 7.07]	0.98 [0.98; 0.98]	10.25 [9.73; 10.75]	50.4	81.6	94.1	98.4
5-210-240	0.983	-2.36 [-2.80; -1.91]	5.38 [5.05; 5.71]	7.05 [7.04; 7.06]	0.98 [0.98; 0.98]	10.25 [9.56; 10.92]	61.5	85.9	93.6	97.6
15-45-180	0.982	0.29 [-0.19; 0.77]	5.95 [5.65; 6.25]	7.08 [7.07; 7.09]	0.98 [0.98; 0.98]	10.29 [9.82; 10.76]	51.8	83.0	94.7	98.3

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	5-45-180	0.981	0.08 [-0.39; 0.55]	5.83 [5.53; 6.12]	7.12 [7.11; 7.13]	0.98 [0.98; 0.98]	10.35 [9.81; 10.91]	50.9	85.0	95.2	98.2
	5-180-240	0.982	-2.26 [-2.72; -1.80]	5.55 [5.21; 5.88]	7.21 [7.20; 7.22]	0.98 [0.98; 0.98]	10.47 [9.69; 11.28]	58.9	85.7	94.1	97.4
	15-150-210	0.982	-2.51 [-2.99; -2.03]	6.03 [5.69; 6.37]	7.29 [7.28; 7.30]	0.98 [0.98; 0.98]	10.59 [10.00; 11.25]	54.7	80.9	92.9	96.8
	60-120-210	0.981	-1.86 [-2.33; -1.39]	5.88 [5.56; 6.19]	7.35 [7.34; 7.36]	0.98 [0.98; 0.98]	10.68 [9.82; 11.80]	53.2	83.2	93.8	97.8
	60-180-210	0.980	-0.94 [-1.41; -0.48]	5.88 [5.59; 6.17]	7.38 [7.37; 7.39]	0.98 [0.98; 0.98]	10.73 [9.81; 11.88]	52.0	82.8	94.8	99.0
	30-150-180	0.981	-2.24 [-2.77; -1.71]	6.70 [6.34; 7.06]	7.41 [7.40; 7.42]	0.98 [0.98; 0.98]	10.76 [10.25; 11.23]	47.1	77.9	91.8	96.6
	30-45-180	0.980	-0.69 [-1.22; -0.17]	6.49 [6.15; 6.83]	7.41 [7.40; 7.42]	0.98 [0.98; 0.98]	10.77 [10.28; 11.23]	48.2	80.1	93.7	97.3
	60-150-210	0.980	-1.51 [-1.98; -1.04]	5.89 [5.58; 6.19]	7.42 [7.41; 7.43]	0.98 [0.98; 0.98]	10.78 [9.76; 12.24]	52.0	83.5	94.7	98.3
	15-120-210	0.981	-3.00 [-3.51; -2.49]	6.30 [5.93; 6.68]	7.52 [7.51; 7.53]	0.98 [0.98; 0.98]	10.92 [10.37; 11.47]	56.1	79.2	91.1	95.2
	60-90-210	0.980	-1.81 [-2.30; -1.33]	6.04 [5.72; 6.36]	7.55 [7.53; 7.56]	0.98 [0.98; 0.98]	10.96 [10.19; 11.83]	52.0	81.6	93.1	97.8
	5-120-240	0.980	-2.36 [-2.86; -1.87]	5.68 [5.31; 6.05]	7.64 [7.63; 7.65]	0.98 [0.98; 0.98]	11.10 [10.30; 12.00]	61.9	83.8	91.4	96.1
	5-15-180	0.979	-1.96 [-2.47; -1.46]	6.43 [6.10; 6.76]	7.67 [7.66; 7.68]	0.98 [0.98; 0.98]	11.15 [10.55; 11.74]	49.2	79.7	91.9	97.2
	5-150-240	0.979	-2.22 [-2.69; -1.74]	5.60 [5.24; 5.95]	7.67 [7.66; 7.68]	0.98 [0.98; 0.98]	11.15 [10.26; 12.17]	60.5	84.7	92.8	96.5
	15-90-210	0.978	0.29 [-0.22; 0.81]	6.21 [5.86; 6.55]	7.71 [7.70; 7.72]	0.98 [0.98; 0.98]	11.21 [10.57; 11.79]	53.8	78.9	91.1	97.5
	45-150-180	0.979	-1.96 [-2.49; -1.43]	6.74 [6.40; 7.09]	7.74 [7.73; 7.75]	0.98 [0.98; 0.98]	11.25 [10.73; 11.76]	45.0	77.9	92.1	96.7
	15-60-180	0.979	1.50 [0.99; 2.00]	6.43 [6.11; 6.75]	7.79 [7.78; 7.80]	0.98 [0.97; 0.98]	11.33 [10.81; 11.83]	48.3	79.7	92.3	97.9
	5-180-210	0.978	-2.09 [-2.61; -1.58]	6.46 [6.11; 6.80]	7.87 [7.86; 7.89]	0.98 [0.97; 0.98]	11.44 [10.81; 12.05]	48.8	79.7	91.9	96.9
	30-60-180	0.978	0.59 [0.04; 1.13]	6.77 [6.42; 7.11]	7.90 [7.89; 7.91]	0.98 [0.97; 0.98]	11.48 [10.98; 11.98]	45.0	77.7	91.6	97.5
	30-120-180	0.979	-3.03 [-3.60; -2.47]	7.07 [6.66; 7.47]	7.91 [7.90; 7.92]	0.98 [0.97; 0.98]	11.50 [10.92; 12.05]	48.0	75.1	89.3	94.8
	45-120-180	0.978	-2.74 [-3.29; -2.18]	7.02 [6.64; 7.41]	8.06 [8.05; 8.07]	0.98 [0.97; 0.98]	11.72 [11.13; 12.30]	45.4	77.3	90.3	95.5
	45-60-180	0.976	-1.06 [-1.62; -0.51]	6.94 [6.58; 7.30]	8.08 [8.07; 8.09]	0.98 [0.97; 0.98]	11.74 [11.21; 12.31]	44.7	76.9	91.0	96.7
	5-90-210	0.976	0.21 [-0.30; 0.73]	6.14 [5.78; 6.49]	8.08 [8.07; 8.09]	0.98 [0.97; 0.98]	11.74 [11.02; 12.47]	54.5	81.8	91.3	97.3
	5-30-150	0.976	-0.11 [-0.65; 0.43]	6.74 [6.40; 7.07]	8.13 [8.12; 8.14]	0.98 [0.97; 0.98]	11.82 [11.18; 12.46]	45.5	77.3	92.5	97.6
	15-150-180	0.976	-1.90 [-2.47; -1.33]	7.11 [6.73; 7.49]	8.18 [8.17; 8.19]	0.98 [0.97; 0.98]	11.89 [11.31; 12.49]	45.1	73.1	89.8	96.4
	5-60-180	0.976	0.89 [0.36; 1.42]	6.53 [6.19; 6.87]	8.22 [8.21; 8.24]	0.98 [0.97; 0.98]	11.95 [11.32; 12.62]	47.6	79.4	92.3	97.3
	45-90-180	0.976	-2.74 [-3.31; -2.16]	7.24 [6.83; 7.64]	8.32 [8.31; 8.33]	0.97 [0.97; 0.98]	12.09 [11.51; 12.68]	46.0	76.8	88.6	95.2
	30-90-180	0.974	-1.61 [-2.22; -1.00]	7.30 [6.88; 7.71]	8.35 [8.34; 8.37]	0.97 [0.97; 0.98]	12.14 [11.55; 12.76]	47.0	74.8	88.0	94.6
	90-150-240	0.975	-1.53 [-2.03; -1.03]	6.01 [5.67; 6.36]	8.36 [8.34; 8.37]	0.97 [0.97; 0.98]	12.14 [11.25; 13.20]	53.6	83.7	92.5	96.7

5-150-210	0.975	-2.12 [-2.66; -1.58]	6.74 [6.36; 7.11]	8.38 [8.37; 8.39]	0.97 [0.97; 0.98]	12.17 [11.49; 12.95]	51.3	78.5	89.7	96.1
90-120-240	0.975	-2.26 [-2.77; -1.75]	6.30 [5.95; 6.66]	8.42 [8.41; 8.43]	0.97 [0.97; 0.98]	12.24 [11.29; 13.19]	51.6	81.0	91.2	96.5
90-210-240	0.975	-2.09 [-2.61; -1.58]	6.28 [5.92; 6.64]	8.46 [8.45; 8.47]	0.97 [0.97; 0.98]	12.29 [11.40; 13.34]	52.2	81.2	90.8	96.4
5-120-210	0.974	-2.23 [-2.80; -1.67]	6.85 [6.45; 7.25]	8.60 [8.58; 8.61]	0.97 [0.97; 0.98]	12.49 [11.77; 13.22]	51.0	78.7	88.9	94.8
90-180-240	0.973	-1.34 [-1.85; -0.82]	6.23 [5.88; 6.58]	8.62 [8.61; 8.63]	0.97 [0.97; 0.98]	12.52 [11.52; 13.59]	51.9	81.4	91.6	96.6
5-15-150	0.972	-1.25 [-1.82; -0.67]	7.32 [6.95; 7.68]	8.75 [8.74; 8.77]	0.97 [0.97; 0.97]	12.72 [12.04; 13.38]	42.9	74.5	89.3	96.0
60-150-180	0.971	-1.16 [-1.75; -0.58]	7.31 [6.94; 7.68]	8.89 [8.88; 8.90]	0.97 [0.97; 0.97]	12.91 [12.04; 14.10]	42.5	73.8	89.1	96.0
5-150-180	0.971	-1.86 [-2.47; -1.25]	7.55 [7.14; 7.95]	8.93 [8.91; 8.94]	0.97 [0.97; 0.97]	12.97 [12.31; 13.60]	43.2	73.6	88.0	94.4
15-30-150	0.971	0.01 [-0.59; 0.60]	7.49 [7.12; 7.86]	8.95 [8.94; 8.96]	0.97 [0.97; 0.97]	13.01 [12.33; 13.66]	41.1	71.2	89.3	96.6
60-120-180	0.971	-1.94 [-2.54; -1.34]	7.51 [7.11; 7.91]	9.01 [8.99; 9.02]	0.97 [0.97; 0.97]	13.09 [12.22; 14.20]	43.1	73.1	88.0	95.2
15-120-180	0.971	-2.78 [-3.41; -2.14]	7.75 [7.31; 8.20]	9.01 [9.00; 9.03]	0.97 [0.97; 0.97]	13.10 [12.46; 13.75]	46.2	69.6	86.5	93.1
5-45-150	0.970	0.59 [0.00; 1.17]	7.24 [6.87; 7.62]	9.12 [9.10; 9.13]	0.97 [0.97; 0.97]	13.25 [12.57; 14.01]	44.2	74.3	89.7	96.0
120-150-240	0.971	-3.03 [-3.57; -2.49]	6.74 [6.36; 7.13]	9.16 [9.14; 9.17]	0.97 [0.96; 0.97]	13.31 [12.18; 14.46]	49.2	78.8	90.7	95.4
15-45-150	0.970	0.95 [0.36; 1.54]	7.46 [7.09; 7.83]	9.19 [9.17; 9.20]	0.97 [0.96; 0.97]	13.35 [12.67; 14.03]	42.2	73.0	89.4	95.9
60-90-180	0.969	-1.62 [-2.24; -1.01]	7.66 [7.27; 8.06]	9.28 [9.27; 9.29]	0.97 [0.96; 0.97]	13.48 [12.73; 14.30]	41.3	73.1	86.5	94.6
120-210-240	0.969	-3.24 [-3.78; -2.69]	6.76 [6.36; 7.16]	9.38 [9.36; 9.39]	0.97 [0.96; 0.97]	13.62 [12.51; 14.85]	50.9	78.5	89.5	95.4
15-90-180	0.971	2.24 [1.66; 2.82]	7.56 [7.19; 7.94]	9.38 [9.37; 9.39]	0.97 [0.96; 0.97]	13.63 [12.98; 14.29]	43.0	71.1	86.7	96.3
120-180-240	0.969	-3.05 [-3.60; -2.50]	6.92 [6.52; 7.31]	9.41 [9.40; 9.43]	0.97 [0.96; 0.97]	13.68 [12.54; 14.95]	49.7	78.3	89.9	95.4
5-120-180	0.967	-1.79 [-2.44; -1.14]	7.72 [7.27; 8.16]	9.51 [9.49; 9.52]	0.97 [0.96; 0.97]	13.81 [13.07; 14.60]	44.8	71.9	87.4	93.8
90-150-210	0.967	-1.44 [-2.03; -0.85]	7.21 [6.82; 7.60]	9.51 [9.49; 9.52]	0.97 [0.96; 0.97]	13.81 [12.90; 14.79]	45.4	75.2	88.3	94.7
30-45-150	0.967	-0.05 [-0.69; 0.59]	8.06 [7.66; 8.46]	9.53 [9.51; 9.54]	0.97 [0.96; 0.97]	13.84 [13.14; 14.54]	38.7	68.5	87.5	94.9
30-120-150	0.966	-1.36 [-2.03; -0.69]	8.29 [7.86; 8.72]	9.54 [9.52; 9.55]	0.97 [0.96; 0.97]	13.86 [13.18; 14.56]	39.7	66.3	86.7	93.4
90-120-210	0.967	-2.29 [-2.88; -1.69]	7.38 [6.98; 7.78]	9.56 [9.54; 9.57]	0.97 [0.96; 0.97]	13.89 [12.94; 14.88]	46.2	74.2	87.2	94.0
5-90-180	0.966	0.82 [0.19; 1.45]	7.55 [7.13; 7.97]	9.67 [9.66; 9.68]	0.96 [0.96; 0.97]	14.05 [13.28; 14.85]	44.6	73.4	86.6	93.6
90-180-210	0.965	-1.13 [-1.74; -0.53]	7.39 [7.00; 7.79]	9.77 [9.76; 9.78]	0.96 [0.96; 0.97]	14.20 [13.22; 15.25]	44.4	73.8	87.7	94.6
45-120-150	0.964	-1.54 [-2.21; -0.87]	8.42 [8.00; 8.85]	9.86 [9.85; 9.87]	0.96 [0.96; 0.97]	14.33 [13.65; 15.05]	36.5	68.8	85.4	93.7
15-60-150	0.966	1.95 [1.33; 2.56]	7.83 [7.43; 8.23]	9.90 [9.88; 9.91]	0.96 [0.96; 0.97]	14.38 [13.73; 15.12]	42.2	69.2	86.8	94.1
180-210-240	0.964	-2.82 [-3.39; -2.25]	7.09 [6.70; 7.49]	9.95 [9.93; 9.96]	0.96 [0.96; 0.97]	14.46 [13.46; 15.49]	47.6	76.6	89.8	95.3
45-60-150	0.963	-0.68 [-1.35; -0.01]	8.30 [7.87; 8.73]	9.96 [9.95; 9.98]	0.96 [0.96; 0.97]	14.48 [13.72; 15.25]	38.6	68.9	85.5	93.2
30-60-150	0.964	0.94 [0.28; 1.59]	8.22 [7.80; 8.64]	10.02 [10.01; 10.03]	0.96 [0.96; 0.97]	14.56 [13.89; 15.27]	38.8	66.9	85.3	93.6
5-60-150	0.964	1.53 [0.91; 2.15]	7.78 [7.38; 8.18]	10.12 [10.11; 10.14]	0.96 [0.96; 0.97]	14.71 [13.86; 15.62]	41.5	69.9	86.8	94.3
120-150-210	0.965	-3.88 [-4.49; -3.27]	7.87 [7.43; 8.30]	10.12 [10.11; 10.14]	0.96 [0.96; 0.97]	14.71 [13.66; 15.88]	43.0	72.1	86.3	93.7

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	120-180-210	0.964	-4.07 [-4.69; -3.45]	7.96 [7.51; 8.41]	10.27 [10.26; 10.29]	0.96 [0.96; 0.96]	14.93 [13.92; 15.99]	42.9	71.2	85.9	93.1
	150-210-240	0.961	-2.94 [-3.52; -2.37]	6.95 [6.53; 7.37]	10.36 [10.35; 10.38]	0.96 [0.95; 0.96]	15.05 [13.34; 16.66]	49.8	78.4	89.4	94.7
	150-180T240	0.961	-3.11 [-3.69; -2.53]	7.10 [6.68; 7.53]	10.39 [10.38; 10.40]	0.96 [0.95; 0.96]	15.10 [13.47; 16.86]	48.3	77.3	89.4	94.7
	30-90-150	0.961	0.33 [-0.38; 1.04]	8.78 [8.32; 9.24]	10.40 [10.38; 10.41]	0.96 [0.95; 0.96]	15.11 [14.40; 15.81]	37.2	65.2	83.5	92.2
	5-30-120	0.960	0.42 [-0.23; 1.08]	8.08 [7.66; 8.51]	10.40 [10.39; 10.42]	0.96 [0.95; 0.96]	15.12 [14.28; 15.87]	42.1	67.7	84.4	93.0
	45-90-150	0.960	-1.56 [-2.26; -0.86]	8.68 [8.22; 9.14]	10.45 [10.43; 10.46]	0.96 [0.95; 0.96]	15.18 [14.44; 15.90]	38.7	67.5	82.8	92.2
	15-120-150	0.961	0.68 [0.00; 1.37]	8.66 [8.23; 9.09]	10.48 [10.47; 10.50]	0.96 [0.95; 0.96]	15.23 [14.42; 16.01]	36.5	65.2	83.2	92.8
	150-180-210	0.961	-3.89 [-4.51; -3.27]	7.86 [7.41; 8.31]	10.57 [10.55; 10.58]	0.96 [0.95; 0.96]	15.36 [13.92; 16.89]	41.9	71.6	86.8	93.7
	5-120-150	0.958	0.14 [-0.55; 0.83]	8.51 [8.06; 8.95]	10.72 [10.70; 10.73]	0.96 [0.95; 0.96]	15.57 [14.72; 16.56]	38.3	66.5	84.0	94.0
	5-15-120	0.957	-0.59 [-1.27; 0.10]	8.39 [7.94; 8.84]	10.77 [10.76; 10.79]	0.96 [0.95; 0.96]	15.65 [14.80; 16.54]	40.5	68.1	83.4	92.1
	60-120-150	0.957	-0.88 [-1.59; -0.18]	8.83 [8.39; 9.28]	10.78 [10.77; 10.80]	0.96 [0.95; 0.96]	15.67 [14.69; 16.62]	36.0	65.0	83.9	91.9
	15-90-150	0.962	2.89 [2.23; 3.54]	8.48 [8.05; 8.91]	10.80 [10.78; 10.81]	0.96 [0.95; 0.96]	15.69 [14.86; 16.57]	40.0	65.8	83.2	92.4
	60-90-150	0.954	-1.13 [-1.86; -0.41]	9.02 [8.56; 9.48]	11.11 [11.09; 11.12]	0.95 [0.95; 0.96]	16.14 [15.19; 17.27]	35.7	65.0	82.7	90.9
	120-150-180	0.958	-4.69 [-5.40; -3.98]	9.14 [8.62; 9.66]	11.11 [11.10; 11.13]	0.95 [0.95; 0.96]	16.15 [15.01; 17.34]	37.8	66.2	81.4	90.1
	90-120-180	0.954	-1.91 [-2.63; -1.20]	8.92 [8.45; 9.38]	11.12 [11.11; 11.14]	0.95 [0.95; 0.96]	16.16 [15.12; 17.33]	38.6	65.8	80.0	91.0
	90-150-180	0.954	-0.66 [-1.36; 0.04]	8.61 [8.16; 9.06]	11.14 [11.13; 11.16]	0.95 [0.95; 0.96]	16.19 [15.17; 17.34]	39.2	66.2	81.9	91.9
	5-90-150	0.956	1.90 [1.21; 2.59]	8.53 [8.07; 9.00]	11.22 [11.20; 11.23]	0.95 [0.95; 0.96]	16.30 [15.37; 17.27]	40.5	68.1	82.5	92.4
	5-45-120	0.954	1.07 [0.38; 1.76]	8.59 [8.15; 9.03]	11.24 [11.22; 11.25]	0.95 [0.95; 0.96]	16.33 [15.42; 17.27]	38.8	65.9	84.3	92.5
	15-30-120	0.953	0.68 [-0.03; 1.39]	8.84 [8.39; 9.29]	11.33 [11.31; 11.34]	0.95 [0.94; 0.96]	16.46 [15.53; 17.47]	37.3	64.7	80.7	91.2
	15-45-120	0.953	1.37 [0.67; 2.06]	8.74 [8.29; 9.19]	11.43 [11.42; 11.45]	0.95 [0.94; 0.96]	16.62 [15.61; 17.54]	37.9	65.0	82.6	92.2
	15-60-120	0.951	2.21 [1.49; 2.94]	9.17 [8.70; 9.63]	11.93 [11.92; 11.95]	0.95 [0.94; 0.95]	17.34 [16.32; 18.25]	36.1	62.8	80.6	91.1
	30-45-120	0.947	0.14 [-0.65; 0.92]	9.53 [9.01; 10.04]	12.03 [12.01; 12.05]	0.94 [0.94; 0.95]	17.48 [16.58; 18.39]	36.4	62.7	79.4	89.3
	5-60-120	0.949	2.01 [1.29; 2.74]	9.13 [8.67; 9.60]	12.11 [12.09; 12.12]	0.94 [0.94; 0.95]	17.59 [16.64; 18.57]	37.2	63.4	80.3	90.8
	45-60-120	0.945	-0.57 [-1.37; 0.23]	9.82 [9.30; 10.34]	12.20 [12.18; 12.21]	0.94 [0.94; 0.95]	17.72 [16.84; 18.63]	34.7	60.1	79.2	88.2
	45-90-120	0.944	-0.82 [-1.62; -0.01]	9.78 [9.25; 10.31]	12.25 [12.24; 12.27]	0.94 [0.93; 0.95]	17.81 [16.85; 18.74]	35.3	61.4	78.8	88.6
	30-60-120	0.946	0.97 [0.18; 1.76]	9.75 [9.24; 10.26]	12.29 [12.27; 12.30]	0.94 [0.93; 0.95]	17.85 [16.87; 18.77]	34.0	62.1	78.0	88.5
	90-120-150	0.943	-0.24 [-1.02; 0.55]	9.78 [9.28; 10.27]	12.42 [12.40; 12.43]	0.94 [0.93; 0.95]	18.04 [16.91; 19.18]	34.9	60.5	78.2	88.3
	30-90-120	0.945	0.72 [-0.08; 1.53]	9.86 [9.34; 10.39]	12.43 [12.41; 12.45]	0.94 [0.93; 0.95]	18.06 [17.22; 18.98]	35.4	61.3	77.1	87.5

	15-90-120	0.948	2.65 [1.90; 3.39]	9.57 [9.10; 10.05]	12.45 [12.44; 12.47]	0.94 [0.93; 0.95]	18.10 [17.15; 19.08]	34.5	61.0	77.1	89.3
	5-30-90	0.941	0.27 [-0.54; 1.09]	9.96 [9.43; 10.49]	12.63 [12.62; 12.65]	0.94 [0.93; 0.95]	18.36 [17.31; 19.38]	32.5	60.5	77.5	88.6
	5-15-90	0.939	-0.50 [-1.33; 0.33]	10.04 [9.49; 10.58]	12.74 [12.72; 12.76]	0.94 [0.93; 0.94]	18.51 [17.42; 19.51]	33.8	60.3	76.4	89.2
	5-90-120	0.945	2.63 [1.88; 3.37]	9.50 [9.02; 9.98]	12.74 [12.72; 12.76]	0.94 [0.93; 0.94]	18.52 [17.55; 19.64]	35.2	60.8	78.0	89.2
	60-90-120	0.937	-0.76 [-1.59; 0.07]	10.15 [9.60; 10.69]	12.96 [12.94; 12.98]	0.94 [0.93; 0.94]	18.84 [17.77; 19.96]	33.7	59.6	77.5	87.3
	5-45-90	0.936	0.74 [-0.10; 1.58]	10.18 [9.63; 10.73]	13.25 [13.23; 13.27]	0.93 [0.92; 0.94]	19.25 [18.11; 20.36]	35.3	58.5	77.6	87.3
	5-60-90	0.936	1.68 [0.85; 2.51]	10.39 [9.86; 10.92]	13.45 [13.43; 13.47]	0.93 [0.92; 0.94]	19.54 [18.34; 20.66]	33.2	56.6	75.4	87.3
	15-45-90	0.934	1.03 [0.18; 1.88]	10.45 [9.90; 11.01]	13.55 [13.53; 13.57]	0.93 [0.92; 0.94]	19.69 [18.58; 20.89]	33.8	57.2	75.9	86.4
	15-30-90	0.933	0.58 [-0.29; 1.45]	10.72 [10.16; 11.29]	13.57 [13.55; 13.59]	0.93 [0.92; 0.94]	19.72 [18.63; 20.81]	31.5	55.8	74.6	86.8
	15-60-90	0.934	1.74 [0.89; 2.59]	10.63 [10.09; 11.18]	13.69 [13.67; 13.71]	0.93 [0.92; 0.93]	19.90 [18.78; 21.08]	32.5	56.8	74.2	87.6
	30-45-90	0.922	-0.36 [-1.31; 0.59]	11.31 [10.68; 11.95]	14.48 [14.46; 14.50]	0.92 [0.91; 0.93]	21.04 [19.88; 22.24]	31.8	55.2	72.5	83.5
	30-60-90	0.922	0.32 [-0.63; 1.26]	11.42 [10.80; 12.04]	14.56 [14.54; 14.58]	0.92 [0.91; 0.92]	21.15 [19.91; 22.29]	30.4	54.8	71.1	83.5
	45-60-90	0.918	-1.56 [-2.53; -0.59]	11.61 [10.95; 12.27]	14.68 [14.66; 14.70]	0.92 [0.91; 0.93]	21.33 [20.03; 22.63]	31.5	54.0	73.2	83.5
	5-45-60	0.914	0.31 [-0.66; 1.28]	12.17 [11.56; 12.78]	15.19 [15.17; 15.22]	0.91 [0.90; 0.92]	22.08 [20.92; 23.12]	25.0	52.1	68.6	82.5
	5-15-60	0.912	-0.73 [-1.72; 0.26]	12.37 [11.75; 13.00]	15.26 [15.24; 15.28]	0.91 [0.90; 0.92]	22.17 [21.06; 23.32]	25.0	48.9	69.0	81.6
	5-30-60	0.912	-0.26 [-1.25; 0.72]	12.33 [11.71; 12.95]	15.30 [15.28; 15.32]	0.91 [0.90; 0.92]	22.23 [21.15; 23.29]	25.7	49.7	68.1	81.4
	15-45-60	0.910	0.56 [-0.43; 1.55]	12.37 [11.75; 12.99]	15.58 [15.56; 15.60]	0.90 [0.89; 0.91]	22.64 [21.47; 23.86]	25.0	50.7	68.6	81.5
	15-30-60	0.905	0.03 [-0.99; 1.04]	12.64 [11.99; 13.28]	15.88 [15.86; 15.91]	0.90 [0.89; 0.91]	23.08 [21.87; 24.39]	24.6	48.4	67.4	81.4
	30-45-60	0.890	-0.46 [-1.54; 0.62]	13.24 [12.54; 13.95]	17.01 [16.99; 17.04]	0.88 [0.87; 0.90]	24.72 [23.25; 26.15]	23.5	48.5	65.5	79.1
	5-30-45	0.882	-1.19 [-2.30; -0.07]	13.85 [13.14; 14.56]	17.55 [17.52; 17.57]	0.87 [0.86; 0.89]	25.50 [24.06; 26.98]	22.2	44.7	63.0	76.8
	5-15-45	0.880	-1.63 [-2.76; -0.49]	14.01 [13.28; 14.74]	17.65 [17.63; 17.67]	0.87 [0.86; 0.89]	25.65 [24.23; 27.06]	22.0	43.8	62.4	77.4
	15-30-45	0.874	-1.39 [-2.54; -0.23]	14.36 [13.62; 15.10]	18.05 [18.03; 18.08]	0.86 [0.85; 0.88]	26.23 [24.86; 27.60]	22.0	42.2	59.5	77.0
	5-15-30	0.835	-2.37 [-3.63; -1.11]	15.71 [14.90; 16.52]	20.41 [20.39; 20.44]	0.82 [0.80; 0.84]	29.66 [27.68; 31.43]	21.2	39.5	56.6	72.0
Four	5-30-45-240	0.996	-0.44 [-0.65; -0.22]	2.64 [2.50; 2.79]	3.15 [3.15; 3.16]	1.00 [1.00; 1.00]	4.58 [4.32; 4.84]	87.7	98.9	99.9	100.0
	5-30-60-240	0.996	-0.28 [-0.50; -0.06]	2.70 [2.55; 2.84]	3.37 [3.36; 3.37]	1.00 [1.00; 1.00]	4.89 [4.60; 5.19]	87.5	98.6	99.8	100.0
	5-30-210-240	0.996	-0.65 [-0.87; -0.43]	2.67 [2.52; 2.82]	3.38 [3.38; 3.39]	1.00 [1.00; 1.00]	4.91 [4.60; 5.22]	86.7	98.8	99.9	100.0
	5-15-45-240	0.996	-0.60 [-0.83; -0.37]	2.83 [2.67; 2.98]	3.44 [3.44; 3.45]	1.00 [1.00; 1.00]	5.00 [4.71; 5.29]	84.3	97.5	99.9	100.0
	5-45-210-240	0.996	0.04 [-0.19; 0.27]	2.80 [2.64; 2.95]	3.47 [3.47; 3.48]	1.00 [1.00; 1.00]	5.05 [4.76; 5.35]	84.7	97.7	100.0	100.0
	5-45-60-240	0.996	0.01 [-0.23; 0.25]	2.87 [2.71; 3.03]	3.52 [3.52; 3.53]	1.00 [0.99; 1.00]	5.12 [4.84; 5.39]	82.6	97.8	99.6	100.0
	5-30-180-240	0.996	-0.67 [-0.91; -0.44]	2.87 [2.71; 3.03]	3.58 [3.58; 3.59]	1.00 [0.99; 1.00]	5.20 [4.89; 5.52]	82.9	98.4	99.7	100.0
	5-45-120-240	0.995	-0.28 [-0.52; -0.04]	2.83 [2.66; 3.00]	3.66 [3.65; 3.66]	1.00 [0.99; 1.00]	5.32 [4.94; 5.73]	84.5	97.8	99.2	100.0
	5-30-150-240	0.995	-0.67 [-0.91; -0.43]	2.90 [2.73; 3.06]	3.68 [3.68; 3.69]	1.00 [0.99; 1.00]	5.35 [5.02; 5.66]	84.8	97.7	99.5	99.9

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	5-45-180-240	0.995	-0.06 [-0.30; 0.19]	2.95 [2.79; 3.12]	3.70 [3.69; 3.70]	1.00 [0.99; 1.00]	5.37 [5.02; 5.77]	81.8	97.5	99.7	100.0
	5-30-120-240	0.995	-0.54 [-0.79; -0.30]	2.87 [2.70; 3.04]	3.73 [3.73; 3.74]	0.99 [0.99; 1.00]	5.42 [5.08; 5.82]	85.8	97.4	99.2	99.8
	5-45-150-240	0.995	-0.13 [-0.37; 0.11]	2.86 [2.70; 3.02]	3.73 [3.72; 3.74]	0.99 [0.99; 1.00]	5.42 [5.00; 5.88]	83.2	97.8	99.4	100.0
	5-45-90-240	0.995	-0.31 [-0.55; -0.06]	2.91 [2.74; 3.08]	3.75 [3.74; 3.76]	0.99 [0.99; 1.00]	5.45 [5.09; 5.80]	83.3	97.3	99.2	100.0
	5-30-90-240	0.995	-0.43 [-0.67; -0.19]	2.86 [2.70; 3.02]	3.77 [3.76; 3.77]	0.99 [0.99; 1.00]	5.48 [5.09; 5.89]	86.0	97.7	99.4	100.0
	5-15-60-240	0.995	-0.36 [-0.61; -0.11]	3.04 [2.87; 3.21]	3.85 [3.84; 3.85]	0.99 [0.99; 1.00]	5.59 [5.28; 5.90]	82.8	97.0	99.6	100.0
	15-45-210-240	0.994	-0.12 [-0.39; 0.15]	3.19 [3.01; 3.37]	3.95 [3.95; 3.96]	0.99 [0.99; 0.99]	5.74 [5.39; 6.07]	80.6	96.4	99.3	99.9
	5-15-30-240	0.995	-1.07 [-1.32; -0.82]	3.17 [3.00; 3.34]	4.01 [4.00; 4.01]	0.99 [0.99; 0.99]	5.82 [5.43; 6.26]	79.6	97.2	99.7	100.0
	15-30-45-240	0.994	-0.58 [-0.85; -0.30]	3.39 [3.21; 3.57]	4.09 [4.09; 4.10]	0.99 [0.99; 0.99]	5.95 [5.61; 6.28]	78.3	96.2	99.5	100.0
	15-45-60-240	0.994	0.14 [-0.14; 0.42]	3.31 [3.12; 3.50]	4.10 [4.09; 4.11]	0.99 [0.99; 0.99]	5.96 [5.65; 6.27]	79.0	95.8	98.8	99.9
	15-45-180-240	0.994	-0.35 [-0.64; -0.06]	3.37 [3.17; 3.57]	4.22 [4.22; 4.23]	0.99 [0.99; 0.99]	6.14 [5.76; 6.50]	78.1	95.2	98.8	99.6
	15-45-150-240	0.993	-0.57 [-0.88; -0.26]	3.36 [3.13; 3.59]	4.27 [4.27; 4.28]	0.99 [0.99; 0.99]	6.21 [5.81; 6.63]	79.8	95.0	98.0	99.3
	15-45-90-240	0.993	-0.81 [-1.12; -0.50]	3.45 [3.22; 3.69]	4.35 [4.34; 4.36]	0.99 [0.99; 0.99]	6.32 [5.93; 6.75]	80.3	94.0	98.0	99.2
	15-30-60-240	0.993	-0.14 [-0.44; 0.15]	3.49 [3.29; 3.69]	4.36 [4.35; 4.37]	0.99 [0.99; 0.99]	6.33 [6.00; 6.66]	77.5	95.9	98.9	99.8
	15-45-120-240	0.993	-0.89 [-1.21; -0.57]	3.42 [3.17; 3.66]	4.38 [4.37; 4.39]	0.99 [0.99; 0.99]	6.36 [5.94; 6.79]	80.6	94.6	97.6	99.0
	30-45-210-240	0.993	-1.07 [-1.37; -0.76]	3.62 [3.41; 3.84]	4.39 [4.38; 4.40]	0.99 [0.99; 0.99]	6.38 [6.03; 6.72]	75.8	94.1	98.2	99.9
	15-30-180-240	0.993	-1.28 [-1.59; -0.98]	3.65 [3.43; 3.88]	4.54 [4.53; 4.54]	0.99 [0.99; 0.99]	6.59 [6.20; 6.99]	75.1	94.2	98.3	99.5
	15-30-210-240	0.993	-1.09 [-1.38; -0.80]	3.50 [3.30; 3.70]	4.54 [4.53; 4.54]	0.99 [0.99; 0.99]	6.59 [6.12; 7.14]	76.2	95.0	99.0	99.9
	15-60-210-240	0.993	0.85 [0.55; 1.16]	3.56 [3.35; 3.78]	4.62 [4.61; 4.63]	0.99 [0.99; 0.99]	6.71 [6.35; 7.10]	76.3	94.4	98.7	99.7
	5-60-210-240	0.992	0.64 [0.35; 0.92]	3.43 [3.24; 3.63]	4.64 [4.63; 4.65]	0.99 [0.99; 0.99]	6.74 [6.26; 7.31]	78.3	95.2	98.9	99.9
	5-60-150-240	0.992	0.23 [-0.05; 0.51]	3.31 [3.11; 3.50]	4.64 [4.63; 4.65]	0.99 [0.99; 0.99]	6.74 [6.14; 7.46]	79.1	96.3	98.7	99.6
	5-30-45-210	0.992	-0.16 [-0.47; 0.15]	3.86 [3.66; 4.06]	4.65 [4.64; 4.65]	0.99 [0.99; 0.99]	6.75 [6.44; 7.07]	70.6	95.1	99.1	99.9
	15-60-180-240	0.992	0.44 [0.13; 0.76]	3.62 [3.40; 3.84]	4.66 [4.65; 4.66]	0.99 [0.99; 0.99]	6.77 [6.36; 7.19]	76.6	94.8	98.6	99.4
	5-60-120-240	0.992	0.15 [-0.14; 0.43]	3.37 [3.18; 3.57]	4.66 [4.65; 4.66]	0.99 [0.99; 0.99]	6.77 [6.14; 7.37]	78.0	95.7	98.7	99.8
	5-60-180-240	0.992	0.51 [0.22; 0.80]	3.49 [3.30; 3.68]	4.68 [4.67; 4.68]	0.99 [0.99; 0.99]	6.79 [6.25; 7.40]	75.4	96.0	99.1	99.7
	30-45-180-240	0.993	-1.34 [-1.67; -1.01]	3.83 [3.58; 4.07]	4.68 [4.68; 4.69]	0.99 [0.99; 0.99]	6.81 [6.43; 7.19]	72.9	93.1	97.9	99.3
	5-30-60-210	0.992	-0.09 [-0.41; 0.22]	3.86 [3.66; 4.07]	4.69 [4.69; 4.70]	0.99 [0.99; 0.99]	6.82 [6.41; 7.18]	71.5	94.1	99.1	99.8
	15-30-150-240	0.992	-1.42 [-1.75; -1.10]	3.71 [3.46; 3.95]	4.73 [4.72; 4.73]	0.99 [0.99; 0.99]	6.87 [6.44; 7.40]	75.9	93.6	97.7	99.1

5-30-180-210	0.992	-0.40 [-0.71; -0.08]	3.89 [3.68; 4.09]	4.73 [4.73; 4.74]	0.99 [0.99; 0.99]	6.88 [6.51; 7.27]	70.7	94.8	98.6	99.9
30-60-210-240	0.992	-0.22 [-0.55; 0.12]	3.84 [3.60; 4.07]	4.75 [4.74; 4.75]	0.99 [0.99; 0.99]	6.90 [6.52; 7.26]	74.5	92.9	97.8	99.7
15-30-90-240	0.992	-1.18 [-1.51; -0.84]	3.78 [3.53; 4.03]	4.76 [4.75; 4.77]	0.99 [0.99; 0.99]	6.92 [6.47; 7.34]	76.3	92.9	97.5	99.1
15-60-150-240	0.992	-0.21 [-0.53; 0.11]	3.53 [3.29; 3.77]	4.77 [4.76; 4.78]	0.99 [0.99; 0.99]	6.93 [6.49; 7.39]	79.4	94.4	97.7	99.1
30-45-150-240	0.992	-1.71 [-2.04; -1.37]	3.86 [3.61; 4.12]	4.79 [4.78; 4.80]	0.99 [0.99; 0.99]	6.96 [6.56; 7.35]	75.6	92.7	97.1	99.3
30-60-180-240	0.992	-0.56 [-0.90; -0.23]	3.86 [3.62; 4.10]	4.79 [4.79; 4.80]	0.99 [0.99; 0.99]	6.97 [6.59; 7.35]	74.7	93.3	98.0	99.3
30-45-60-240	0.992	-0.43 [-0.76; -0.09]	3.88 [3.65; 4.11]	4.82 [4.81; 4.83]	0.99 [0.99; 0.99]	7.00 [6.61; 7.40]	73.3	93.1	97.6	99.6
5-15-90-240	0.992	-0.98 [-1.30; -0.65]	3.72 [3.49; 3.95]	4.83 [4.82; 4.83]	0.99 [0.99; 0.99]	7.01 [6.54; 7.46]	77.4	93.3	97.6	99.3
30-60-150-240	0.992	-1.16 [-1.50; -0.82]	3.83 [3.58; 4.09]	4.83 [4.82; 4.84]	0.99 [0.99; 0.99]	7.02 [6.57; 7.46]	76.2	93.2	97.0	99.1
30-45-120-240	0.992	-1.90 [-2.24; -1.56]	3.90 [3.63; 4.16]	4.84 [4.83; 4.85]	0.99 [0.99; 0.99]	7.03 [6.58; 7.47]	77.0	92.5	96.5	98.8
15-60-120-240	0.991	-0.39 [-0.73; -0.04]	3.69 [3.43; 3.94]	4.89 [4.89; 4.90]	0.99 [0.99; 0.99]	7.11 [6.67; 7.57]	78.1	93.5	97.3	98.8
5-60-90-240	0.991	0.24 [-0.06; 0.54]	3.53 [3.33; 3.74]	4.89 [4.89; 4.90]	0.99 [0.99; 0.99]	7.11 [6.50; 7.68]	76.3	94.8	98.4	99.9
15-30-120-240	0.992	-1.58 [-1.92; -1.24]	3.80 [3.54; 4.07]	4.91 [4.90; 4.91]	0.99 [0.99; 0.99]	7.13 [6.63; 7.62]	76.9	92.8	97.0	98.7
30-180-210-240	0.992	-2.17 [-2.49; -1.84]	3.99 [3.74; 4.24]	4.91 [4.91; 4.92]	0.99 [0.99; 0.99]	7.14 [6.74; 7.53]	73.5	91.1	97.0	99.4
5-15-45-210	0.991	-0.38 [-0.71; -0.06]	4.03 [3.81; 4.24]	4.92 [4.91; 4.93]	0.99 [0.99; 0.99]	7.15 [6.80; 7.50]	69.5	94.1	99.0	99.8
15-60-90-240	0.991	-0.13 [-0.46; 0.20]	3.76 [3.53; 4.00]	4.94 [4.93; 4.94]	0.99 [0.99; 0.99]	7.17 [6.75; 7.59]	76.4	92.7	98.0	99.1
45-60-210-240	0.992	-1.15 [-1.48; -0.83]	3.90 [3.68; 4.13]	4.94 [4.94; 4.95]	0.99 [0.99; 0.99]	7.18 [6.72; 7.68]	72.8	93.7	98.3	99.5
30-60-120-240	0.992	-1.36 [-1.72; -1.01]	4.00 [3.74; 4.27]	4.95 [4.94; 4.95]	0.99 [0.99; 0.99]	7.19 [6.76; 7.61]	75.7	92.6	96.6	98.7
5-30-150-210	0.991	-0.35 [-0.68; -0.02]	4.03 [3.81; 4.24]	4.95 [4.94; 4.96]	0.99 [0.99; 0.99]	7.19 [6.74; 7.62]	70.4	93.7	98.6	99.9
30-150-210-240	0.992	-2.33 [-2.67; -2.00]	3.97 [3.70; 4.24]	4.97 [4.97; 4.98]	0.99 [0.99; 0.99]	7.22 [6.82; 7.63]	74.9	91.4	96.1	98.9
30-60-90-240	0.991	-1.47 [-1.81; -1.12]	3.98 [3.72; 4.23]	5.00 [5.00; 5.01]	0.99 [0.99; 0.99]	7.27 [6.80; 7.73]	73.9	92.0	96.7	99.4
5-15-30-210	0.991	-0.84 [-1.17; -0.51]	4.14 [3.93; 4.35]	5.03 [5.02; 5.03]	0.99 [0.99; 0.99]	7.31 [6.96; 7.68]	69.1	93.5	98.8	99.9
5-30-90-210	0.991	-0.33 [-0.66; 0.00]	3.95 [3.72; 4.17]	5.05 [5.04; 5.05]	0.99 [0.99; 0.99]	7.33 [6.89; 7.79]	72.2	93.1	98.0	99.7
30-45-90-240	0.992	-2.05 [-2.41; -1.69]	4.07 [3.79; 4.36]	5.06 [5.06; 5.07]	0.99 [0.99; 0.99]	7.36 [6.90; 7.81]	74.0	91.1	95.9	98.8
5-30-120-210	0.991	-0.27 [-0.61; 0.06]	4.00 [3.77; 4.22]	5.07 [5.06; 5.08]	0.99 [0.99; 0.99]	7.37 [6.92; 7.85]	72.0	93.2	98.3	99.7
45-150-210-240	0.992	-2.00 [-2.32; -1.68]	3.95 [3.71; 4.19]	5.09 [5.08; 5.10]	0.99 [0.99; 0.99]	7.39 [6.89; 7.94]	72.5	92.4	97.8	99.1
30-120-210-240	0.992	-2.44 [-2.79; -2.10]	4.05 [3.77; 4.34]	5.10 [5.09; 5.11]	0.99 [0.99; 0.99]	7.41 [6.98; 7.82]	75.5	89.8	95.7	98.6
30-90-210-240	0.991	-2.07 [-2.44; -1.71]	4.11 [3.82; 4.40]	5.14 [5.14; 5.15]	0.99 [0.99; 0.99]	7.47 [7.04; 7.92]	75.9	89.1	95.2	98.4
45-60-180-240	0.991	-1.37 [-1.71; -1.02]	4.08 [3.83; 4.32]	5.16 [5.15; 5.16]	0.99 [0.99; 0.99]	7.49 [7.01; 8.02]	70.8	93.1	97.8	99.2
5-15-210-240	0.991	-1.71 [-2.02; -1.40]	3.75 [3.52; 3.98]	5.16 [5.16; 5.17]	0.99 [0.99; 0.99]	7.50 [6.85; 8.18]	74.0	92.9	97.9	99.4
5-15-210-240	0.991	-1.71 [-2.02; -1.40]	3.75 [3.52; 3.98]	5.16 [5.16; 5.17]	0.99 [0.99; 0.99]	7.50 [6.85; 8.18]	74.0	92.9	97.9	99.4
5-45-180-210	0.990	0.29 [-0.05; 0.62]	4.17 [3.95; 4.39]	5.16 [5.15; 5.17]	0.99 [0.99; 0.99]	7.50 [7.11; 7.92]	67.9	93.1	98.6	99.9

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	45-180-210-240	0.991	-1.75 [-2.08; -1.43]	4.06 [3.82; 4.29]	5.16 [5.15; 5.17]	0.99 [0.99; 0.99]	7.50 [6.98; 8.07]	71.1	93.2	98.0	99.3
	45-60-150-240	0.991	-1.73 [-2.07; -1.39]	4.00 [3.75; 4.26]	5.17 [5.16; 5.18]	0.99 [0.99; 0.99]	7.52 [7.00; 8.06]	71.6	93.4	97.2	99.0
	30-150-180-240	0.992	-2.41 [-2.76; -2.05]	4.26 [3.98; 4.54]	5.19 [5.18; 5.20]	0.99 [0.99; 0.99]	7.54 [7.12; 7.98]	71.9	90.9	95.5	98.7
	5-15-60-210	0.990	-0.16 [-0.50; 0.19]	4.21 [3.99; 4.44]	5.19 [5.19; 5.20]	0.99 [0.99; 0.99]	7.55 [7.17; 7.92]	67.7	92.1	98.4	99.8
	45-120-210-240	0.991	-2.12 [-2.45; -1.79]	3.96 [3.70; 4.21]	5.21 [5.21; 5.22]	0.99 [0.99; 0.99]	7.58 [6.97; 8.28]	74.0	92.2	97.3	98.7
	30-120-180-240	0.991	-2.41 [-2.77; -2.04]	4.31 [4.02; 4.60]	5.23 [5.22; 5.24]	0.99 [0.99; 0.99]	7.60 [7.14; 8.04]	71.6	90.2	95.2	98.1
	5-45-150-210	0.990	0.18 [-0.16; 0.52]	4.19 [3.97; 4.41]	5.23 [5.23; 5.24]	0.99 [0.99; 0.99]	7.60 [7.16; 8.03]	67.3	93.3	98.8	99.8
	30-90-180-240	0.991	-1.74 [-2.11; -1.37]	4.13 [3.85; 4.42]	5.23 [5.23; 5.24]	0.99 [0.99; 0.99]	7.61 [7.13; 8.12]	72.8	89.8	95.7	98.6
	5-15-150-240	0.991	-1.65 [-1.99; -1.31]	3.90 [3.64; 4.16]	5.25 [5.24; 5.25]	0.99 [0.99; 0.99]	7.62 [7.09; 8.21]	75.5	92.2	97.1	98.8
	5-45-60-210	0.990	0.29 [-0.05; 0.64]	4.25 [4.03; 4.48]	5.25 [5.25; 5.26]	0.99 [0.99; 0.99]	7.63 [7.23; 8.05]	67.1	92.4	98.6	99.8
	5-45-120-210	0.990	0.01 [-0.33; 0.35]	4.10 [3.87; 4.33]	5.25 [5.24; 5.26]	0.99 [0.99; 0.99]	7.63 [7.16; 8.10]	68.9	92.9	98.2	99.6
	5-15-120-240	0.991	-1.58 [-1.93; -1.23]	3.91 [3.64; 4.18]	5.27 [5.26; 5.27]	0.99 [0.99; 0.99]	7.65 [7.11; 8.21]	77.0	91.7	96.6	98.6
	45-90-210-240	0.991	-2.14 [-2.48; -1.80]	4.11 [3.85; 4.38]	5.27 [5.26; 5.28]	0.99 [0.99; 0.99]	7.66 [7.15; 8.18]	71.0	91.5	97.0	98.9
	5-15-180-240	0.991	-1.75 [-2.08; -1.42]	4.01 [3.77; 4.26]	5.28 [5.27; 5.29]	0.99 [0.99; 0.99]	7.67 [7.14; 8.24]	72.3	92.4	97.5	99.1
	30-90-150-240	0.991	-1.77 [-2.14; -1.39]	4.20 [3.91; 4.48]	5.28 [5.28; 5.29]	0.99 [0.99; 0.99]	7.68 [7.18; 8.15]	73.6	90.6	95.5	98.6
	45-150-180-240	0.991	-2.02 [-2.36; -1.68]	4.22 [3.97; 4.47]	5.31 [5.30; 5.32]	0.99 [0.99; 0.99]	7.71 [7.20; 8.26]	69.3	92.8	97.1	99.0
	45-60-90-240	0.991	-2.14 [-2.49; -1.80]	4.17 [3.91; 4.43]	5.33 [5.32; 5.34]	0.99 [0.99; 0.99]	7.75 [7.22; 8.33]	70.9	91.5	96.8	99.1
	5-45-90-210	0.990	-0.07 [-0.43; 0.28]	4.19 [3.95; 4.43]	5.34 [5.33; 5.35]	0.99 [0.99; 0.99]	7.76 [7.28; 8.24]	69.3	92.0	98.0	99.4
	30-120-150-240	0.991	-2.48 [-2.85; -2.11]	4.39 [4.10; 4.68]	5.40 [5.39; 5.40]	0.99 [0.99; 0.99]	7.84 [7.37; 8.32]	72.4	89.5	95.2	98.6
	45-90-150-240	0.990	-1.94 [-2.29; -1.58]	4.22 [3.95; 4.49]	5.43 [5.42; 5.44]	0.99 [0.99; 0.99]	7.89 [7.28; 8.44]	71.8	90.7	96.5	98.8
	45-90-180-240	0.990	-1.95 [-2.30; -1.59]	4.25 [3.99; 4.52]	5.43 [5.42; 5.44]	0.99 [0.99; 0.99]	7.89 [7.32; 8.44]	70.5	92.1	96.8	98.9
	30-90-120-240	0.990	-2.29 [-2.67; -1.91]	4.49 [4.19; 4.79]	5.46 [5.45; 5.47]	0.99 [0.99; 0.99]	7.93 [7.49; 8.41]	71.2	88.9	94.9	98.3
	45-120-180-240	0.990	-2.13 [-2.48; -1.78]	4.27 [4.01; 4.54]	5.47 [5.46; 5.47]	0.99 [0.99; 0.99]	7.94 [7.35; 8.58]	70.2	92.3	96.5	98.9
	45-60-120-240	0.990	-1.99 [-2.34; -1.64]	4.10 [3.84; 4.37]	5.48 [5.47; 5.49]	0.99 [0.99; 0.99]	7.96 [7.08; 9.03]	70.7	92.5	96.9	98.5
	15-45-180-210	0.989	0.24 [-0.12; 0.61]	4.49 [4.25; 4.73]	5.50 [5.49; 5.51]	0.99 [0.99; 0.99]	7.99 [7.60; 8.38]	65.3	90.9	98.2	99.5
	15-30-45-210	0.989	-0.11 [-0.48; 0.26]	4.58 [4.34; 4.82]	5.53 [5.52; 5.53]	0.99 [0.99; 0.99]	8.03 [7.62; 8.41]	63.6	91.3	98.0	99.6
	45-120-150-240	0.990	-2.23 [-2.58; -1.88]	4.30 [4.04; 4.56]	5.54 [5.53; 5.55]	0.99 [0.99; 0.99]	8.05 [7.42; 8.75]	69.8	91.3	97.1	99.1
	45-90-120-240	0.990	-2.26 [-2.62; -1.91]	4.33 [4.05; 4.60]	5.58 [5.57; 5.59]	0.99 [0.99; 0.99]	8.11 [7.46; 8.83]	69.1	90.8	96.6	98.7

15-30-180-210	0.989	-0.71 [-1.08; -0.34]	4.63 [4.39; 4.87]	5.61 [5.60; 5.61]	0.99 [0.99; 0.99]	8.14 [7.70; 8.62]	64.5	89.8	97.6	99.9
15-45-60-210	0.989	0.67 [0.30; 1.05]	4.55 [4.30; 4.79]	5.64 [5.63; 5.64]	0.99 [0.99; 0.99]	8.19 [7.72; 8.61]	64.3	90.3	97.8	99.3
15-30-60-210	0.988	0.38 [-0.01; 0.76]	4.68 [4.42; 4.94]	5.74 [5.74; 5.75]	0.99 [0.99; 0.99]	8.35 [7.85; 8.82]	65.8	89.0	97.0	99.0
30-45-180-210	0.988	-0.84 [-1.24; -0.44]	4.98 [4.72; 5.25]	5.76 [5.75; 5.76]	0.99 [0.99; 0.99]	8.37 [8.00; 8.73]	60.0	88.8	96.7	98.9
15-180-210-240	0.989	-2.21 [-2.59; -1.83]	4.47 [4.18; 4.76]	5.78 [5.77; 5.78]	0.99 [0.99; 0.99]	8.39 [7.86; 8.99]	69.0	89.5	96.2	97.8
15-90-150-240	0.988	-0.68 [-1.08; -0.28]	4.37 [4.06; 4.67]	5.82 [5.81; 5.83]	0.99 [0.99; 0.99]	8.45 [7.90; 9.02]	72.7	89.1	95.9	98.1
15-45-150-210	0.988	-0.10 [-0.49; 0.29]	4.64 [4.38; 4.90]	5.81 [5.81; 5.82]	0.99 [0.99; 0.99]	8.45 [7.96; 8.94]	63.8	90.8	96.5	98.8
15-90-210-240	0.987	-0.79 [-1.22; -0.36]	4.64 [4.31; 4.96]	5.94 [5.94; 5.95]	0.99 [0.99; 0.99]	8.64 [8.13; 9.14]	70.1	86.4	94.8	97.9
5-60-120-210	0.987	0.51 [0.13; 0.88]	4.57 [4.32; 4.82]	5.96 [5.95; 5.96]	0.99 [0.99; 0.99]	8.65 [8.11; 9.26]	65.1	90.0	96.9	99.8
60-120-210-240	0.988	-1.59 [-1.95; -1.23]	4.34 [4.08; 4.60]	5.96 [5.95; 5.97]	0.99 [0.99; 0.99]	8.66 [7.70; 9.98]	68.6	92.2	97.4	98.5
15-150-210-240	0.988	-2.35 [-2.74; -1.96]	4.45 [4.13; 4.77]	5.96 [5.96; 5.97]	0.99 [0.99; 0.99]	8.67 [8.08; 9.25]	70.3	88.0	95.6	97.5
15-45-90-210	0.987	-0.37 [-0.76; 0.03]	4.64 [4.36; 4.91]	5.99 [5.98; 5.99]	0.99 [0.99; 0.99]	8.70 [8.12; 9.19]	66.4	89.3	96.4	98.7
15-45-120-210	0.987	-0.54 [-0.95; -0.12]	4.73 [4.43; 5.02]	6.01 [6.00; 6.02]	0.99 [0.98; 0.99]	8.74 [8.19; 9.25]	65.4	88.7	95.8	98.2
5-15-90-210	0.987	-0.69 [-1.09; -0.29]	4.73 [4.46; 5.01]	6.05 [6.04; 6.05]	0.99 [0.98; 0.99]	8.79 [8.26; 9.34]	65.6	88.7	95.9	98.9
30-45-150-210	0.987	-1.32 [-1.74; -0.90]	5.13 [4.85; 5.42]	6.06 [6.05; 6.07]	0.99 [0.98; 0.99]	8.80 [8.37; 9.19]	61.8	87.1	95.3	98.6
5-60-150-210	0.987	0.75 [0.37; 1.12]	4.65 [4.40; 4.89]	6.06 [6.05; 6.06]	0.99 [0.98; 0.99]	8.80 [8.15; 9.43]	63.4	89.8	97.2	99.6
5-30-150-180	0.987	-0.28 [-0.69; 0.13]	5.00 [4.73; 5.27]	6.06 [6.05; 6.07]	0.99 [0.98; 0.99]	8.81 [8.31; 9.29]	59.4	87.8	96.6	99.0
5-15-180-210	0.987	-1.49 [-1.87; -1.10]	4.83 [4.57; 5.09]	6.07 [6.06; 6.08]	0.99 [0.98; 0.99]	8.82 [8.22; 9.51]	62.5	88.3	96.8	99.3
15-30-90-210	0.987	-0.80 [-1.21; -0.38]	4.82 [4.52; 5.11]	6.07 [6.06; 6.08]	0.99 [0.98; 0.99]	8.82 [8.31; 9.31]	65.2	88.4	95.5	98.4
15-30-150-210	0.986	-0.88 [-1.29; -0.47]	4.94 [4.66; 5.21]	6.10 [6.10; 6.11]	0.99 [0.98; 0.99]	8.87 [8.35; 9.40]	64.4	87.1	95.6	99.1
15-150-180-240	0.988	-2.38 [-2.79; -1.97]	4.71 [4.39; 5.04]	6.12 [6.12; 6.13]	0.99 [0.98; 0.99]	8.90 [8.33; 9.48]	69.0	86.6	94.9	97.6
15-30-120-210	0.986	-1.17 [-1.59; -0.74]	4.95 [4.65; 5.25]	6.13 [6.12; 6.13]	0.99 [0.98; 0.99]	8.90 [8.36; 9.45]	65.0	87.3	95.0	98.0
15-60-180-210	0.987	1.34 [0.95; 1.74]	4.90 [4.64; 5.17]	6.12 [6.12; 6.13]	0.99 [0.98; 0.99]	8.90 [8.44; 9.37]	62.1	88.1	96.9	99.3
15-90-120-240	0.987	-1.55 [-1.98; -1.12]	4.80 [4.47; 5.12]	6.13 [6.12; 6.14]	0.99 [0.98; 0.99]	8.91 [8.38; 9.45]	69.3	86.7	94.4	97.2
30-45-60-210	0.986	0.06 [-0.37; 0.48]	5.10 [4.82; 5.39]	6.13 [6.12; 6.14]	0.99 [0.98; 0.99]	8.91 [8.45; 9.36]	59.6	87.9	96.1	98.5
30-150-180-210	0.987	-2.47 [-2.90; -2.05]	5.41 [5.11; 5.72]	6.15 [6.14; 6.15]	0.99 [0.98; 0.99]	8.93 [8.51; 9.33]	58.9	85.2	94.7	98.3
60-120-180-240	0.987	-1.64 [-2.02; -1.26]	4.63 [4.37; 4.90]	6.15 [6.14; 6.16]	0.99 [0.98; 0.99]	8.93 [7.94; 10.21]	66.4	91.8	96.7	98.6
30-45-120-210	0.987	-1.89 [-2.33; -1.45]	5.23 [4.91; 5.55]	6.15 [6.14; 6.16]	0.99 [0.98; 0.99]	8.94 [8.52; 9.41]	62.0	87.8	94.0	97.0
60-120-150-240	0.987	-1.78 [-2.16; -1.40]	4.66 [4.39; 4.93]	6.17 [6.16; 6.18]	0.99 [0.98; 0.99]	8.96 [8.04; 10.32]	66.1	90.3	96.7	98.4
60-150-210-240	0.987	-1.50 [-1.86; -1.13]	4.36 [4.10; 4.62]	6.18 [6.17; 6.19]	0.99 [0.98; 0.99]	8.98 [7.68; 10.87]	68.1	91.2	97.0	98.8
5-15-150-210	0.986	-1.29 [-1.69; -0.89]	4.89 [4.61; 5.17]	6.22 [6.21; 6.23]	0.99 [0.98; 0.99]	9.03 [8.39; 9.76]	63.0	87.9	95.9	99.0
15-90-180-240	0.986	-0.27 [-0.70; 0.16]	4.71 [4.40; 5.02]	6.22 [6.21; 6.23]	0.99 [0.98; 0.99]	9.04 [8.43; 9.58]	69.1	87.5	94.7	98.1

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	60-180-210-240	0.987	-1.23 [-1.59; -0.87]	4.41 [4.16; 4.65]	6.22 [6.22; 6.23]	0.99 [0.98; 0.99]	9.04 [7.77; 11.00]	67.2	92.0	97.3	98.9
	15-120-210-240	0.987	-2.50 [-2.92; -2.08]	4.69 [4.34; 5.03]	6.24 [6.23; 6.25]	0.99 [0.98; 0.99]	9.07 [8.48; 9.59]	71.5	85.9	94.1	96.8
	60-90-150-240	0.986	-1.52 [-1.90; -1.14]	4.61 [4.34; 4.87]	6.24 [6.23; 6.25]	0.99 [0.98; 0.99]	9.07 [8.14; 10.30]	67.4	90.4	96.5	98.9
	30-120-180-210	0.987	-2.75 [-3.19; -2.32]	5.40 [5.07; 5.72]	6.25 [6.25; 6.26]	0.99 [0.98; 0.99]	9.09 [8.62; 9.56]	61.3	84.7	93.3	97.4
	30-60-180-210	0.986	0.19 [-0.24; 0.61]	5.23 [4.95; 5.51]	6.25 [6.24; 6.26]	0.99 [0.98; 0.99]	9.09 [8.67; 9.54]	59.6	86.3	95.9	98.7
	60-90-210-240	0.986	-1.53 [-1.92; -1.15]	4.59 [4.32; 4.86]	6.27 [6.26; 6.27]	0.99 [0.98; 0.99]	9.10 [8.15; 10.26]	66.1	89.2	96.4	98.8
	5-30-45-180	0.986	-0.22 [-0.64; 0.20]	5.13 [4.86; 5.40]	6.27 [6.26; 6.28]	0.99 [0.98; 0.99]	9.11 [8.59; 9.63]	58.4	87.7	96.3	98.7
	5-60-90-210	0.986	0.71 [0.32; 1.09]	4.70 [4.45; 4.96]	6.27 [6.26; 6.28]	0.99 [0.98; 0.99]	9.11 [8.46; 9.80]	64.2	88.3	97.1	99.6
	15-60-120-210	0.986	0.12 [-0.30; 0.54]	4.85 [4.55; 5.14]	6.28 [6.28; 6.29]	0.99 [0.98; 0.99]	9.13 [8.54; 9.65]	63.9	88.4	95.1	98.3
	30-45-90-210	0.986	-1.85 [-2.30; -1.41]	5.29 [4.97; 5.61]	6.29 [6.28; 6.30]	0.99 [0.98; 0.99]	9.14 [8.65; 9.63]	60.5	86.0	94.2	97.6
	5-15-120-210	0.986	-1.19 [-1.60; -0.77]	4.86 [4.57; 5.16]	6.30 [6.29; 6.31]	0.99 [0.98; 0.99]	9.15 [8.56; 9.74]	64.2	87.4	95.3	98.4
	5-30-60-180	0.985	-0.26 [-0.68; 0.16]	5.09 [4.82; 5.37]	6.31 [6.30; 6.32]	0.99 [0.98; 0.99]	9.17 [8.66; 9.66]	58.1	87.9	96.6	98.7
	60-90-120-240	0.986	-1.75 [-2.14; -1.36]	4.77 [4.49; 5.04]	6.33 [6.32; 6.34]	0.99 [0.98; 0.99]	9.19 [8.32; 10.32]	64.8	89.8	96.8	98.5
	60-90-180-240	0.986	-1.45 [-1.83; -1.07]	4.61 [4.34; 4.87]	6.32 [6.31; 6.33]	0.99 [0.98; 0.99]	9.19 [8.11; 10.50]	66.1	91.3	96.7	98.9
	15-60-150-210	0.986	0.63 [0.21; 1.04]	4.92 [4.63; 5.20]	6.33 [6.32; 6.34]	0.99 [0.98; 0.99]	9.20 [8.68; 9.70]	63.2	87.2	95.7	98.5
	15-120-150-240	0.987	-2.36 [-2.78; -1.93]	4.85 [4.52; 5.19]	6.34 [6.33; 6.35]	0.99 [0.98; 0.99]	9.21 [8.58; 9.91]	68.3	86.0	94.1	96.9
	45-150-180-210	0.986	-2.03 [-2.45; -1.61]	5.40 [5.11; 5.68]	6.35 [6.34; 6.36]	0.99 [0.98; 0.99]	9.23 [8.74; 9.76]	56.7	87.1	95.4	98.6
	5-30-120-180	0.985	-0.32 [-0.75; 0.10]	5.17 [4.88; 5.45]	6.37 [6.36; 6.38]	0.99 [0.98; 0.99]	9.25 [8.74; 9.79]	57.6	87.1	96.3	98.9
	5-60-180-210	0.986	1.04 [0.65; 1.43]	4.86 [4.60; 5.12]	6.37 [6.36; 6.37]	0.99 [0.98; 0.99]	9.25 [8.63; 9.86]	63.1	89.2	97.0	99.2
	60-150-180-240	0.986	-1.64 [-2.02; -1.26]	4.60 [4.34; 4.87]	6.36 [6.35; 6.37]	0.99 [0.98; 0.99]	9.25 [7.95; 11.44]	66.9	90.9	96.7	98.6
	45-60-180-210	0.985	-1.00 [-1.43; -0.57]	5.37 [5.10; 5.65]	6.38 [6.37; 6.39]	0.99 [0.98; 0.99]	9.27 [8.80; 9.77]	58.1	86.3	95.7	99.0
	30-60-150-210	0.985	-0.58 [-1.01; -0.14]	5.22 [4.93; 5.51]	6.39 [6.38; 6.40]	0.99 [0.98; 0.99]	9.28 [8.80; 9.76]	61.7	85.9	94.9	98.6
	45-120-180-210	0.986	-2.45 [-2.87; -2.02]	5.41 [5.11; 5.72]	6.39 [6.38; 6.40]	0.99 [0.98; 0.99]	9.29 [8.77; 9.85]	59.8	86.8	95.1	97.9
	5-90-210-240	0.985	0.14 [-0.27; 0.55]	4.64 [4.35; 4.93]	6.41 [6.40; 6.42]	0.99 [0.98; 0.99]	9.31 [8.64; 10.02]	67.6	87.5	95.3	98.7
	15-120-180-240	0.986	-2.20 [-2.64; -1.76]	4.90 [4.55; 5.24]	6.46 [6.45; 6.46]	0.98 [0.98; 0.99]	9.38 [8.68; 10.06]	68.7	86.1	93.6	96.4
	45-60-120-210	0.986	-1.93 [-2.37; -1.50]	5.34 [5.03; 5.64]	6.45 [6.44; 6.46]	0.98 [0.98; 0.99]	9.38 [8.87; 9.88]	58.2	86.4	94.6	97.7
	5-15-30-180	0.985	-0.99 [-1.42; -0.55]	5.35 [5.07; 5.63]	6.46 [6.45; 6.47]	0.98 [0.98; 0.99]	9.38 [8.91; 9.91]	56.2	86.6	95.9	98.9
	30-60-120-210	0.985	-1.14 [-1.59; -0.68]	5.32 [4.99; 5.64]	6.48 [6.47; 6.49]	0.98 [0.98; 0.99]	9.41 [8.84; 9.92]	61.1	85.5	93.7	97.4

5-30-90-180	0.985	-0.42 [-0.85; 0.00]	5.12 [4.84; 5.41]	6.48 [6.47; 6.49]	0.98 [0.98; 0.99]	9.41 [8.82; 9.98]	60.0	86.9	96.0	98.5
30-120-150-210	0.986	-2.71 [-3.16; -2.26]	5.64 [5.31; 5.97]	6.52 [6.51; 6.52]	0.98 [0.98; 0.99]	9.47 [9.02; 9.92]	59.7	83.7	92.8	97.3
15-60-90-210	0.985	0.53 [0.11; 0.95]	5.06 [4.77; 5.34]	6.53 [6.52; 6.54]	0.98 [0.98; 0.99]	9.48 [8.95; 10.03]	62.1	86.6	95.8	98.7
5-15-45-180	0.984	-0.51 [-0.95; -0.08]	5.35 [5.07; 5.64]	6.54 [6.53; 6.54]	0.98 [0.98; 0.99]	9.50 [8.99; 10.00]	55.9	87.3	95.7	98.6
45-90-180-210	0.985	-2.26 [-2.70; -1.82]	5.46 [5.15; 5.77]	6.54 [6.53; 6.55]	0.98 [0.98; 0.99]	9.51 [8.99; 10.09]	59.1	86.4	94.0	98.0
5-90-120-240	0.984	-0.57 [-1.01; -0.13]	4.82 [4.50; 5.15]	6.57 [6.56; 6.57]	0.98 [0.98; 0.99]	9.54 [8.75; 10.31]	67.1	87.5	94.7	97.5
45-60-150-210	0.985	-1.54 [-1.97; -1.11]	5.35 [5.06; 5.64]	6.57 [6.56; 6.58]	0.98 [0.98; 0.99]	9.55 [8.88; 10.47]	57.6	87.1	95.4	98.4
30-60-90-210	0.984	-1.17 [-1.63; -0.71]	5.44 [5.12; 5.76]	6.59 [6.58; 6.60]	0.98 [0.98; 0.99]	9.58 [9.09; 10.12]	61.0	84.9	94.1	97.7
45-120-150-210	0.985	-2.47 [-2.90; -2.03]	5.53 [5.22; 5.84]	6.59 [6.58; 6.60]	0.98 [0.98; 0.99]	9.58 [9.04; 10.16]	57.1	86.4	94.3	97.7
30-90-150-210	0.984	-1.74 [-2.20; -1.27]	5.53 [5.19; 5.86]	6.60 [6.59; 6.61]	0.98 [0.98; 0.99]	9.59 [9.09; 10.07]	60.5	84.3	93.2	97.1
45-60-90-210	0.985	-2.23 [-2.67; -1.79]	5.52 [5.21; 5.83]	6.62 [6.61; 6.62]	0.98 [0.98; 0.99]	9.61 [9.10; 10.17]	56.4	85.4	94.9	97.8
30-90-180-210	0.984	-1.86 [-2.33; -1.39]	5.60 [5.26; 5.95]	6.64 [6.64; 6.65]	0.98 [0.98; 0.99]	9.65 [9.19; 10.12]	60.9	82.6	92.2	97.2
30-90-120-210	0.985	-2.32 [-2.79; -1.84]	5.70 [5.36; 6.05]	6.64 [6.63; 6.65]	0.98 [0.98; 0.99]	9.65 [9.18; 10.16]	59.9	83.5	92.4	96.7
5-45-120-180	0.984	0.08 [-0.36; 0.52]	5.43 [5.14; 5.72]	6.71 [6.70; 6.72]	0.98 [0.98; 0.99]	9.75 [9.21; 10.24]	56.0	86.9	95.7	98.3
45-90-120-210	0.985	-2.52 [-2.96; -2.07]	5.60 [5.28; 5.92]	6.71 [6.70; 6.72]	0.98 [0.98; 0.99]	9.76 [9.17; 10.30]	57.4	86.2	94.4	97.2
5-90-150-240	0.983	0.17 [-0.26; 0.59]	4.65 [4.34; 4.95]	6.74 [6.73; 6.75]	0.98 [0.98; 0.99]	9.79 [8.94; 10.65]	68.1	88.6	95.2	97.8
5-45-90-180	0.983	-0.22 [-0.67; 0.23]	5.43 [5.13; 5.73]	6.77 [6.76; 6.78]	0.98 [0.98; 0.99]	9.84 [9.30; 10.36]	57.2	86.3	95.0	98.0
5-45-150-180	0.983	0.27 [-0.17; 0.72]	5.45 [5.16; 5.75]	6.79 [6.78; 6.80]	0.98 [0.98; 0.99]	9.87 [9.31; 10.46]	56.6	85.9	95.7	98.6
15-30-45-180	0.983	0.10 [-0.36; 0.56]	5.69 [5.39; 5.98]	6.80 [6.79; 6.81]	0.98 [0.98; 0.98]	9.88 [9.39; 10.38]	55.7	84.2	94.6	98.6
45-90-150-210	0.984	-2.07 [-2.53; -1.62]	5.56 [5.24; 5.89]	6.80 [6.79; 6.81]	0.98 [0.98; 0.98]	9.88 [9.30; 10.50]	58.3	85.4	94.0	97.2
5-90-180-240	0.983	0.43 [0.01; 0.86]	4.82 [4.52; 5.12]	6.87 [6.86; 6.88]	0.98 [0.98; 0.98]	9.98 [9.16; 10.85]	64.5	87.9	95.3	98.3
5-15-60-180	0.982	-0.38 [-0.83; 0.08]	5.57 [5.27; 5.87]	6.93 [6.92; 6.94]	0.98 [0.98; 0.98]	10.06 [9.56; 10.60]	55.0	85.5	94.8	98.1
15-30-150-180	0.982	-0.43 [-0.90; 0.05]	5.80 [5.48; 6.11]	6.97 [6.96; 6.98]	0.98 [0.98; 0.98]	10.13 [9.61; 10.68]	54.5	82.6	94.2	98.1
5-45-60-180	0.982	0.25 [-0.21; 0.71]	5.65 [5.35; 5.94]	6.98 [6.97; 6.99]	0.98 [0.98; 0.98]	10.15 [9.60; 10.67]	54.6	84.9	95.1	98.1
15-45-150-180	0.982	0.50 [0.02; 0.97]	5.78 [5.47; 6.09]	7.03 [7.02; 7.04]	0.98 [0.98; 0.98]	10.21 [9.70; 10.76]	55.4	84.1	94.4	98.3
5-180-210-240	0.983	-2.06 [-2.51; -1.61]	5.27 [4.94; 5.60]	7.04 [7.03; 7.05]	0.98 [0.98; 0.98]	10.23 [9.46; 10.98]	63.2	87.0	94.5	97.6
15-150-180-210	0.983	-2.40 [-2.87; -1.92]	5.85 [5.52; 6.19]	7.09 [7.08; 7.10]	0.98 [0.98; 0.98]	10.30 [9.71; 11.04]	55.4	82.1	93.2	97.2
60-120-180-210	0.982	-1.68 [-2.14; -1.22]	5.70 [5.40; 6.01]	7.13 [7.12; 7.14]	0.98 [0.98; 0.98]	10.36 [9.48; 11.55]	54.6	84.6	94.2	98.1
15-30-60-180	0.982	0.64 [0.16; 1.12]	5.90 [5.59; 6.21]	7.15 [7.14; 7.16]	0.98 [0.98; 0.98]	10.39 [9.89; 10.86]	53.0	81.7	93.7	98.1
5-15-150-180	0.981	-1.29 [-1.77; -0.82]	5.86 [5.54; 6.17]	7.17 [7.16; 7.18]	0.98 [0.98; 0.98]	10.41 [9.78; 11.01]	54.1	82.2	93.2	97.7
15-45-60-180	0.981	0.86 [0.38; 1.34]	5.93 [5.62; 6.24]	7.22 [7.21; 7.23]	0.98 [0.98; 0.98]	10.49 [9.97; 10.97]	52.9	83.3	93.8	98.1
60-120-150-210	0.981	-1.82 [-2.28; -1.36]	5.84 [5.53; 6.15]	7.27 [7.26; 7.28]	0.98 [0.98; 0.98]	10.56 [9.69; 11.74]	51.6	82.8	94.3	97.9

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	60-150-180-210	0.981	-1.37 [-1.82; -0.91]	5.78 [5.48; 6.08]	7.31 [7.30; 7.32]	0.98 [0.98; 0.98]	10.62 [9.59; 12.09]	52.3	84.2	94.9	98.4
	15-45-120-180	0.980	-0.06 [-0.55; 0.44]	5.94 [5.61; 6.28]	7.33 [7.32; 7.34]	0.98 [0.98; 0.98]	10.66 [10.05; 11.26]	53.0	83.1	93.4	97.4
	60-90-120-210	0.981	-1.86 [-2.33; -1.38]	5.88 [5.56; 6.21]	7.37 [7.36; 7.38]	0.98 [0.98; 0.98]	10.70 [9.90; 11.74]	52.7	83.5	93.4	97.4
	60-90-150-210	0.981	-1.58 [-2.05; -1.11]	5.84 [5.53; 6.16]	7.36 [7.35; 7.37]	0.98 [0.98; 0.98]	10.70 [9.87; 11.82]	52.7	83.5	93.5	97.8
	15-45-90-180	0.980	0.07 [-0.42; 0.56]	5.99 [5.67; 6.31]	7.42 [7.41; 7.43]	0.98 [0.98; 0.98]	10.78 [10.25; 11.36]	53.4	82.2	92.9	97.5
	30-45-150-180	0.980	-0.77 [-1.29; -0.25]	6.41 [6.07; 6.75]	7.44 [7.43; 7.45]	0.98 [0.98; 0.98]	10.80 [10.33; 11.35]	49.7	79.5	93.5	97.4
	5-120-150-240	0.980	-1.82 [-2.30; -1.35]	5.35 [4.99; 5.70]	7.45 [7.44; 7.46]	0.98 [0.98; 0.98]	10.83 [9.98; 11.78]	64.8	86.8	92.8	96.4
	15-30-120-180	0.980	-0.84 [-1.37; -0.32]	6.16 [5.80; 6.52]	7.46 [7.45; 7.47]	0.98 [0.98; 0.98]	10.84 [10.17; 11.50]	53.8	80.2	92.6	96.5
	15-90-150-210	0.980	0.09 [-0.41; 0.59]	5.86 [5.51; 6.20]	7.46 [7.45; 7.47]	0.98 [0.98; 0.98]	10.84 [10.27; 11.40]	57.7	81.3	92.4	97.0
	60-90-180-210	0.980	-1.51 [-1.98; -1.04]	5.85 [5.54; 6.16]	7.48 [7.47; 7.49]	0.98 [0.98; 0.98]	10.87 [9.96; 11.94]	54.3	81.9	93.3	98.1
	15-120-180-210	0.980	-2.63 [-3.15; -2.12]	6.18 [5.80; 6.56]	7.52 [7.51; 7.53]	0.98 [0.98; 0.98]	10.93 [10.36; 11.54]	57.2	79.1	90.9	96.1
	15-30-90-180	0.979	-0.49 [-1.02; 0.03]	6.18 [5.82; 6.54]	7.52 [7.51; 7.53]	0.98 [0.98; 0.98]	10.93 [10.36; 11.50]	53.8	81.1	92.0	96.6
	15-120-150-210	0.980	-2.41 [-2.92; -1.90]	6.11 [5.74; 6.48]	7.54 [7.53; 7.55]	0.98 [0.98; 0.98]	10.96 [10.29; 11.61]	58.0	80.0	91.2	95.9
	15-90-120-210	0.979	-0.66 [-1.18; -0.14]	5.94 [5.57; 6.31]	7.56 [7.55; 7.57]	0.98 [0.98; 0.98]	10.98 [10.35; 11.64]	59.3	80.3	91.0	96.2
	5-15-90-180	0.979	-0.80 [-1.30; -0.30]	5.96 [5.62; 6.30]	7.57 [7.56; 7.58]	0.98 [0.98; 0.98]	11.00 [10.30; 11.73]	55.1	82.3	92.7	96.7
	5-150-180-240	0.980	-2.05 [-2.53; -1.58]	5.53 [5.18; 5.88]	7.57 [7.56; 7.58]	0.98 [0.98; 0.98]	11.00 [10.08; 11.97]	61.6	85.4	92.7	96.8
	5-15-120-180	0.979	-1.11 [-1.61; -0.61]	6.07 [5.73; 6.42]	7.65 [7.64; 7.66]	0.98 [0.98; 0.98]	11.12 [10.42; 11.79]	53.6	81.3	92.4	96.8
	30-120-150-180	0.980	-2.78 [-3.34; -2.22]	6.91 [6.51; 7.31]	7.68 [7.67; 7.69]	0.98 [0.98; 0.98]	11.15 [10.61; 11.62]	49.3	77.0	89.2	95.5
	5-120-150-180	0.979	-2.00 [-2.47; -1.53]	5.32 [4.96; 5.67]	7.68 [7.67; 7.69]	0.98 [0.98; 0.98]	11.16 [10.25; 12.15]	64.8	85.5	93.2	96.4
	5-150-210-240	0.979	-2.00 [-2.47; -1.53]	5.32 [4.96; 5.67]	7.68 [7.67; 7.69]	0.98 [0.98; 0.98]	11.16 [10.20; 12.16]	64.8	85.5	93.2	96.4
	30-45-120-180	0.978	-1.65 [-2.21; -1.09]	6.60 [6.20; 7.00]	7.73 [7.72; 7.74]	0.98 [0.97; 0.98]	11.23 [10.65; 11.80]	50.9	79.0	91.0	95.4
	30-45-60-180	0.978	0.29 [-0.25; 0.82]	6.60 [6.26; 6.95]	7.76 [7.75; 7.77]	0.98 [0.97; 0.98]	11.27 [10.78; 11.80]	47.4	78.5	92.3	97.1
	5-120-210-240	0.978	-1.99 [-2.48; -1.50]	5.44 [5.06; 5.82]	7.81 [7.80; 7.82]	0.98 [0.97; 0.98]	11.34 [10.39; 12.34]	65.8	83.5	91.7	96.0
	15-90-180-210	0.978	0.76 [0.25; 1.27]	6.11 [5.77; 6.46]	7.83 [7.82; 7.84]	0.98 [0.97; 0.98]	11.38 [10.83; 11.97]	55.7	80.7	91.3	97.3
	45-60-150-180	0.978	-1.19 [-1.74; -0.65]	6.70 [6.35; 7.06]	7.84 [7.83; 7.85]	0.98 [0.97; 0.98]	11.40 [10.89; 11.94]	46.5	76.8	91.5	96.7
	5-120-180-240	0.978	-1.58 [-2.07; -1.09]	5.47 [5.11; 5.83]	7.85 [7.84; 7.87]	0.98 [0.97; 0.98]	11.41 [10.44; 12.38]	63.2	85.2	92.5	96.8
	15-60-150-180	0.978	1.52 [1.01; 2.03]	6.25 [5.91; 6.59]	7.89 [7.88; 7.90]	0.98 [0.97; 0.98]	11.47 [10.86; 12.07]	52.7	79.7	91.4	97.2
	45-120-150-180	0.978	-2.53 [-3.08; -1.98]	6.89 [6.51; 7.26]	7.91 [7.90; 7.92]	0.98 [0.97; 0.98]	11.49 [10.95; 12.02]	45.6	77.4	90.8	96.0

30-45-90-180	0.977	-1.34 [-1.90; -0.78]	6.70 [6.32; 7.08]	7.91 [7.90; 7.92]	0.98 [0.97; 0.98]	11.49 [10.92; 12.03]	50.5	79.0	90.0	95.8
5-60-120-180	0.977	0.64 [0.14; 1.14]	6.10 [5.77; 6.43]	7.91 [7.89; 7.92]	0.98 [0.97; 0.98]	11.49 [10.75; 12.22]	51.2	81.9	93.1	98.0
5-30-60-150	0.977	0.11 [-0.41; 0.63]	6.42 [6.09; 6.75]	7.91 [7.90; 7.92]	0.98 [0.97; 0.98]	11.50 [10.86; 12.14]	48.7	79.8	93.1	97.3
5-15-30-150	0.977	-0.52 [-1.05; 0.01]	6.54 [6.20; 6.87]	7.94 [7.93; 7.95]	0.98 [0.97; 0.98]	11.54 [10.89; 12.19]	47.6	79.1	92.4	97.2
5-60-150-180	0.977	0.95 [0.44; 1.46]	6.12 [5.77; 6.46]	7.95 [7.94; 7.96]	0.98 [0.97; 0.98]	11.55 [10.85; 12.27]	53.5	80.5	91.9	97.3
5-30-120-150	0.977	0.37 [-0.15; 0.88]	6.39 [6.06; 6.73]	7.96 [7.95; 7.97]	0.98 [0.97; 0.98]	11.56 [10.87; 12.30]	49.4	79.6	92.9	97.4
5-60-90-180	0.977	0.78 [0.28; 1.28]	6.15 [5.82; 6.49]	7.97 [7.96; 7.98]	0.98 [0.97; 0.98]	11.58 [10.95; 12.26]	50.6	80.3	92.0	97.2
5-30-45-150	0.977	0.23 [-0.30; 0.76]	6.55 [6.21; 6.88]	8.01 [8.00; 8.02]	0.98 [0.97; 0.98]	11.64 [11.00; 12.24]	47.9	77.5	93.2	97.7
5-30-90-150	0.977	0.14 [-0.38; 0.67]	6.42 [6.09; 6.76]	8.01 [8.00; 8.03]	0.98 [0.97; 0.98]	11.64 [10.98; 12.32]	49.1	79.3	92.7	97.2
15-60-90-180	0.977	1.21 [0.69; 1.73]	6.45 [6.11; 6.79]	8.06 [8.05; 8.07]	0.98 [0.97; 0.98]	11.72 [11.13; 12.27]	49.0	80.0	90.8	97.0
15-60-120-180	0.977	0.73 [0.19; 1.27]	6.46 [6.09; 6.82]	8.08 [8.07; 8.09]	0.98 [0.97; 0.98]	11.74 [11.12; 12.41]	51.7	79.1	91.1	96.4
90-150-180-240	0.976	-1.31 [-1.80; -0.83]	5.91 [5.57; 6.24]	8.08 [8.07; 8.09]	0.98 [0.97; 0.98]	11.74 [10.94; 12.54]	53.8	83.7	92.9	97.2
45-90-150-180	0.977	-2.06 [-2.63; -1.50]	6.91 [6.52; 7.30]	8.09 [8.08; 8.10]	0.98 [0.97; 0.98]	11.76 [11.17; 12.30]	48.4	76.9	89.3	95.2
30-60-150-180	0.976	0.15 [-0.41; 0.71]	6.74 [6.37; 7.11]	8.10 [8.09; 8.11]	0.98 [0.97; 0.98]	11.77 [11.19; 12.36]	46.4	76.7	90.0	96.6
45-60-120-180	0.976	-2.02 [-2.58; -1.45]	6.97 [6.58; 7.35]	8.11 [8.10; 8.13]	0.98 [0.97; 0.98]	11.79 [11.17; 12.40]	47.4	77.4	90.2	95.6
45-90-120-180	0.977	-2.77 [-3.34; -2.21]	7.02 [6.62; 7.42]	8.12 [8.11; 8.13]	0.98 [0.97; 0.98]	11.80 [11.20; 12.38]	47.5	77.5	89.2	95.0
5-15-45-150	0.976	-0.20 [-0.74; 0.34]	6.53 [6.18; 6.88]	8.13 [8.12; 8.14]	0.98 [0.97; 0.98]	11.81 [11.13; 12.53]	48.8	78.1	91.8	97.0
30-60-120-180	0.976	-0.73 [-1.31; -0.15]	6.93 [6.53; 7.33]	8.14 [8.13; 8.15]	0.98 [0.97; 0.98]	11.83 [11.23; 12.38]	46.2	77.2	90.2	95.2
5-90-180-210	0.976	0.80 [0.29; 1.30]	5.94 [5.59; 6.29]	8.16 [8.14; 8.17]	0.98 [0.97; 0.98]	11.85 [11.05; 12.65]	56.7	82.0	91.3	96.9
30-90-150-180	0.975	-1.12 [-1.72; -0.53]	7.01 [6.60; 7.43]	8.18 [8.17; 8.19]	0.97 [0.97; 0.98]	11.89 [11.27; 12.49]	49.7	75.5	88.6	94.9
5-150-180-210	0.976	-2.01 [-2.54; -1.47]	6.56 [6.19; 6.93]	8.19 [8.18; 8.20]	0.98 [0.97; 0.98]	11.90 [11.17; 12.60]	50.8	78.9	90.0	96.3
30-60-90-180	0.975	-0.44 [-1.01; 0.14]	6.89 [6.51; 7.27]	8.20 [8.19; 8.21]	0.97 [0.97; 0.98]	11.92 [11.36; 12.51]	47.9	76.3	89.4	96.1
90-150-210-240	0.975	-1.40 [-1.88; -0.91]	5.79 [5.44; 6.13]	8.22 [8.21; 8.23]	0.97 [0.97; 0.98]	11.95 [10.90; 13.03]	56.8	84.3	92.9	97.1
30-90-120-180	0.975	-1.97 [-2.56; -1.37]	7.17 [6.75; 7.59]	8.24 [8.23; 8.25]	0.97 [0.97; 0.98]	11.98 [11.39; 12.58]	48.3	75.5	88.5	94.3
5-90-150-210	0.975	0.75 [0.24; 1.25]	5.96 [5.61; 6.31]	8.25 [8.24; 8.26]	0.97 [0.97; 0.98]	11.98 [11.13; 12.86]	56.6	82.3	90.9	96.9
90-120-150-240	0.975	-1.63 [-2.13; -1.14]	5.96 [5.62; 6.30]	8.25 [8.24; 8.26]	0.97 [0.97; 0.98]	11.98 [11.00; 13.03]	54.0	84.1	92.5	96.8
45-60-90-180	0.976	-2.07 [-2.65; -1.50]	7.05 [6.66; 7.44]	8.26 [8.25; 8.27]	0.97 [0.97; 0.98]	12.00 [11.41; 12.63]	46.4	76.4	89.2	95.6
5-90-120-210	0.975	0.12 [-0.41; 0.66]	6.21 [5.84; 6.58]	8.26 [8.25; 8.27]	0.97 [0.97; 0.98]	12.00 [11.21; 12.84]	56.3	80.8	90.3	96.2
90-120-210-240	0.975	-1.94 [-2.44; -1.45]	5.98 [5.63; 6.33]	8.26 [8.25; 8.27]	0.97 [0.97; 0.98]	12.01 [11.04; 12.93]	55.9	83.0	91.9	96.5
5-15-60-150	0.975	-0.02 [-0.57; 0.52]	6.59 [6.24; 6.95]	8.30 [8.29; 8.31]	0.97 [0.97; 0.98]	12.06 [11.36; 12.79]	48.0	76.9	92.2	96.8
90-120-180-240	0.974	-1.59 [-2.09; -1.08]	6.13 [5.78; 6.48]	8.41 [8.40; 8.42]	0.97 [0.97; 0.98]	12.22 [11.30; 13.17]	53.9	81.4	91.6	96.7
90-180-210-240	0.974	-1.11 [-1.61; -0.61]	6.02 [5.68; 6.36]	8.44 [8.43; 8.46]	0.97 [0.97; 0.98]	12.27 [11.34; 13.24]	54.3	82.3	92.4	96.9

Table S5.3 continues on next page.

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Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	5-15-120-150	0.973	-0.40 [-0.96; 0.15]	6.84 [6.48; 7.20]	8.53 [8.52; 8.54]	0.97 [0.97; 0.98]	12.40 [11.67; 13.17]	47.4	77.1	89.9	96.4
	5-15-90-150	0.972	-0.21 [-0.78; 0.35]	6.86 [6.49; 7.23]	8.73 [8.72; 8.74]	0.97 [0.97; 0.97]	12.69 [11.95; 13.45]	47.5	76.7	89.9	95.7
	5-45-90-150	0.972	0.45 [-0.11; 1.02]	6.86 [6.49; 7.22]	8.75 [8.74; 8.76]	0.97 [0.97; 0.97]	12.71 [11.95; 13.48]	46.7	75.9	90.9	96.3
	5-120-150-210	0.972	-1.74 [-2.30; -1.17]	6.71 [6.31; 7.10]	8.76 [8.75; 8.77]	0.97 [0.97; 0.97]	12.73 [11.90; 13.62]	53.2	79.1	89.1	94.7
	15-120-150-180	0.972	-2.13 [-2.75; -1.51]	7.46 [7.03; 7.89]	8.77 [8.75; 8.78]	0.97 [0.97; 0.97]	12.74 [12.11; 13.41]	47.6	72.0	87.6	93.6
	5-45-120-150	0.972	0.87 [0.31; 1.43]	6.87 [6.50; 7.23]	8.84 [8.83; 8.85]	0.97 [0.97; 0.97]	12.84 [12.09; 13.65]	49.0	76.6	91.1	96.3
	60-120-150-180	0.972	-1.74 [-2.33; -1.15]	7.36 [6.97; 7.75]	8.84 [8.83; 8.86]	0.97 [0.97; 0.97]	12.85 [12.03; 13.82]	44.5	74.0	88.0	95.0
	5-45-60-150	0.972	0.77 [0.20; 1.33]	6.93 [6.56; 7.30]	8.86 [8.84; 8.87]	0.97 [0.97; 0.97]	12.87 [12.08; 13.62]	46.2	76.0	90.5	96.3
	5-120-180-210	0.971	-1.78 [-2.35; -1.20]	6.74 [6.34; 7.14]	8.86 [8.84; 8.87]	0.97 [0.97; 0.97]	12.87 [12.08; 13.70]	53.5	77.5	88.2	94.3
	60-90-150-180	0.971	-1.38 [-1.97; -0.79]	7.30 [6.92; 7.68]	8.93 [8.92; 8.95]	0.97 [0.97; 0.97]	12.98 [12.19; 13.80]	44.7	74.0	88.2	95.5
	15-30-45-150	0.971	0.66 [0.08; 1.25]	7.34 [6.97; 7.71]	8.94 [8.93; 8.95]	0.97 [0.97; 0.97]	12.99 [12.30; 13.62]	43.6	72.8	91.0	96.3
	15-30-120-150	0.971	0.44 [-0.15; 1.03]	7.29 [6.90; 7.67]	9.00 [8.99; 9.01]	0.97 [0.97; 0.97]	13.08 [12.31; 13.91]	43.4	73.4	88.7	95.7
	60-90-120-180	0.971	-1.91 [-2.52; -1.31]	7.47 [7.06; 7.87]	9.00 [8.99; 9.01]	0.97 [0.97; 0.97]	13.08 [12.22; 14.00]	43.7	73.8	87.1	94.7
	120-150-210-240	0.971	-2.85 [-3.38; -2.32]	6.51 [6.13; 6.90]	9.08 [9.07; 9.09]	0.97 [0.97; 0.97]	13.19 [12.07; 14.39]	52.5	80.3	91.0	95.9
	15-30-90-150	0.970	0.42 [-0.19; 1.03]	7.36 [6.96; 7.76]	9.10 [9.08; 9.11]	0.97 [0.96; 0.97]	13.22 [12.48; 13.94]	45.7	73.3	89.1	94.8
	120-150-180-240	0.970	-2.79 [-3.34; -2.25]	6.71 [6.33; 7.10]	9.20 [9.19; 9.21]	0.97 [0.96; 0.97]	13.37 [12.20; 14.65]	50.3	79.9	90.6	95.4
	15-90-150-180	0.971	1.72 [1.14; 2.31]	7.21 [6.82; 7.60]	9.23 [9.22; 9.24]	0.97 [0.96; 0.97]	13.41 [12.70; 14.06]	47.2	72.0	87.2	95.3
	15-45-120-150	0.970	1.13 [0.54; 1.72]	7.31 [6.93; 7.70]	9.25 [9.24; 9.26]	0.97 [0.96; 0.97]	13.44 [12.68; 14.24]	44.4	75.0	89.2	95.2
	15-30-60-150	0.969	1.13 [0.53; 1.72]	7.44 [7.06; 7.82]	9.29 [9.28; 9.30]	0.97 [0.96; 0.97]	13.50 [12.75; 14.24]	43.7	71.7	88.8	95.3
	15-45-60-150	0.969	1.42 [0.83; 2.01]	7.37 [6.99; 7.76]	9.37 [9.36; 9.38]	0.97 [0.96; 0.97]	13.62 [12.83; 14.30]	43.5	72.5	89.0	95.3
	15-90-120-180	0.968	0.40 [-0.24; 1.04]	7.65 [7.23; 8.08]	9.40 [9.38; 9.41]	0.97 [0.96; 0.97]	13.65 [12.90; 14.34]	46.2	71.4	84.7	94.2
	90-120-150-210	0.967	-1.79 [-2.37; -1.20]	7.21 [6.81; 7.60]	9.41 [9.40; 9.42]	0.97 [0.96; 0.97]	13.68 [12.68; 14.77]	46.0	75.9	88.6	94.6
	15-45-90-150	0.968	0.77 [0.16; 1.37]	7.44 [7.04; 7.83]	9.45 [9.44; 9.46]	0.97 [0.96; 0.97]	13.73 [12.97; 14.46]	44.9	74.2	88.2	94.3
	120-180-210-240	0.968	-2.83 [-3.38; -2.29]	6.71 [6.32; 7.11]	9.46 [9.45; 9.48]	0.97 [0.96; 0.97]	13.75 [12.60; 14.99]	51.6	78.8	89.8	95.9
	90-120-180-210	0.967	-1.91 [-2.51; -1.32]	7.29 [6.88; 7.69]	9.50 [9.48; 9.51]	0.97 [0.96; 0.97]	13.80 [12.85; 14.74]	47.0	74.7	87.2	93.9
	30-45-120-150	0.966	-0.17 [-0.83; 0.49]	8.06 [7.62; 8.49]	9.58 [9.57; 9.59]	0.97 [0.96; 0.97]	13.92 [13.25; 14.63]	40.5	69.3	86.5	93.6
	90-150-180-210	0.966	-1.29 [-1.87; -0.70]	7.10 [6.71; 7.49]	9.59 [9.57; 9.60]	0.97 [0.96; 0.97]	13.93 [12.83; 15.11]	47.1	75.8	88.7	94.4
	5-90-120-180	0.966	0.67 [0.04; 1.29]	7.39 [6.96; 7.81]	9.65 [9.64; 9.66]	0.97 [0.96; 0.97]	14.02 [13.11; 14.86]	47.4	74.1	86.5	93.1

5-90-150-180	0.966	1.21 [0.60; 1.83]	7.22 [6.79; 7.66]	9.72 [9.71; 9.74]	0.96 [0.96; 0.97]	14.13 [13.24; 15.01]	49.2	75.5	85.9	94.1
15-60-120-150	0.967	2.12 [1.50; 2.73]	7.72 [7.31; 8.12]	9.90 [9.88; 9.91]	0.96 [0.96; 0.97]	14.38 [13.58; 15.19]	43.0	70.2	86.4	94.1
30-45-60-150	0.965	0.81 [0.16; 1.46]	8.09 [7.67; 8.51]	9.93 [9.91; 9.94]	0.96 [0.96; 0.97]	14.42 [13.69; 15.18]	39.3	68.2	84.8	93.6
5-60-120-150	0.966	1.76 [1.16; 2.36]	7.49 [7.09; 7.89]	9.94 [9.92; 9.95]	0.96 [0.96; 0.97]	14.44 [13.50; 15.32]	44.3	71.9	87.5	95.0
5-60-90-150	0.965	1.39 [0.78; 2.00]	7.51 [7.11; 7.92]	9.98 [9.97; 10.00]	0.96 [0.96; 0.97]	14.51 [13.56; 15.43]	45.4	71.4	87.2	94.6
45-60-120-150	0.963	-0.82 [-1.48; -0.15]	8.30 [7.87; 8.72]	10.01 [10.00; 10.03]	0.96 [0.96; 0.97]	14.55 [13.79; 15.42]	38.3	69.2	85.2	93.0
30-60-120-150	0.964	0.73 [0.06; 1.41]	8.26 [7.81; 8.70]	10.02 [10.01; 10.04]	0.96 [0.96; 0.97]	14.56 [13.84; 15.26]	41.0	67.6	85.5	92.9
120-150-180-210	0.965	-3.68 [-4.29; -3.07]	7.74 [7.30; 8.18]	10.04 [10.02; 10.05]	0.96 [0.96; 0.97]	14.58 [13.47; 15.74]	43.6	72.2	86.8	93.6
15-60-90-150	0.965	1.94 [1.31; 2.58]	7.92 [7.50; 8.34]	10.12 [10.11; 10.13]	0.96 [0.96; 0.97]	14.71 [13.91; 15.46]	42.8	69.5	86.1	93.3
45-90-120-150	0.962	-1.31 [-1.99; -0.62]	8.40 [7.95; 8.85]	10.13 [10.12; 10.15]	0.96 [0.96; 0.97]	14.72 [13.97; 15.45]	39.2	69.5	84.0	92.4
5-30-90-120	0.963	0.70 [0.06; 1.34]	7.86 [7.44; 8.28]	10.16 [10.15; 10.18]	0.96 [0.96; 0.97]	14.77 [13.92; 15.63]	43.1	70.0	85.2	93.8
30-90-120-150	0.962	0.28 [-0.41; 0.98]	8.54 [8.09; 8.99]	10.22 [10.21; 10.24]	0.96 [0.95; 0.96]	14.86 [14.13; 15.59]	39.2	66.2	84.3	91.8
30-45-90-150	0.961	-0.07 [-0.76; 0.62]	8.45 [8.00; 8.89]	10.24 [10.22; 10.25]	0.96 [0.96; 0.96]	14.88 [14.13; 15.60]	39.7	67.0	83.7	92.5
5-30-45-120	0.962	0.60 [-0.04; 1.25]	7.96 [7.55; 8.38]	10.25 [10.24; 10.27]	0.96 [0.96; 0.96]	14.90 [14.09; 15.75]	41.8	69.3	86.2	93.5
5-30-60-120	0.962	0.48 [-0.17; 1.13]	8.00 [7.58; 8.42]	10.25 [10.24; 10.27]	0.96 [0.96; 0.96]	14.90 [14.05; 15.68]	41.2	69.5	84.5	94.0
5-15-45-120	0.961	0.04 [-0.62; 0.70]	7.97 [7.53; 8.40]	10.26 [10.24; 10.27]	0.96 [0.96; 0.96]	14.90 [14.06; 15.72]	43.7	70.7	85.2	93.8
5-15-30-120	0.961	-0.12 [-0.78; 0.54]	7.97 [7.54; 8.41]	10.29 [10.28; 10.31]	0.96 [0.96; 0.96]	14.96 [14.08; 15.75]	43.2	69.4	85.0	93.8
30-60-90-150	0.962	0.69 [0.01; 1.37]	8.33 [7.89; 8.77]	10.30 [10.29; 10.31]	0.96 [0.95; 0.96]	14.97 [14.16; 15.71]	40.5	68.2	84.7	92.9
5-15-60-120	0.960	0.17 [-0.50; 0.84]	8.06 [7.62; 8.50]	10.37 [10.36; 10.38]	0.96 [0.95; 0.96]	15.07 [14.16; 15.88]	41.3	69.7	85.5	93.5
45-60-90-150	0.960	-1.11 [-1.81; -0.41]	8.59 [8.13; 9.04]	10.42 [10.40; 10.43]	0.96 [0.95; 0.96]	15.14 [14.35; 15.97]	38.5	67.5	83.7	91.9
5-15-90-120	0.959	0.00 [-0.67; 0.67]	8.07 [7.62; 8.51]	10.53 [10.52; 10.55]	0.96 [0.95; 0.96]	15.30 [14.44; 16.20]	43.2	69.4	84.6	92.1
150-180-210-240	0.959	-2.84 [-3.42; -2.27]	6.95 [6.53; 7.38]	10.57 [10.56; 10.59]	0.96 [0.95; 0.96]	15.37 [13.82; 17.28]	50.5	78.1	89.9	94.8
60-90-120-150	0.955	-0.97 [-1.69; -0.25]	8.93 [8.47; 9.39]	10.97 [10.96; 10.99]	0.96 [0.95; 0.96]	15.95 [15.05; 16.96]	37.9	65.0	82.4	90.9
15-90-120-150	0.961	2.75 [2.08; 3.43]	8.62 [8.17; 9.06]	10.98 [10.96; 11.00]	0.95 [0.95; 0.96]	15.96 [15.17; 16.72]	41.0	65.6	81.8	91.4
5-45-90-120	0.956	1.09 [0.41; 1.78]	8.35 [7.90; 8.79]	11.03 [11.02; 11.05]	0.95 [0.95; 0.96]	16.03 [15.05; 17.01]	40.0	67.7	85.6	92.8
90-120-150-180	0.954	-1.48 [-2.19; -0.77]	8.76 [8.30; 9.22]	11.07 [11.06; 11.09]	0.95 [0.95; 0.96]	16.09 [15.02; 17.18]	40.5	66.0	81.0	91.3
5-45-60-120	0.956	1.16 [0.48; 1.84]	8.46 [8.02; 8.90]	11.11 [11.09; 11.12]	0.95 [0.95; 0.96]	16.14 [15.20; 17.06]	39.0	66.3	84.1	92.9
15-30-45-120	0.955	1.14 [0.45; 1.83]	8.60 [8.15; 9.04]	11.19 [11.17; 11.20]	0.95 [0.95; 0.96]	16.26 [15.35; 17.18]	38.8	66.7	83.0	91.9
5-90-120-150	0.955	1.87 [1.17; 2.56]	8.38 [7.91; 8.86]	11.39 [11.37; 11.41]	0.95 [0.94; 0.96]	16.55 [15.57; 17.54]	43.4	68.4	83.3	92.1
15-45-60-120	0.954	1.83 [1.14; 2.53]	8.72 [8.27; 9.17]	11.43 [11.42; 11.45]	0.95 [0.94; 0.96]	16.61 [15.65; 17.63]	37.3	65.4	82.6	92.3
15-30-60-120	0.953	1.39 [0.68; 2.10]	8.90 [8.45; 9.35]	11.45 [11.43; 11.46]	0.95 [0.94; 0.96]	16.63 [15.73; 17.62]	36.8	64.8	80.9	91.3

Table S5.3 continues on next page.

Table S5.3: *Continued*

N	LSS	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
	15-30-90-120	0.953	1.04 [0.32; 1.76]	8.89 [8.42; 9.37]	11.45 [11.43; 11.46]	0.95 [0.94; 0.96]	16.63 [15.63; 17.57]	37.2	66.5	80.6	90.8
	15-45-90-120	0.953	1.51 [0.81; 2.21]	8.72 [8.26; 9.18]	11.50 [11.48; 11.52]	0.95 [0.94; 0.95]	16.71 [15.70; 17.61]	38.0	65.2	81.8	91.7
	15-60-90-120	0.951	2.39 [1.67; 3.12]	9.15 [8.68; 9.63]	12.00 [11.98; 12.02]	0.94 [0.94; 0.95]	17.44 [16.46; 18.43]	37.4	62.9	81.7	90.8
	5-60-90-120	0.949	2.05 [1.33; 2.76]	8.92 [8.45; 9.39]	12.07 [12.05; 12.08]	0.94 [0.94; 0.95]	17.54 [16.52; 18.58]	38.1	63.2	81.1	90.8
	30-45-60-120	0.947	0.90 [0.12; 1.69]	9.60 [9.09; 10.11]	12.17 [12.16; 12.19]	0.94 [0.94; 0.95]	17.69 [16.74; 18.68]	34.7	62.7	78.9	88.8
	30-45-90-120	0.946	0.46 [-0.33; 1.25]	9.51 [8.98; 10.04]	12.22 [12.21; 12.24]	0.94 [0.93; 0.95]	17.76 [16.86; 18.64]	36.7	63.5	79.6	88.2
	45-60-90-120	0.943	-0.47 [-1.28; 0.34]	9.84 [9.31; 10.37]	12.37 [12.35; 12.39]	0.94 [0.93; 0.95]	17.97 [17.05; 18.95]	35.2	60.0	79.2	88.3
	30-60-90-120	0.945	1.23 [0.44; 2.02]	9.70 [9.18; 10.22]	12.39 [12.37; 12.41]	0.94 [0.93; 0.95]	18.01 [17.12; 18.93]	36.3	62.3	77.6	88.0
	5-30-60-90	0.943	0.48 [-0.33; 1.28]	9.81 [9.29; 10.34]	12.42 [12.40; 12.43]	0.94 [0.93; 0.95]	18.04 [17.06; 19.02]	34.0	59.6	78.2	89.1
	5-15-60-90	0.943	-0.13 [-0.94; 0.69]	9.84 [9.29; 10.38]	12.45 [12.44; 12.47]	0.94 [0.93; 0.95]	18.09 [17.05; 19.20]	35.1	60.3	78.8	89.7
	5-15-45-90	0.942	-0.24 [-1.05; 0.57]	9.76 [9.22; 10.30]	12.46 [12.44; 12.48]	0.94 [0.93; 0.95]	18.11 [17.08; 19.13]	36.0	60.5	78.6	89.8
	5-15-30-90	0.942	-0.22 [-1.03; 0.60]	9.88 [9.35; 10.41]	12.47 [12.45; 12.49]	0.94 [0.93; 0.95]	18.12 [17.04; 19.18]	33.5	60.8	78.7	89.3
	5-30-45-90	0.942	0.39 [-0.42; 1.20]	9.84 [9.31; 10.38]	12.53 [12.51; 12.54]	0.94 [0.93; 0.95]	18.20 [17.23; 19.20]	34.1	60.5	78.6	88.5
	5-45-60-90	0.938	1.03 [0.20; 1.86]	10.11 [9.57; 10.66]	13.07 [13.05; 13.09]	0.93 [0.93; 0.94]	18.99 [17.95; 20.08]	35.0	58.2	76.7	87.3
	15-30-45-90	0.935	0.83 [-0.02; 1.68]	10.45 [9.90; 11.00]	13.40 [13.38; 13.41]	0.93 [0.92; 0.94]	19.46 [18.40; 20.58]	33.1	58.0	76.3	86.9
	15-45-60-90	0.935	1.37 [0.53; 2.21]	10.39 [9.85; 10.94]	13.45 [13.43; 13.47]	0.93 [0.92; 0.94]	19.54 [18.40; 20.66]	33.4	57.8	76.5	86.6
	15-30-60-90	0.934	1.10 [0.24; 1.95]	10.62 [10.07; 11.16]	13.50 [13.48; 13.52]	0.93 [0.92; 0.94]	19.61 [18.51; 20.88]	30.4	56.2	75.7	86.8
	30-45-60-90	0.922	0.26 [-0.67; 1.20]	11.31 [10.69; 11.94]	14.51 [14.49; 14.53]	0.92 [0.91; 0.93]	21.09 [19.90; 22.42]	31.8	54.3	72.3	82.7
	5-15-45-60	0.918	-0.38 [-1.34; 0.59]	12.06 [11.46; 12.67]	14.80 [14.78; 14.82]	0.91 [0.90; 0.92]	21.50 [20.39; 22.59]	24.6	51.7	70.0	83.2
	5-30-45-60	0.916	-0.01 [-0.98; 0.96]	12.10 [11.49; 12.72]	15.03 [15.01; 15.05]	0.91 [0.90; 0.92]	21.84 [20.73; 23.00]	25.2	51.6	68.8	82.9
	5-15-30-60	0.914	-0.63 [-1.61; 0.35]	12.30 [11.68; 12.92]	15.08 [15.06; 15.10]	0.91 [0.90; 0.92]	21.92 [20.84; 23.01]	25.6	50.2	68.5	82.4
	15-30-45-60	0.910	0.27 [-0.73; 1.27]	12.41 [11.77; 13.04]	15.55 [15.53; 15.57]	0.90 [0.89; 0.91]	22.60 [21.36; 23.82]	24.6	49.8	68.4	82.0
	5-15-30-45	0.885	-1.33 [-2.44; -0.22]	13.79 [13.08; 14.50]	17.34 [17.31; 17.36]	0.88 [0.86; 0.89]	25.19 [23.84; 26.58]	21.1	44.8	63.2	78.0

95% CI 95% confidence interval; *CCC* concordance correlation coefficient; *LSS* limited sampling schedule; *MAPE* mean absolute prediction error; *MPE* mean prediction error; *N* number of sampling instances in the limited sampling schedule; P_5-P_{20} percentages of individual iohexol clearance predictions within 5%-20% of the reference individual iohexol clearance; R^2 Pearson's correlation coefficient; *RMSE* root mean squared prediction error; *TDI* total deviation index.

Table S5.4: Population pharmacokinetic parameter estimates from the final full covariate model (Model 1), and the reduced models without fat-free mass (Model 2), patient type (Model 3), or without both (Model 4) on the development cohort

Parameters	Model 1	Model 2	Model 3	Model 4
	Final model Estimate (RSE; shrinkage)	*No FFM* Estimate (RSE; shrinkage)	*No patient type* Estimate (RSE; shrinkage)	*Covariate-free* Estimate (RSE; shrinkage)
Fixed effects				
CL (L/h)	4.07 (5%)	3.76 (5%)	4.73 (4%)	4.19 (4%)
V_c (L)	8.36 (9%)	7.66 (8%)	9.32 (6%)	8.15 (5%)
Q (L/h)	7.71 (9%)	6.52 (9%)	7.89 (8%)	6.50 (8%)
V_p (L)	6.88 (5%)	6.05 (5%)	6.90 (5%)	6.07 (5%)
Covariate relationships				
Patient type on CL	0.483 (21%)	0.344 (28%)		
Patient type on V_c	0.342 (38%)	0.180 (65%)		
Between-subject variability				
CL (CV%)	29.8 (11%; 4%)	31.9% (9%; 3%)	34.5% (7%; 4%)	34.1% (8%; 3%)
V_c (CV%)	40.4 (8%; 5%)	40.9% (8%; 6%)	43.4% (9%; 5%)	42.2% (8%; 5%)
Q (CV%)	61.7 (12%; 27%)	68.0% (11%; 24%)	60.7% (14%; 28%)	67.7% (10%; 25%)
V_p (CV%)	23.5 (18%; 30%)	29.2% (26%; 26%)	23.2% (20%; 31%)	28.2% (23%; 27%)
Random residual variability				
Proportional error (CV%)	22.9 (14%; 30%)	22.9 (13%; 31%)	22.9 (13%; 31%)	23.0 (12%; 31%)
Additive error (CV%)	0 (FIX)	0 (FIX)	0 (FIX)	0 (FIX)

95% CI 95% confidence interval; *CL* total body clearance; *CV%* coefficient of variation; *FIX* fixed; *Q* intercompartmental clearance; *RSE* relative standard error; V_c volume of distribution of the central compartment; V_p volume of distribution of the peripheral compartment.

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Table S5.5: Predictive performances of the best limited sampling schedules (LSSs) with the final covariate model (Model 1), the model without fat-free mass (Model 2), the model without patient type (Model 3), or the covariate-free model (Model 4), for glomerular filtration rate (GFR) estimation on the LSS dataset (GFR_{lss}), as compared to GFR estimation based on the full dataset (GFR_{ref})

LSS	Model	R^2	MPE [95% CI] (%)	MAPE [95% CI] (%)	RMSE [95% CI] (%)	CCC [95% CI]	TDI [95% CI] (%)	P_5 (%)	P_{10} (%)	P_{15} (%)	P_{20} (%)
5-30-180	1	0.984	-0.72 [-1.15; -0.28]	5.43 [5.15; 5.71]	6.52 [6.51; 6.53]	0.98 [0.98; 0.99]	9.48 [8.97; 9.98]	54.4	85.0	96.4	98.9
	2	0.983	-2.53 [-3.00; -2.06]	6.03 [5.70; 6.35]	7.15 [7.14; 7.16]	0.98 [0.98; 0.98]	10.4 [9.82; 11.0]	53.0	80.6	93.1	98.2
	3	0.984	-0.55 [-1.00; -0.11]	5.52 [5.24; 5.81]	6.60 [6.59; 6.61]	0.98 [0.98; 0.99]	9.59 [9.11; 10.1]	54.9	84.6	96.3	98.9
	4	0.982	-2.44 [-2.92; -1.96]	6.17 [5.84; 6.49]	7.20 [7.19; 7.21]	0.98 [0.98; 0.98]	10.5 [9.93; 11.0]	52.3	80.1	92.4	97.9
5-30-150-180	1	0.987	-0.28 [-0.69; 0.13]	5.00 [4.73; 5.27]	6.06 [6.05; 6.07]	0.99 [0.98; 0.99]	8.81 [8.31; 9.29]	59.4	87.8	96.6	99.0
	2	0.985	-2.28 [-2.73; -1.83]	5.66 [5.35; 5.97]	6.73 [6.72; 6.73]	0.98 [0.98; 0.99]	9.77 [9.26; 10.3]	55.3	83.2	93.9	98.3
	3	0.986	-0.12 [-0.54; 0.30]	5.09 [4.81; 5.36]	6.16 [6.15; 6.17]	0.99 [0.98; 0.99]	8.95 [8.46; 9.45]	59.0	87.5	96.3	99.2
	4	0.984	-2.19 [-2.65; -1.73]	5.78 [5.46; 6.09]	6.75 [6.74; 6.76]	0.98 [0.98; 0.99]	9.81 [9.32; 10.3]	55.0	82.2	93.9	98.0
5-45-240	1	0.995	-0.33 [-0.58; -0.07]	3.14 [2.98; 3.31]	3.76 [3.75; 3.76]	0.99 [0.99; 1.00]	5.46 [5.17; 5.73]	79.0	97.2	99.8	100
	2	0.994	-1.40 [-1.69; -1.12]	3.67 [3.48; 3.86]	4.26 [4.26; 4.27]	0.99 [0.99; 0.99]	6.19 [5.88; 6.51]	73.5	95.4	99.2	100
	3	0.995	-0.29 [-0.55; -0.03]	3.18 [3.01; 3.35]	3.78 [3.77; 3.78]	0.99 [0.99; 1.00]	5.49 [5.19; 5.80]	80.0	96.7	99.8	100
	4	0.994	-1.30 [-1.59; -1.02]	3.67 [3.48; 3.87]	4.21 [4.20; 4.21]	0.99 [0.99; 0.99]	6.11 [5.81; 6.40]	73.4	95.2	99.3	99.9
5-30-45-240	1	0.996	-0.44 [-0.65; -0.22]	2.64 [2.50; 2.79]	3.15 [3.15; 3.16]	1.00 [1.00; 1.00]	4.58 [4.32; 4.84]	87.7	98.9	99.9	100
	2	0.995	-1.54 [-1.79; -1.30]	3.24 [3.07; 3.41]	3.79 [3.78; 3.79]	0.99 [0.99; 1.00]	5.50 [5.20; 5.79]	78.8	97.0	99.7	100
	3	0.996	-0.37 [-0.59; -0.15]	2.70 [2.56; 2.85]	3.20 [3.20; 3.21]	1.00 [1.00; 1.00]	4.65 [4.40; 4.88]	86.2	98.7	99.8	100
	4	0.995	-1.48 [-1.73; -1.23]	3.27 [3.09; 3.44]	3.78 [3.77; 3.78]	0.99 [0.99; 1.00]	5.49 [5.21; 5.78]	78.4	96.6	99.7	99.9

95% CI 95% confidence interval; *CCC* concordance correlation coefficient; *LSS* limited sampling schedule; *MAPE* mean absolute prediction error; *MPE* mean prediction error; P_5-P_{20} percentage of the GFR_{lss} within 5-20% of those of the GFR_{ref}; R^2 Pearson's correlation coefficient; *RMSE* root mean squared prediction error; *TDI* total deviation index.

Table S5.6: InsightRX verification: numeric summary

Test	Result
Data ≤ LOQ: absolute deltas <15% of LOQ	Passed
Data > LOQ: relative deltas <1%	Passed
Primary parameter estimates differ <5%	Passed

Table S5.7: InsightRX verification: configuration

Setting	Value
rLOQ	1
Max absolute concentration delta < rLOQ	0.15
Max relative concentration delta ≥ rLOQ	0.01
Max delta model parameters	0.05
Max delta derived parameters	0.01

Table S5.8: InsightRX verification: libraries

Library	Version
PKPDsim	1.0.78
PKPDmap	0.33
pkiohexolzwartrenal	0.1.1

Supplementary Figures

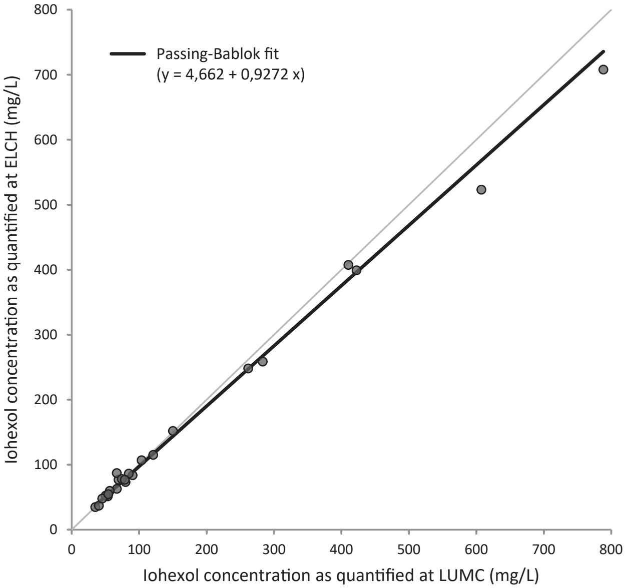

Figure S5.1: Passing-Bablok regression fit of the iohexol concentrations quantified at Evelina London Children's Hospital (ELCH) and those re-quantified at Leiden University Medical Center (LUMC). The solid black line represents the Passing-Bablok regression fit, whereas the solid grey line represents the line of equality.

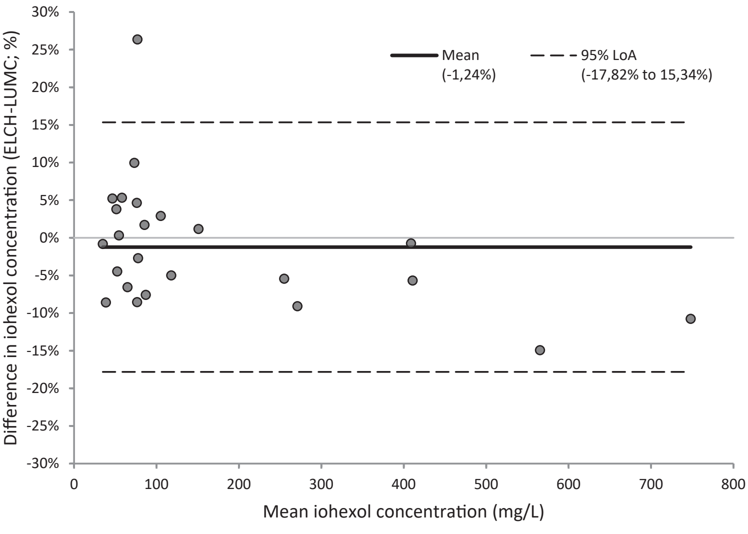

Figure S5.2: Bland-Altman relative difference plot of iohexol concentrations quantified at Evelina London Children's Hospital (ELCH) and those re-quantified at Leiden University Medical Center (LUMC). The solid black line represents the mean bias, whereas the dashed black lines represent the 95% limits of agreement (LoA) around the mean bias. The solid grey line represents the line of equality.

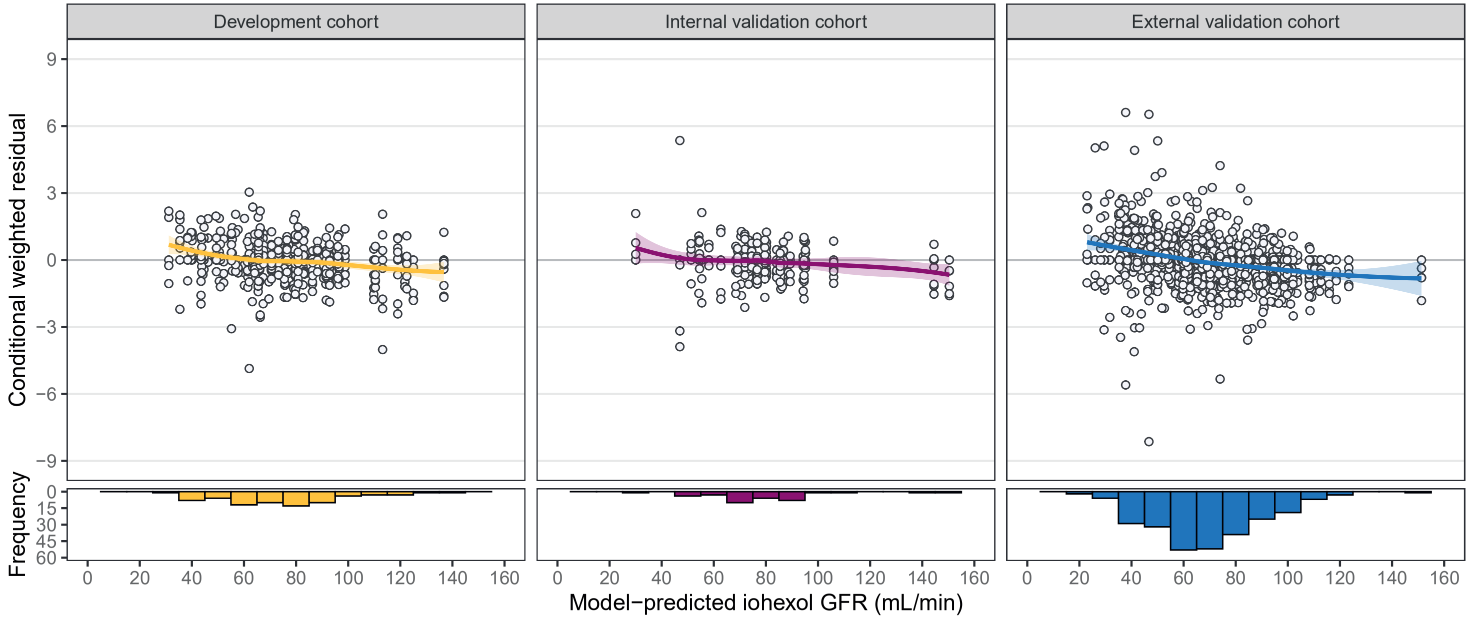

Figure S5.3: Conditional-weighted residuals versus the model-predicted iohexol glomerular filtration rate (GFR), for the development and validation cohorts. The solid gold, purple, and blue lines and gold-, purple- and blue-shaded areas represent the loess regression fits and their standard errors, respectively. The frequency histogram depicts the number of subjects within each iohexol GFR bin.

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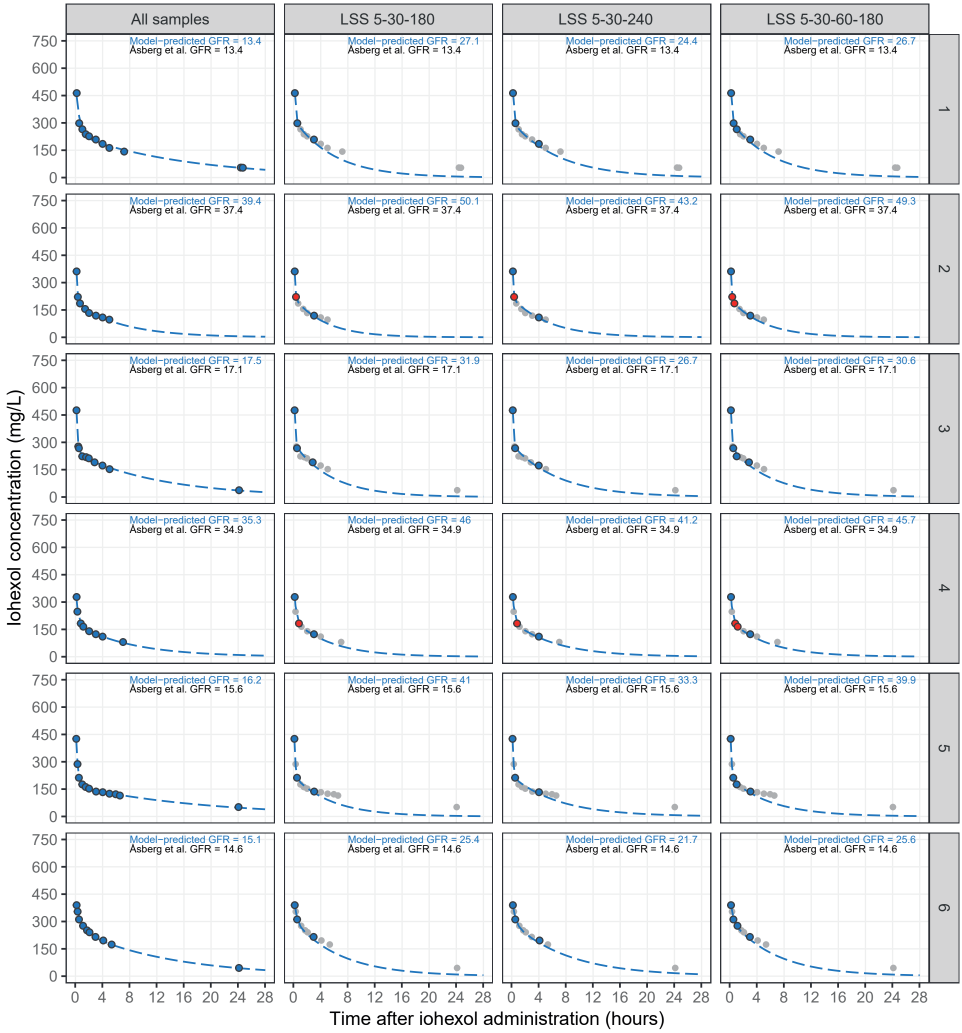

Figure S5.4: Individual plots of observed and model-predicted iohexol curves in patients with impaired renal function. The dashed blue lines depict the individual predicted iohexol curve. Observed iohexol concentrations utilized for the individual GFR prediction within an acceptable range of the limited sampling schedule times are shaded blue, whereas those with substantially deviating sampling times are shaded red. Observed iohexol concentrations not utilized for the individual GFR prediction are shaded grey. Individual plots with one or more missing samples for that particular limited sampling schedule are greyed out. *Figure S5.4 continues on the next pages.*

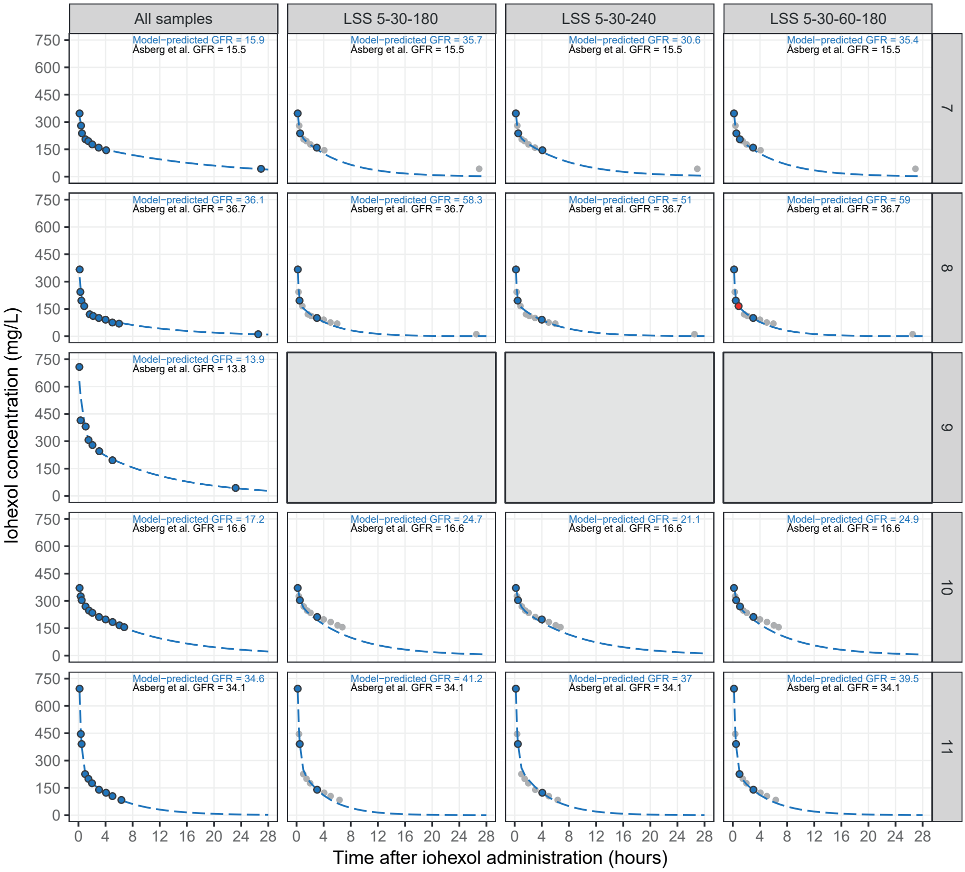

Figure S5.4: *Continued.*

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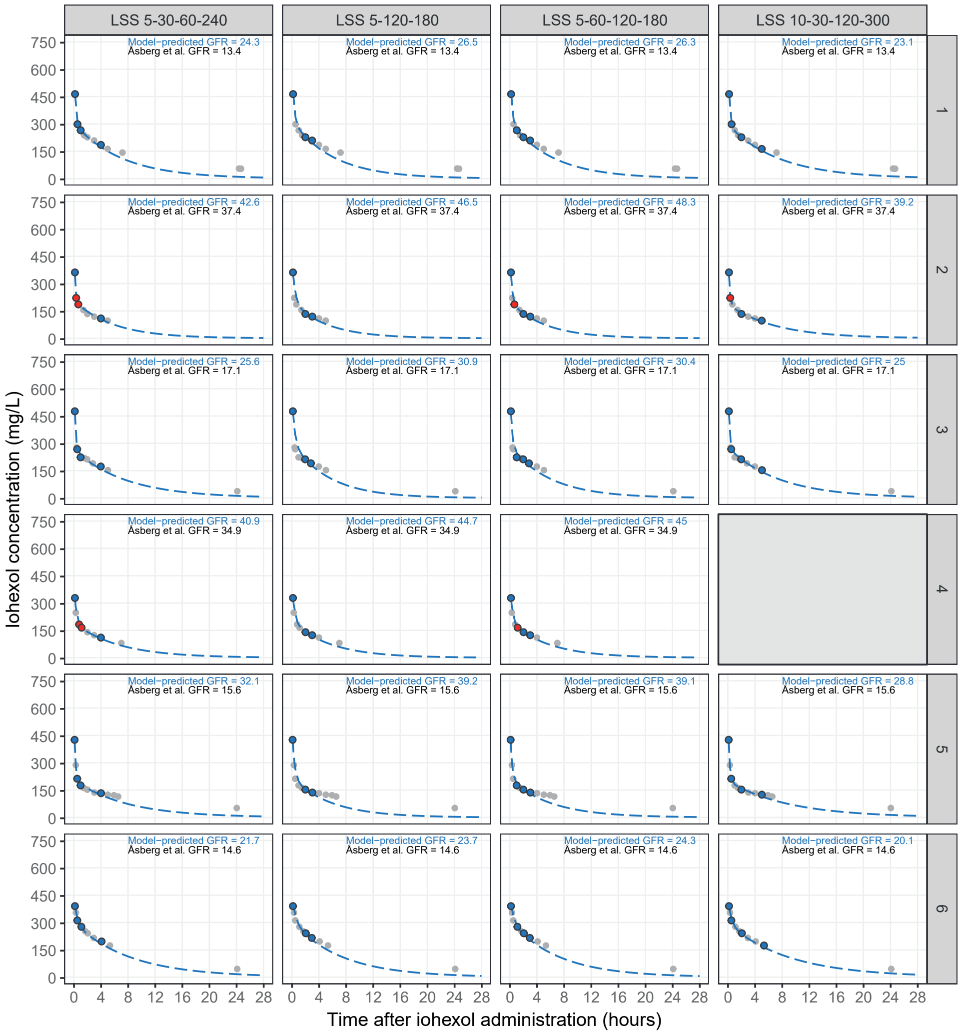

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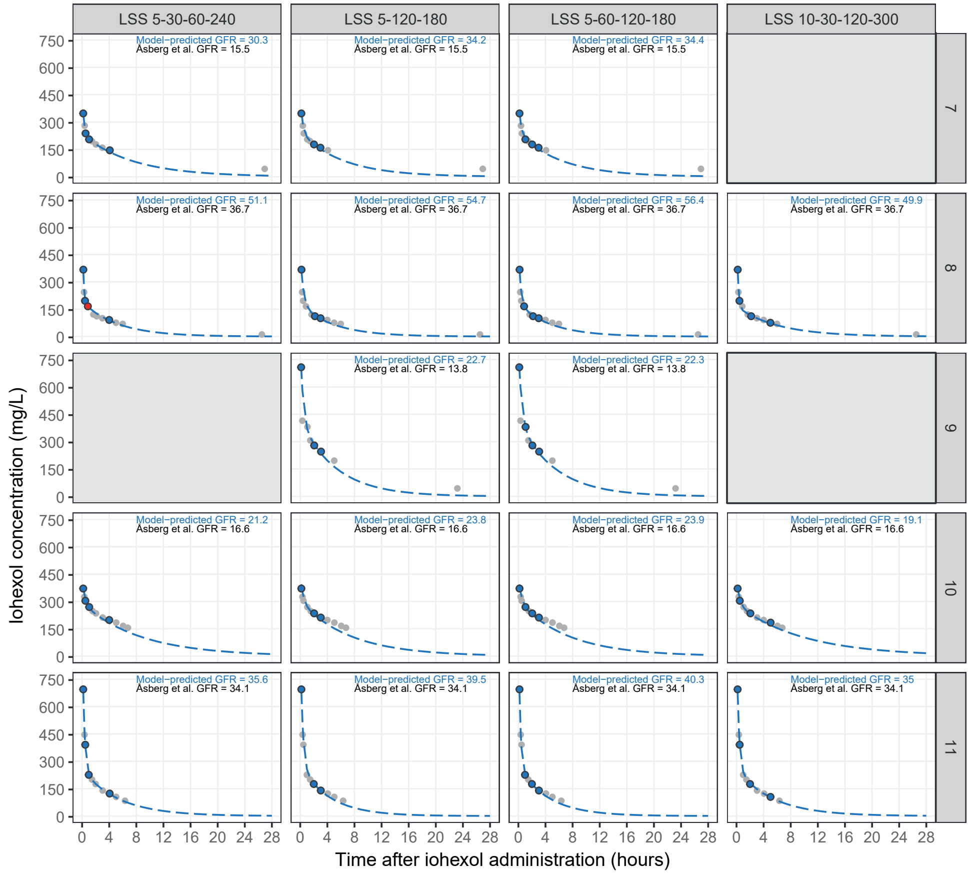

Figure S5.4: *Continued.*

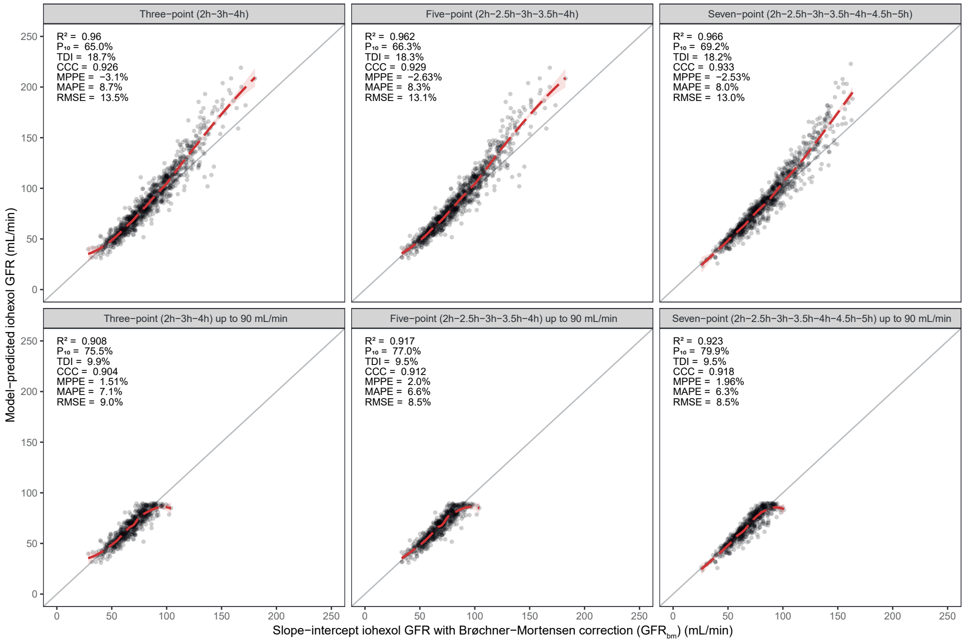

Figure S5.5: Scatter plots of the model-predicted iohexol glomerular filtration rate (GFR) and the iohexol GFR as derived from the slope-intercept method with Brøchner-Mortensen correction (GFR_{bm}). The solid red lines and red-shaded areas represent the loess regression fits and their standard errors, respectively.

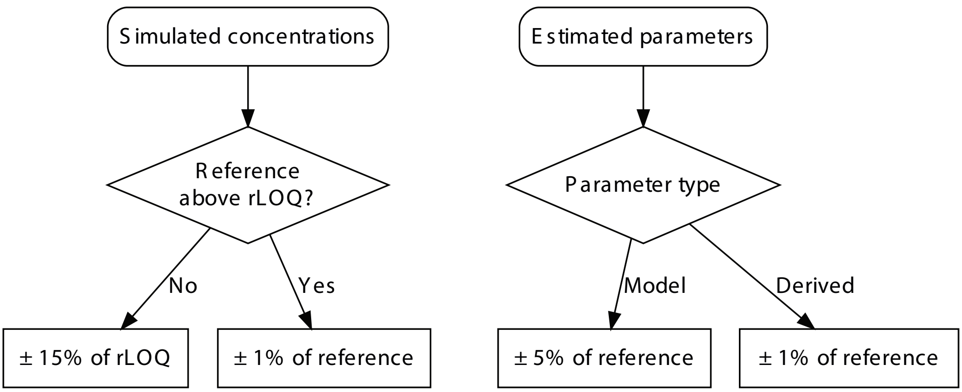

Figure S5.6: Limits for comparison with reference values.

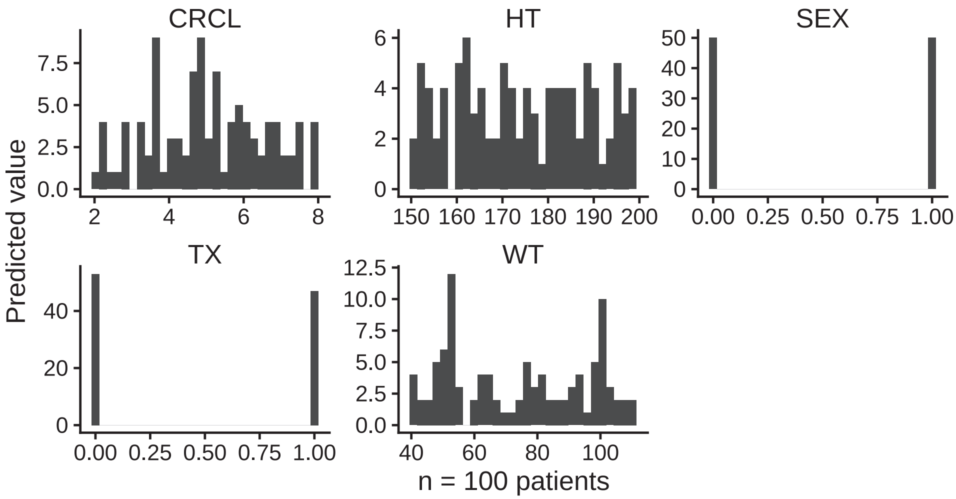

Figure S5.7: Distributions of simulated population characteristics.

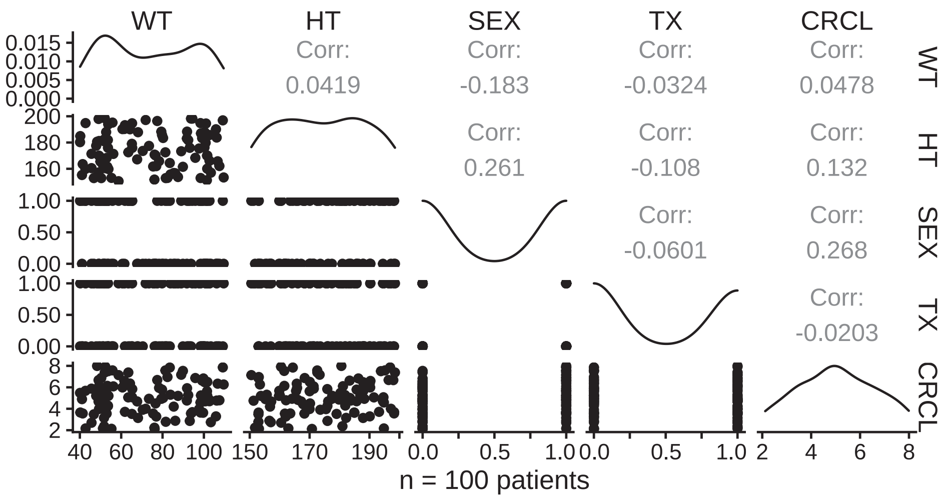

Figure S5.8: Correlations between simulated population characteristics.

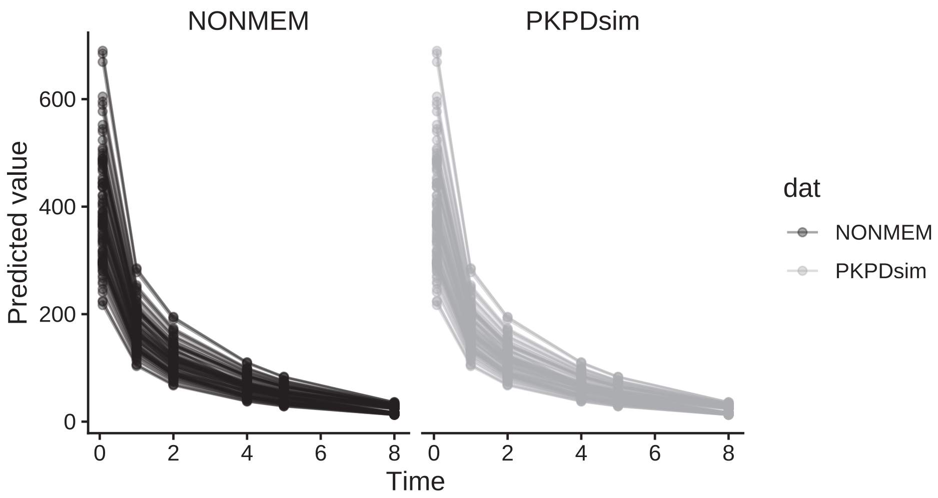

Figure S5.9: Predicted concentrations from PKPDsim and NONMEM.

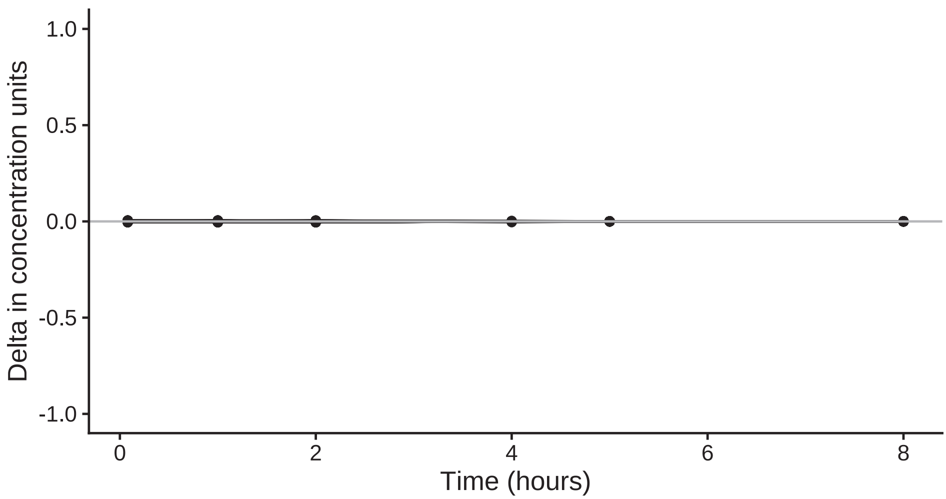

Figure S5.10: Differences between predicted concentrations from PKPDsim *vs*. NONMEM over time.

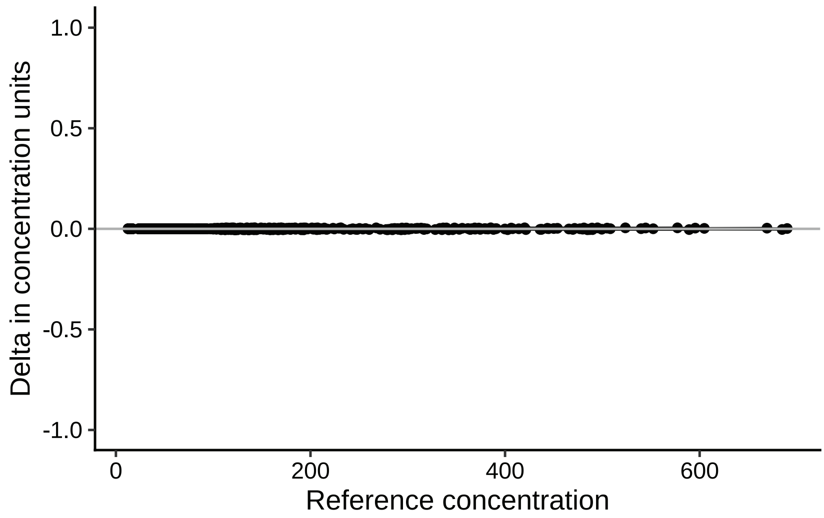

Figure S5.11: Differences between predicted concentrations from PKPDsim *vs.* NONMEM over concentration.

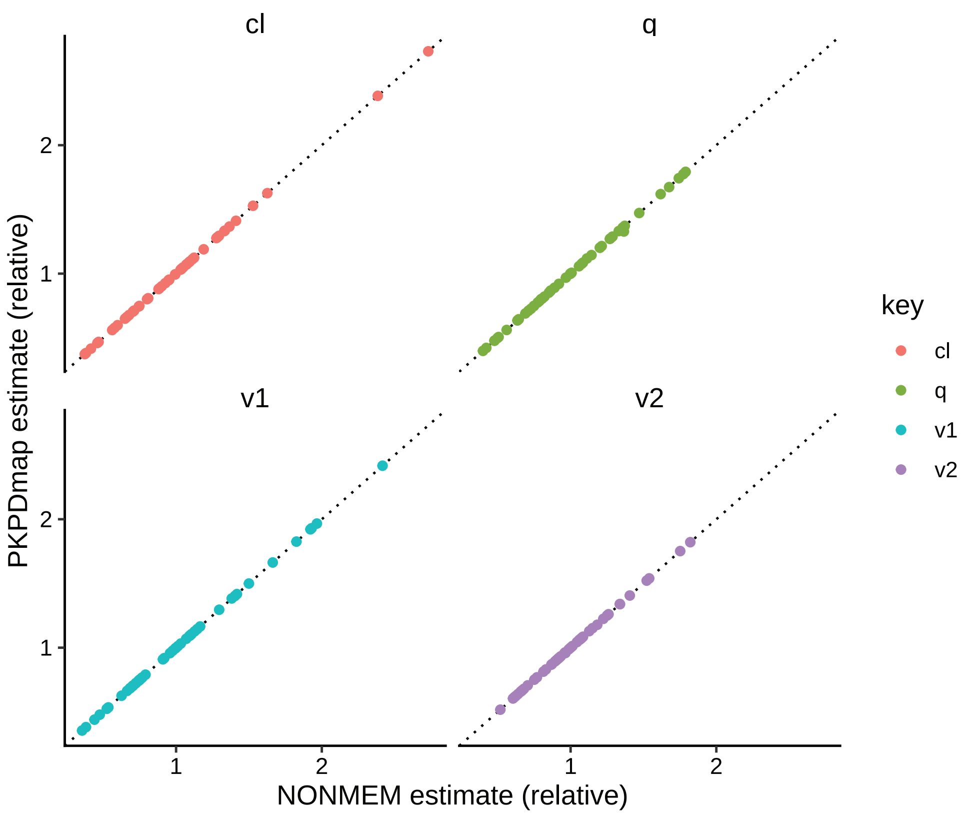

Figure S5.12: Correlation between estimated parameters from PKPDsim *vs.* NONMEM.

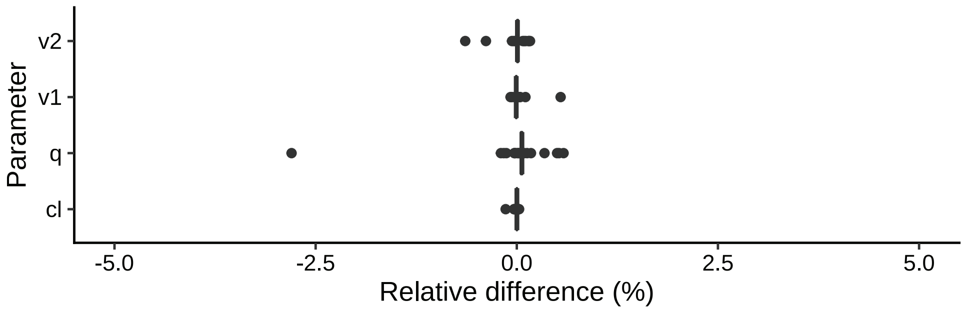

Figure S5.13: Difference in estimated parameters from PKPDsim *vs.* NONMEM.

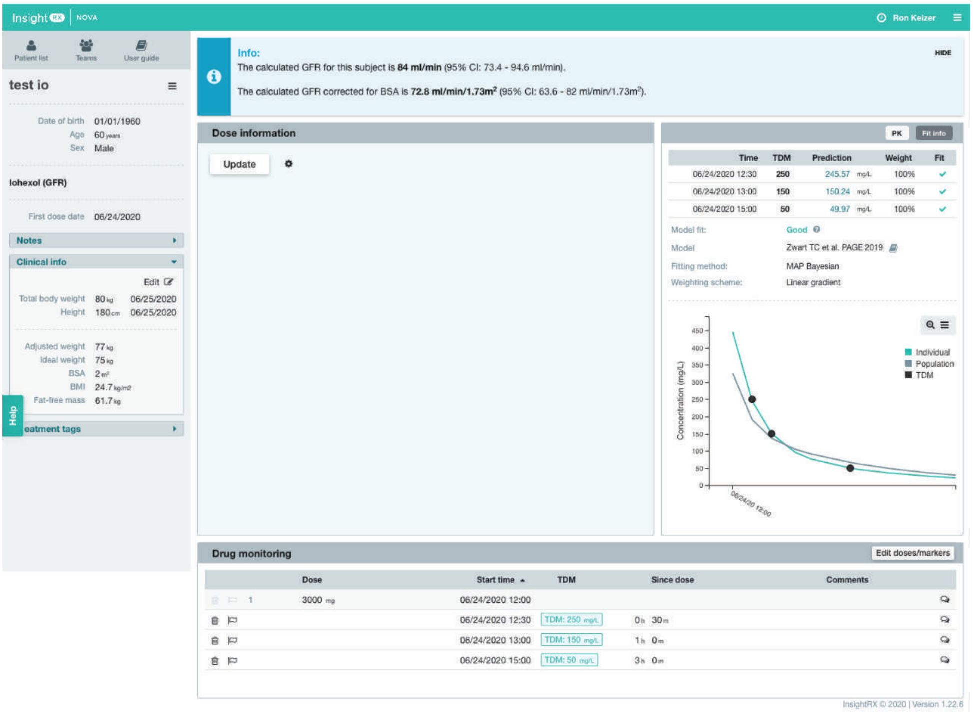

Figure S5.14: InsightRX user interface.