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Population model of serum creatinine as time dependent covariate in neonates

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Dear Leung,

Please consider for publication in the AAPS Journal our manuscript entitled “Population model of serum creatinine as time dependent covariate in neonates”. Our objective was to develop a mechanistic population model describing the time course and variability of serum creatinine in neonates so it be used as part of full random effects models of renally cleared drugs. Our work is a continuation of population modeling of time variant covariates that we published in the AAPS Journal (AAPS J 21:68 (2019)) where a covariate of interest was the body weight. We believe our manuscript will be of interest to all modelers who need to deal with sparse or missing serum creatinine data for pediatric population models. We are looking forward to hearing from you about suitability of our manuscript for publication.

Regards,

Wojciech Krzyzanski

Population model of serum creatinine as time dependent covariate in neonates

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Abstract

Serum creatinine (sCr) is a commonly measured and readily accessible biomarker to estimate glomerular filtration rate (GFR) and therefore widely used as a covariate in population pharmacokinetic models of renally excreted drugs. In neonates sCr dynamically changes during the first few weeks after birth. Missing covariates are a common problem in pharmacokinetic modeling of neonates due to limited availability of blood sampling in number and volume. The objective of this work is to develop a parsimonious population model describing time courses of sCr in neonates with the intent to be incorporated in pharmacokinetic models of various drugs where sCr values are sparse or missing. The data for model development consisted of sCr measurements in 1080 newborns with a gestational age of 24-42 weeks. The model is based on the assumption of a steady state pharmacokinetic model of sCr that involves GFR, back-flow of creatinine from the renal tubules, and urinary flow. Our model uses only gestational age (GA) as covariate explaining between-subject variability of sCr. The model adequately describes distinct features of the sCr time course such as a peak and decline to a plateau. For a neonate with a GAof 35 weeks, the typical value of sCr at birth was 0.584 mg/dL, the peak occurred 2.3 days after birth and its value was 0.794 mg/dL, to reach a plateau of 0.255 mg/dL approximately after 24.7 days. Model simulations reveal that in neonates with a similar postnatal age, sCr decreases with increasing GA. In summary, our model is designed to be a part of full random effects pharmacokinetic models where sCr is a significant covariate.

Key words: serum creatinine, neonates, time-dependent covariate; full random effects model

Introduction

Selection of an optimal dose of drugs for use in neonates is challenging since drug pharmacokinetics is highly variable due to postnatal development of body organs and their functions. The U.S. FDA has issued specific guidelines for clinical studies in neonates implicating gestational age (GA) at birth, and postnatal age (PNA) as essential components of any clinical pharmacology assessment because these two factors can alter the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug (1, 2). Glomerular filtration rate (GFR) is the key contributor to renal clearance of drugs. Renally cleared drugs encompass antibiotics (e. g. amikacin, gentamicin, vancomycin), analgesics (e.g. morphine), antiarrhythmics (e.g. digoxin), and diuretics (e.g. chlorothiazide) or pharmacodynamically relevant metabolites, like α-hydroxy-midazolam or morphine-6-glucuronide. Serum creatinine (sCr) is a commonly measured and readily accessible biomarker to estimate GFR.

Creatinine is a by-product of muscle metabolism in which creatine in the muscle is converted non-enzymatically to creatinine. Creatinine is cleared from the plasma almost exclusively by glomerular filtration with minimal active secretion by the renal tubules. In the first days after birth a significant tubular creatinine reabsorption is present leading to a peak in sCr. This phenomenon is attributed to back-flow of creatinine across leaky immature tubular and vascular structures that vanishes with time when maturational renal changes impose a barrier to creatinine (3). After the peak, sCr decreases with PNA to reach a plateau during infancy. Although nephrogenesis is completed before term birth, the kidney continues to mature both from a functional and anatomical point of view potentially through increased filtration surface area, capillary growth, blood flow characteristics and maturation of tubular cells (4).

SCr is used as a covariate in population pharmacokinetic models of drugs in neonates (5-6). Blood sampling in neonates is limited and measurements of sCr are sparse, resulting in missing data. Missing time dependent covariates create a particular challenge for population modeling of pharmacokinetic data. One of the recommended solutions to account for missing observations is a full random effects model (FREM) that consists of a mathematical model describing the time course of the covariate that is combined with a PK model (7). Then the missing covariate observations are generated by the covariate model that is consistent with available data and a mixed effects pharmacokinetic model.

The objective of this work is to develop a mechanistic population model describing the time course and variability of sCr in neonates with GAs from 24 weeks onwards during the first 42 days after birth. Our intention is that our model will be used as part of future full random effects models of renally cleared drugs in neonates rather than to derive sCr reference ranges to facilitate monitoring and evaluation of kidney function in neonates (8).

Methods

Data

Two data sets were used for our analysis: one for model development and another for model qualification. The data for model development consisted of measurements of individual sCr values

at varying postnatal ages (PNA), gestational ages (GA), and birth weights (BWT) collected from neonates admitted to the neonatal intensive care unit (NICU) of the University Hospitals Leuven (Belgium) between 2007 and 2011 and previously published as results of a retrospective study (9). The data were reduced by the following inclusion criteria: neonates with a GA of at least 24 weeks with at least one measurement of sCr during 42 days after birth and sCr value ≤ 2 mg/dL. The final dataset consisted of 1080 subjects with 7977 sCr observations. A spaghetti plot of individual sCr is shown in Fig. 1. The GA distribution ranged from 24 to 42 weeks with a median of 35 weeks and an interquartile range (IQR) between 31and 38 weeks. The BWT distribution ranged between 370 and 4860 g with a median of 2300 g and an IQR between 1486 and 3203 g. Frequency histograms of GA and BWT distributions are shown in Fig. 2. The scatter plot of BWT vs GA is shown in Fig. 3. No additional covariates were included in the analysis.

The data for model qualification were retrieved from an additional dataset of a retrospective study that explored postnatal albumin trends, but co-collected sCr values. This dataset included all neonates admitted to the NICU of the University Hospitals Leuven between June 2015 and March 2017 whose albumin data were available. The dataset was reduced using the same inclusion criteria as for the development dataset. The final qualification dataset consisted of 765 subjects with 5095 sCr observations. A spaghetti plot of individual sCr is shown in Fig. 1. The GA distribution ranged between 25 and 42 weeks with a median of 35 weeks and an IQR between 33 and 38 weeks. The BWT distribution ranged between 1014 and 6000 g with a median of 2505 g and an IQR between 1860 and 3200 g. Frequency histograms of GA and BWT distributions are shown in Fig. 2. No additional covariates were included in the analysis.

Creatinine assays

The isotope dilution mass spectrometry (IDMS)-traceable enzymatic assay was used to measure serum creatinine concentrations (10). The colorimetric Jaffe assay is also broadly used for creatinine measurements (10). The enzymatic assay is preferable over the Jaffe assay in neonates and young infants due to potential interference with bilirubin. Hyperbilirubinemia is common in this population (9,11). sCR measurements prior to 2012 were based on the IDMS enzymatic CREA PLUS assay on the Modular P (Roche, Mannheim, Germany). In 2012 the CREA PLUS assay was replaced by the enzymatic CREP2 assay on the Cobas c702 (Roche, Mannheim, Germany) by the local lab. It has been reported that the CREP2 assay overestimated sCR in relation to the CREA PLUS assay and the following linear regression relationship has been established (12):

$$\mathrm{sCr_{CREP}}\,(\mu\mathrm{mol/L}) = 0.997 \cdot \mathrm{sCr_{CREA}}(\mu\mathrm{mol/L}) - 5.011 \quad (1)$$

Consequently, we corrected the qualification sCr (sCr_{qual}) using the inverse relationship Eq. (1):

$$\mathrm{sCr_{qual}} = 1.003 \cdot \mathrm{sCr_{devel}} + 0.057 \quad (2)$$

where sCr_{devel} denotes the sCr values from the development data set. The creatinine molecular weight of 113.12 g/mol was assumed.

Quasi steady state pharmacokinetic model for serum creatinine

We adopted a mechanistic pharmacokinetic model of renally cleared drugs which exhibit reabsorption as developed by Felmlee at al. (13). A schematic diagram of the model for sCr in neonates is shown in Fig. 4. Serum creatinine is secreted from the muscle at a rate k_{syn} that depends on the muscle mass. Given that the muscle mass changes much slower than the changes in creatinine clearance by the kidney, we assume that k_{syn} is constant. Creatinine is cleared from plasma by glomerular filtration. Since glomerular filtration rate GFR(t) increases with the infant age, we assume it is time dependent and subject to a separate model presented in the following section. Creatinine in the renal tubules (rtCr) is secreted into urine by the urinary flow UF. Based on an increase in sCr during the first days after birth, we have attributed this phenomenon to a transient back flow of the creatinine from the renal tubules to the plasma $Q(t)$ (2). The back flow vanishes after several days as the kidney of the neonate matures. We have introduced an empirical model for transient changes of $Q(t)$ in the section below. The model equations are as follow:

$$V_p \frac{dsCr}{dt} = k_{syn} - GFR(t) \cdot sCr + Q(t) \cdot rtCr \quad (3)$$

$$V_{rt} \frac{drtCr}{dt} = GFR(t) \cdot sCr - Q(t) \cdot rtCr - UF \cdot rtCr \quad (4)$$

where V_p and V_{rt} are the creatinine plasma and renal tubules volumes, respectively. The half-life of creatinine in plasma is in the order of hours. Indeed, for a typical term neonate with a BWT of 2.5 kg, and a BSA of 0.18 m^2 the GFR at birth is approximately GFR_0 = 3.1 ml/min (8). Given the plasma volume V_p of 1250 mL, the calculated half-life ($t_{1/2}$) is 4.6 h. On the other hand, a change in the sCr baseline reflects kidney maturation in the order of days if not weeks as seen in Fig. 1. In view of a many fold difference in the time scales present in our model, we have looked for a solution using a quasi-steady state assumption:

$$\frac{V_p}{GFR_0}\frac{dsCr}{dt} = 0 \quad \text{and} \quad \frac{V_{rt}}{GFR_0}\frac{drtCr}{dt} = 0 \quad (5)$$

that yields

$$sCr = \left(1 + \frac{Q(t)}{UF}\right)\frac{k_{syn}}{GFR(t)} \quad (6)$$

Derivation of Eq. (6) is shown in Appendix 1.

Model for GFR(t)

In our study the observed sCr decreases after birth to reach a plateau at 30-40 days after birth. This implies that GFR(t) increases with time (t) to reach a steady-state GFR_{ss}. Therefore, we selected the sigmoidal E_{max} model to describe the time course of GFR in infants (14)

$$GFR(PNA) = GFR_0 + \frac{(GFR_{ss} - GFR_0)\cdot PNA^{\gamma}}{PNA_{50}^{\gamma} + PNA^{\gamma}} \quad (7)$$

where GFR_0 is the glomerular filtration rate at birth, PNA_{50} is the time after birth at which 50% of GFR_{ss} is reached, and γ is the Hill coefficient. Since sCr in the both datasets were observed as functions of PNA with day as unit, we replaced the time after birth t with PNA. A hypothetical plot of GFR vs. PNA is shown in Fig. 5.

Model for Q(t)

The back-flow of creatinine from the renal tubules to the plasma Q(t) was modeled by the truncated Gaussian distribution function designed to control its onset, peak and a gradual disappearance:

$$\mathrm{Q(PNA)} = \mathrm{Q_{max}} \cdot \exp\left(-\frac{\mathrm{K^2}}{2} \cdot \left(\mathrm{PNA} - \mathrm{PNA_p}\right)^2\right) \quad (8)$$

where $\mathrm{Q_{max}}$ is the peak of the back flow that occurs at time $\mathrm{PNA_p}$. The parameter K is the time scale factor that controls the width of Q (1/K is equal to the standard deviation of the Gaussian distribution). As for GFR we replaced the time t with PNA. A hypothetical plot of Q vs. PNA is shown in Fig. 5.

Identifiability of model parameters

Substitution of Eqs. (7) and (8) for GFR(t) and Q(t) into Eq. (6) provides insights on identifiability of the model parameters based on sCr observations:

$$\mathrm{sCr} = \left(\frac{\mathrm{Q_{max}}}{\mathrm{UF}} \cdot \exp\left(-\frac{\mathrm{K^2}}{2} \cdot \left(\mathrm{PNA} - \mathrm{PNA_p}\right)^2\right)\right) \frac{\mathrm{k_{syn}/GFR_0}}{1 + \frac{(\mathrm{GFR_{ss}/GFR_0} - 1) \cdot \mathrm{PNA}^\gamma}{\mathrm{PNA_{50}^\gamma} + \mathrm{PNA}^\gamma}}$$

Therefore, the structurally identifiable parameters (15) are $\mathrm{Q_{max}/UF}$, $\mathrm{PNA_p}$, K, $\mathrm{GFR_{ss}/GFR_0}$, $\mathrm{k_{syn}/GFRk_0}$, $\mathrm{PNA_{50}}$, and γ.

Random effects models

All identifiable model parameters (P?)were assumed to be log-normally distributed among subjects:

$$\mathrm{P} = \theta_\mathrm{P}\exp(\eta_\mathrm{P}) \text{ and } \eta_\mathrm{P} \sim \mathrm{N}(0, \omega_\mathrm{P}^2) \quad (9)$$

where $\mathrm{P} \in \{\mathrm{Q_{max}/UF}, \mathrm{PNA_p}, \mathrm{K}, \mathrm{GFR_{ss}/GFR_0}, \mathrm{k_{syn}/GFRk_0}, \mathrm{PNA_{50}}, \gamma\}$. Serum creatinine observations for subject i time $\mathrm{t_j}$ $\mathrm{sCr_{ij}}$were log-transformed and the constant residual error was assumed:

$$\log\left(\mathrm{sCr_{ij}}\right) = \log\left(\mathrm{sCr}(\mathrm{t_j})\right) + \varepsilon_{\mathrm{ij}} \text{ and } \varepsilon_{\mathrm{ij}} \sim \mathrm{N}(0, \sigma^2) \quad (10)$$

Covariate models

The two available covariates GA and BWT were highly correlated with the Pearson correlation coefficient r = 0.91 (see Fig. 3). Therefore, only one covariate at the time was used for a covariate relationship with the model parameters. We assumed linear models for all relationships:

$$\mathrm{P} = \left(\theta_\mathrm{P} + \theta_{\mathrm{COV\_P}}(\mathrm{COV} - \mathrm{COV_{mean}})\right)\exp(\eta_\mathrm{P}) \quad (11)$$

where $\mathrm{COV} \in \{\mathrm{GA}, \mathrm{BWT}\}$. The forward-inclusion backward-elimination technique for covariate selection was applied (16). We used the log-likelihood ratio test of the change in the objection

function value with significance levels for inclusion and elimination 0.001 and 0.0001, respectively.

Assessment of model performance

We evaluated the final model performance by applying pre-specified criteria for maximization of the likelihood, precision of parameter estimation (relative standard errors, RSEs), and goodness-of-fit plots, such as predicted vs observed and conditional individual weighted residuals (CIWRES) vs PNA plots. Additionally, our model predictive performance was tested using the visual predictive check (VPC) method (17). To obtain VPC, 100 simulations of the data were performed with parameters estimates from the final model. Simulated 5th, median, and 95th percentiles and their 95% CIs were compared with observed values.

Model qualification

To assess our model predictive performance we used the qualification dataset. The VPC method was applied to compare model predictions with observations as described above. The predictive performance of the final model was numerically evaluated by calculating mean prediction error (MPE) to assess prediction bias and mean absolute prediction error (MAPE) to estimate prediction accuracy:

$$\mathrm{MPE} = \frac{1}{\sum_{i=1}^{N} n_i} \sum_{i=1}^{N} \sum_{j=1}^{n_i} \frac{sCr(PNA_{ij}) - sCr_{ij}}{sCr_{ij}} \quad (12)$$

$$\mathrm{MAPE} = \frac{1}{\sum_{i=1}^{N} n_i} \sum_{i=1}^{N} \sum_{j=1}^{n_i} \frac{|sCr(PNA_{ij}) - sCr_{ij}|}{sCr_{ij}} \quad (13)$$

Software

All models were implemented in NONMEM 7.4 (ICON Development Solutions, Ellicott City, MD). Population model parameters were estimated using the first order conditional estimation (FOCE) method with η-ε interaction. The model performance diagnostic plots were obtained using R packages ggplot2, lattice, and vpc (18) implemented in RStudio version 1.2.5033 (RStudio Inc., Boston, MA).

Results

Parameter estimation for the base model

The model without covariate relationships (base model) was fitted to the log-transformed *sCr* data. The estimates of the population parameters are listed in Table 1. The relative standard errors (%RSEs) of estimates of the typical values of all model are within the range 1.2%-5.3%. The RSEs for estimates of inter-individual variability (IIV) parameters were less than 19%. The observed vs. predicted diagnostic plots did not show signs of model misspecification (data not shown).

Covariate analysis

Individual estimates of the base model fixed effects parameters were correlated with two available covariates GA and BWT. Only parameters with a correlation coefficient $r^2 < 0.1$ were added to

the model to test for significance. Since the model performance (measured as the change in the objective function value) was slightly better for GA then BWT we selected GA as the only covariate contributing to the explanation of the data variability. We did not consider using both covariates as they were highly correlated (see Fig. 3). Table 2 shows successful steps in the covariate selection process. GA significantly contributed to IIV of the following parameters Q_{max}/UF, PNA_p, GFR_{ss}/GFR_0, k_{syn}/GFR_0, and PNA_{50}. The parameter GFR_{ss}/GFR_0 failed the inclusion criteria for forward selection (P=0.0013) and backward elimination (P=0.00063) by narrow margins. However, given the importance of both GFR_{ss} and GFR_0 in controlling the sCr curve we decided to include it in the final model.

Final model

The estimates of the final model parameters are shown in Table 1. Addition of covariate not only decreased the objective function value, but also reduced the IIV of all parameters. The RSEs of fixed effects model parameters do not increase compared to the base model and are in the range 1.2%-5.3%. The RSEs of estimates of the IIV parameters are less than 14%. The observed vs. predicted diagnostic plots are shown in Fig. 6. They confirm the population model captured the trend in the data as well as the individual sCr vs. time profiles. The visual predictive check plot shown in Fig. 7 assesses the model ability to describe variability in sCr data. The 95% confidence intervals for model predicted 5th, 50th, and 95th percentiles of observed sCr at any moment of time are very narrow but still close to or covering the observed percentiles. The model slightly underpredicted the 95th observed sCr percentile for infants of postnatal ages 5 to 15 days. Overall, the population model well captured the variability in the observed data.

The model estimate of the peak time in sCr coincides with the backflow peak time at 2.42 days. The peak back flow is estimated to be 57.5% of the urinary flow. The average duration of the back flow expressed as PNA_p+2/K is 5.2 days. The estimate of the typical value of GFR_{ss}/GFR_0 is 1.97 implying that GFR increases almost two-fold from its value at birth and 50% of this increase occurs on average at 18.5 days of postnatal age. The Hill coefficient of 3.57 indicates a sigmoidal shape of GFR vs. PNA curve with an inflection point at PNA_{50}.

Model qualification

VPC plot of the final model predictions overlaid with sCr observations from the qualification dataset is shown in Fig. 8. The median observations are well captured whereas the 95th percentile is slightly over predicted for days 8-13 and 20-27 and the 5th percentile is under predicted for days 6-10. The over and under predictions are noticeable but acceptable. The MPE = -0.0021 and MPAE=0.0651 values indicate no bias and high accuracy of the model predictions. Overall, the final model satisfactory well described the qualification data.

Simulations

We used the estimated parameters to simulate time courses of sCr, GFR/GFR_0, and Q/UF for the typical subject with a GA_{mean} of 34.2 weeks and representative neonates with a GA of 25 weeks (extremely preterm), 30 weeks (very preterm), 35 weeks (preterm), and 40 weeks (term). The

simulated curves are shown in Fig. 9 and Fig. 1S. In general terms, sCr decreases with increasing GA. The peak time becomes shorter and the peak value smaller. For GA of 40 weeks one can hardly observe a peak. The sCr at birth (sCr_0), peak time (PNA_{max}), peak (sCr_{max}), and steady-state (sCr_{ss}) parameters characterizing sCr vs PNA curve are listed in Table 3 as functions of GA. The relationship between GFR and GA is the opposite of one for sCr. The GFR increases with increasing GA. Since we were able only to simulate GFR/GFR_0 values, all curves start at 1 at birth and increase to reach steady state GFR_{ss}/GFR_0. The steady state value is higher for neonates with greater GA. Also, the time to reach 50% of GFR_{ss} is shorter for such subjects. The values of GFR_{ss}/GFR_0 and PNA_{50} as functions of GA are listed in Table 3. Finally, the simulations of Q/UF for different GA values are shown in Supplementary Materials Fig. 1S. The peak time of the back flow PNA_p and the peak value Q_{max}/UF decrease with increasing GA. The values of Q_{max}/UF and PNA_p as functions of GA are listed in Table 3.

Discussion

Many publications providing reference values for sCr in neonates and other pediatric populations are available. A statistical approach was to pool all observations, often allowing only one measurement per subject, and apply regression analysis to determine a mathematical relationship between sCr and subject age. Various empirical curves such as fractional polynomials (19), and a broken stick (19) were used to describe the data. The naïve pooled data approach is unable to quantify various sources of variability and does not permit additional covariates as explanatory variables. Moreover, discarding serial individual sCr measurements resulted in neglecting the presence of a peak in sCr during 2-3 days after birth (see for example (20)).

Only recently a nonlinear mixed effects modeling approach has been applied to provide GA-adjusted reference values in extremely low birth weight neonates (8). Besides GA, and BWT, current body weight, delivery mode, and treatment with ibuprofen or inotropic agents were considered as covariates for quantifications of data variability. The mathematical model used for description of sCr time course in neonates employed a mechanistic turnover model where creatinine is synthesized by the muscle and cleared by the kidneys. The time-dependent reabsorption term in the creatinine clearance accounted for the peak in sCr data. We applied the same nonlinear mixed-effects statistical approach to a larger population based on data retrieved form the same retrospective clinical studies (9). However, our mathematical model is fundamentally different from the turnover model. Also, our objectives were not to provide GA-adjusted reference values for sCr in neonates but rather to develop a parsimonious model of time-dependent *sCr* that can be implemented in pharmacokinetic models of therapeutic agents as a covariate contributing to the clearance variability in neonates.

Our initial model describing sCr time courses in neonates was a simplification of mechanistic pharmacokinetic models for renally cleared drugs with reabsorption (13). We added a zero-order production rate k_{syn} of creatinine and assumed a time dependent reabsorption from the renal tubules Q(t). After simulating sCr for a typical term neonate we observed that the changes in the sCr time course occurred much faster than in the observed data. This prompted us to consider a quasi steady state approximation of the pharmacokinetic model where the time dependent GFR(t) reflects kidney maturation and sCr is a direct function of GFR(t) and it is not described by a

pharmacokinetic system of differential equations. While k_{syn} and the urinary flow UF were assumed to be constant, we tested various functions to describe Q(t) and GFRT(t). These included the Bateman function, truncated gamma and normal probability density functions for Q(t) and logistic growth and sigmoidal Hill functions for GFR(t).

Because of the quasi steady state, we were able to estimate parameters describing Q(t) peak and GFR(t) steady state relative to UF and GFR_0, respectively. The time characteristics of Q(t) such as the peak time and duration of the back-flow were well estimated as well as the PNA_{50} that informs about the time to reach 50% of the GFR steady state. The typical value of 18.4 days is the time scale for kidney maturation that should be compared to the sCr half-life of 4.6 h when explaining the nature of the sCr dynamics in neonates. PNA_{50} allows us calculation of the time to reach 90% of GFR_{ss} $PNA_{90}=10^{1/\gamma}PNA_{50}$ =38.9 days. This value can be compared to the 65 day period necessary to reach sCr steady-state reported by Boer et al. (20). As our data set ended at 42 days of PNA, it possible that the PNA_{90} is shortened and does not reflect the actual time to reach the GFR values observed in infants.

In our model k_{syn} represents the production of creatinine by the muscle that is assumed to be constant. Brion et al. (21) reported the muscle mass as percentage of body weight in two groups of infants PNA of 7 days and PNA 14-56 days as 17.2±1% (~245 g) and 19.6±1.1% (~254 g), respectively, for premature infants ($25 \leq GA \leq 34$) and term infants ($38 \leq GA \leq 42$) 21.3±1.3 % (~707 g) and 22.2±1.6% (~1072 g), respectively. This implies only a 3.7% increase in the muscle mass for neonates of $GA \leq 34$ weeks, but a 51.6% increase for infants of $GA \geq 38$ weeks. Consequently, k_{syn} values for patients in this GA group might have been about 50% higher at PNA > 14 days than assumed in our model, introducing a bias in the estimates of k_{syn}/GFR_0 and GA_k_{syn}/GFR_0 parameters. This calls for a future refinement of our model that should have k_{syn} that depends on time similarly to GFR. Another factor in our model contributing to sCr is the urinary flow UF that is assumed to be constant. Gubhaju et al. (4) reported the urinary output for pre-term neonates of GA less 36 weeks. During first 7 days PNA, there was no changes in the urinary output for all GA groups. However, on days 14, 21, and 28 the infants in the group $32 \leq GA \leq 36$ showed an increased the urinary output about 5 mL/kg/h whereas the remaining GA groups showed no change and remained at the level of 4 mL/kg/h. These data suggest that UF is relatively constant for neonates with lower GA and keeps increasing for patients with $GA \geq 32$ weeks. Since UF is present in Eq. (6) as the ratio Q(t)/UF and Q(t) vanishes after first week of PNA (see Fig. 1S), the reported increase in UF does not affect our predicted sCr.

Our simulations of sCr and GFR/GFR_0 vs PNA show a strong dependence of these markers on GA. sCr profile exhibits three phases: a peak that lasts about a week, a decline to a plateau that lasts about two to three weeks, and a plateau itself that starts at three to four weeks of PNA. The sCr level decreases with increasing GA except during first few days after birth when this trend is reversed. A decrease in sCr with GA for neonates of PNA = 7 days was reported by Go et al. (22). For later PNA, the impact of GA on sCr is in concordance with reports of reference values for neonates with similar PNA where the sCr values for premature infants are higher than ones for term infants (23). It is noteworthy to observe that the sCr peak diminishes with increasing GA both in the amplitude and the peak time to be virtually absent in neonates of $GA \geq 40$ weeks. Our

simulations show that GFR increases with PNA to a plateau in a sigmoidal rather than hyperbolic fashion. During the first week after birth, the GFR increase is minimal to speed up between the second and third week of PNA to slow down before reaching the plateau. Our model has flexibility to account for both types of the GFR increase due to the presence of the shape Hill coefficient γ. Any value of $\gamma \leq 1$ would result in the hyperbolic behavior of the GFR vs PNA curve while $\gamma > 1$ yields sigmoidicity. Our data supported the latter. Similarly to sCr, the GA strongly impacts the GFR plateau values as well as the time to reach the plateau. For neonates of a given PNA, GFR increases with GA, and the time to reach the plateau decreases.

Missing data is a common problem in pharmacokinetic modeling of neonates due to limited availability of blood sampling and small volume of blood. Covariates such as body weight, GA, sCr are used to explore and explain between and within-subject variability of pharmacokinetic parameters. If a covariate does not change during the duration of the study, it can be measured once. However, in neonates covariates such as body weight and sCr vary in time, particularly in the first weeks after birth. Implementation of covariates in a mixed effects model requires knowledge of their values at each observation time. When such values are missing statistical techniques such as data imputation are used to account for the absent covariate. The pros and cons data imputation are discussed elsewhere (24). Full random effects model (FREM) has been proposed as an alternative approach (7). We have applied FREM to account for missing body weight measurements in a pharmacokinetic model of paracetamol in neonates (25). One of the biggest challenges for FREM of time-dependent covariates is that a covariate model is often more complex than a pharmacokinetic model. On the other hand, covariate models are drug independent and therefore they are universal. Once developed, they can be applied to the same or similar patient population together with various pharmacokinetic models. Hence, there is a need for parsimonious and simplistic models of time-dependent covariates. The presented here population model has been developed to fulfill this need for sCr in neonates. We plan to demonstrate the utility of our model in a future analysis of amikacin data in neonates.

In summary, we have developed a semi-mechanistic population model describing time courses of sCr in neonates with a GA greater than 24 weeks. Our model used only GA as a covariate explaining between subject variability of sCr. The model is based on the quasi steady state assumption for a pharmacokinetic model of sCr that involves GFR, back-flow of creatinine from renal tubules, and UF. The model adequately describes distinct features of sCr time course such as a peak and decline to a plateau. Model simulations reveal that in neonates of similar PNA, sCr decreases with increasing GA. The model was built with intent to be applied together with pharmacokinetic models of various drugs in neonates where sCr are sparse or missing.

Appendix 1

Derivation of the quasi-steady state Eq. (6)

Dividing Eqs. (3)-(4) by GFR_0, one can obtain the time scale for creatinine clearance V_p/GFR_0 that is equal to 0.3 days for a typical term neonate of BWT =2.5 kg. If the time scale for GFR(t)

due to kidney maturation is several days or longer, the factor V_p/GFR_0 will be proportionally decreased, justifying the quasi-steady state assumption Eq. (5). Consequently,

$$0 = \frac{k_{syn}}{GFR_0} - \frac{GFR(t)}{GFR_0} \cdot sCr + \frac{Q(t)}{GFR_0} \cdot rtCr \quad (A1)$$

$$0 = \frac{GFR(t)}{GFR_0} \cdot sCr - \frac{Q(t)}{GFR_0} \cdot rtCr - \frac{UF}{GFR_0} \cdot rtCr \quad (A2)$$

One can add Eqs. (A1) and (A2) side by side and arrive at

$$0 = \frac{k_{syn}}{GFR_0} - \frac{UF}{GFR_0} \cdot rtCr \quad (A3)$$

Hence

$$rtCr = \frac{k_{syn}}{UF} \quad (A4)$$

On the other hand, solving Eq. (A2) for yields

$$sCr = (UF + Q(t)) \frac{rtCr}{GFR(t)} \quad (A5)$$

Substituting rtCr from Eq. (A4) into Eq. (A5) results in Eq. (6).

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Table 1. Estimates and their percent relative standard errors (%RSE) of the population parameters for the base and final models. Estimates of IIV parameters are presented as variance and coefficient of variation for lognormal distribution (%CV*).

Parameter	Estimate of θ_P(%RSE) Base	Estimate of ω_P^2 (%RSE, %CV) Base	Estimate of θ_P(%RSE) Final	Estimate of ω_P^2 (%RSE, %CV) Final
PNA_{50}, day	18.4 (4.0)	0.427 (12.4, 73.0)	18.5 (3.0)	0.145 (12.2, 39.5)
GFR_{ss}/GFR_0	2.09 (1.8)	0.0215 (18.5, 14.7)	1.97 (1.8)	0.0141 (18.9, 11.9)
k_{syn}/GFR_0, dL/mg	0.55 (1.2)	0.0259 (9.3, 16.2)	0.516 (1.2)	0.0169 (8.5, 13.1)
γ	3.08 (5.3)	0.431 (13.0, 73.4)	3.57 (5.3)	0.52 (11.8, 82.6)
K, 1/day	0.77 (3.8)	0.229 (13.5, 50.7)	0.709 (3.3)	0.207 (13.9, 48.0)
PNA_p, day	2.52 (2.4)	0.22 (19.0, 49.6)	2.42 (1.5)	0.11 (7.0, 34.1)
Q_{max}/UF	0.496 (3.3)	0.154 (11.6, 40.8)	0.575 (3.2)	0.153 (9.4, 40.7)
GA_PNA_p, day/week	NA	NA	-0.0747 (4.8)	NA
GA_PNA_{50}, day/week	NA	NA	-0.0547 (16.9)	NA
GA_k_{syn}/GFR_0, dL/mg/week	NA	NA	-0.0255 (7.9)	NA
GA_GFR_{ss}/GFR_0, 1/week	NA	NA	0.00763 (30.9)	NA
GA_Q_{max}/UF , 1/week	NA	NA	0.0178 (27.9)	NA
σ^2	0.0153 (2.2)	NA	0.0151 (2.2)	NA

* $\%CV = 100\%\sqrt{\exp(\omega_P^2) - 1}$

** Parameter was fixed

NA = not applicable

GFR_{ss} = glomerular filtration rate (GFR) value at steady state ; GFR_0 = GFR value at birth; PNA_{50} = postnatal age (PNA) at which GFR is equal to 50% of GFR_{ss}; k_{syn} = sCr synthesis rate constant; γ = Hill factor; K= time scale factor that controls the width of the back-flow curve Q; PNA_p = PNA at the back-flow peak; Q_{max}= back-flow peak value; UF=urinary flow; GA_PNA_p= slope in the covariate relationship between PNA_p and GA; GA_PNA_{50}= slope in the covariate relationship between PNA_{50} and GA; GA_k_{syn}/GFR_0 = slope in the covariate relationship between k_{syn}/GFR_0 and GA; GA_GFR_{ss}/GFR_0 = slope in the covariate relationship between GFR_{ss}/GFR_0 and GA; GA_Q_{max}/UF = slope in the covariate relationship between Q_{max}/UF and GA; σ^2= variance of residual error for sCr observations;

Table 2. Objective function value (OFV) and its change (ΔOFV) for the successful steps of the forward-inclusion covariate selection process and the final model in the backward elimination process. P value is calculated for the chi square distribution of |ΔOFV| with one degree of freedom.

Covariate relationship	OFV (ΔOFV)	P
Base model	-18275.6 (0)	NA
GA_PNA_p	-18682.4 (-424.8)	2.20E-94
GA_PNA_p & GA_PNA_{50}	-19049.2 (-366.8)	9.31E-82
GA_PNA_p & GA_PNA_{50} & GA_k_{syn}/GFR_0	-19300.0 (-250.8)	1.74E-56
GA_PNA_p & GA_PNA_{50} & GA_k_{syn}/GFR_0& GA_GFR_{ss}/GFR_0	-19319.9 (-10.4)	0.0013
GA_PNA_p & GA_PNA_{50} & GA_k_{syn}/GFR_0& GA_GFR_{ss}/GFR_0& GA_Q_{max}/UF	**-19330.3 (-26.2)**	**3.08E-07**
GA_PNA_{50} & GA_k_{syn}/GFR_0& GA_GFR_{ss}/GFR_0& GA_Q_{max}/UF	-18962.6 (367.7)	5.93E-82
GA_PNA_p & GA_k_{syn}/GFR_0& GA_GFR_{ss}/GFR_0& GA_Q_{max}/UF	-19270.3 (60.0)	9.49E-15
GA_PNA_p & GA_PNA_{50} & GA_GFR_{ss}/GFR_0& GA_Q_{max}/UF	-19162.8 (168.3)	1.74E-38
GA_PNA_p & GA_PNA_{50} & GA_k_{syn}/GFR_0& GA_Q_{max}/UF	-19318.612 (11.7)	0.00063

NA = not applicable

GA_PNA_p= slope in the covariate relationship between PNA_p and GA; GA_PNA_{50}= slope in the covariate relationship between PNA_{50} and GA; GA_k_{syn}/GFR_0 = slope in the covariate relationship between k_{syn}/GFR_0 and GA; GA_GFR_{ss}/GFR_0 = slope in the covariate relationship between GFR_{ss}/GFR_0 and GA; GA_Q_{max}/UF = slope in the covariate relationship between Q_{max}/UF and GA;

Table 3. The parameters characterizing sCr, GFR/GFR_0, and Q/UF vs PNA curves calculated for the indicated values of GA.

GA, weeks	**25**	**30**	**35**	**40**
sCr_0, mg/dL	0.643	0.598	0.584	0.589
PNA_{max}, days	4.1	3.2	2.3	1.4
sCr_{max}, mg/dL	1.04	0.914	0.794	0.679
sCr_{ss}, mg/dL	0.35	0.30	0.255	0.214
GFR_{ss}/GFR_0	1.83	1.91	1.98	2.06
PNA_{50}, days	27.8	22.8	11.7	12.7
Q_0/UF	0.00941	0.0468	0.154	0.337
Q_{max}/UF	0.630	0.60	0.571	0.543
PNA_p, days	4.09	3.19	2.28	1.38

sCr_0=sCr at birth; PNA_{max}= PNA at sCr peak; sCr_{max}= sCr peak value; sCr_{ss}=sCr at steady state; GFR_{ss} = GFR value at steady state; GFR_0 = GFR value at birth; PNA_{50} = PNA at which GFR is equal to 50% of GFR_{ss}; PNA_p = PNA at the back-flow peak; Q_0= back-flow value at birth; Q_{max}= back-flow peak value; UF=urinary flow;

Figure legends

Fig. 1. Time courses of individual serum creatinine sCr measurements for 1083 patients from the development dataset (upper panel) and the 765 patients from the qualification dataset (lower panel). The bold line is the mean of observed values.

Fig. 2. Frequency histograms of distributions of gestational age and birth weight in the population of (pre)term neonates from the development dataset (upper panels) and qualification dataset (lower panels) (Q1, Q2 and Q3 indicated)

Fig. 3. Scatter plot between the body weight at birth BWT and the gestational age GA for subjects in the study. The LOESS line is red. The regression line is added to the plot for assessment of the linearity.

Fig. 4. Schematic diagram of pharmacokinetic model of creatinine. Serum creatinine (sCr) is synthesized from the muscle at a zero-order rate (k_{syn}) and cleared by the kidney glomerular filtration (GFR(t)) into the renal tubules (rtCr). The creatinine from the renal tubules is excreted into the urine by the urinary flow (UF). Transiently, rtCr is also secreted into the plasma by the back-flow (Q).

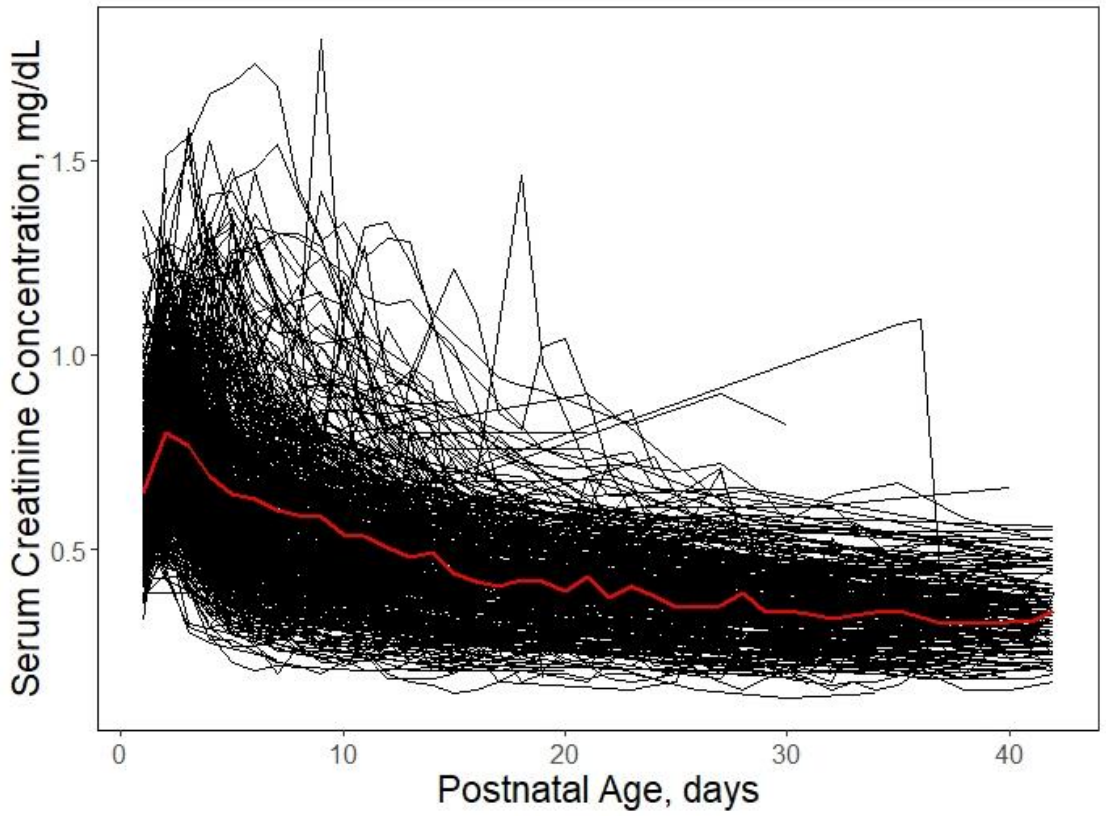
Fig. 5. a) A plot of a sigmoidal curve describing a hypothetical GFR vs. postnatal age (PNA) time course. The curve is normalized by the GFR value at birth GFR_0. It starts at 1 and increases to approach the steady-state GFR_{ss}/GFR_0. PNA_{50} indicates PNA at which GFR reaches the midpoint between GFR_{ss} and GFR_0 b) A plot of a hypothetical time course of the back-flow Q(t). The curve is normalized by the urinary flow UF. The back flow reaches a peak Q_{max} at the time PNA_p. After the peak Q declines to a value of 0.

Fig. 6. Upper panels: Observed vs. predicted diagnostic plots for sCr. The left panel shows sCr predicted using the typical values of model parameters and the right panel shows sCr predicted using the individual subject parameter values. Lower panel: Conditional individual weighted residuals (CIWRES) vs. postnatal age diagnostic plot. The solid line is the LOESS regression line.

Fig. 7. Visual predictive check plots for sCr from the development data set. Symbols represent observed sCr, the continuous line is the median, and the dashed lines are 5^{th} and 95^{th} percentiles of observed values. The shaded regions are model predicted confidence intervals for these percentiles.

Fig. 8. Visual predictive check plots for sCr from the qualification dataset. Symbols represent observed sCr, the continuous line is the median, and the dashed lines are 5^{th} and 95^{th} percentiles of observed values. The shaded regions are model predicted confidence intervals for these percentiles.

Fig. 9. Simulated time courses of sCr (upper panel) and GFR/GFR_0 (lower panel) for a typical patient of the indicated GA. GFR_0 is the GFR at birth. GA=34.2 weeks represents the population mean. The parameter values used for simulations are listed in Table 1.


Serum Creatinine Concentration, mg/dL
1.5
1.0
0.5
0
10
20
30
40
Postnatal Age, days

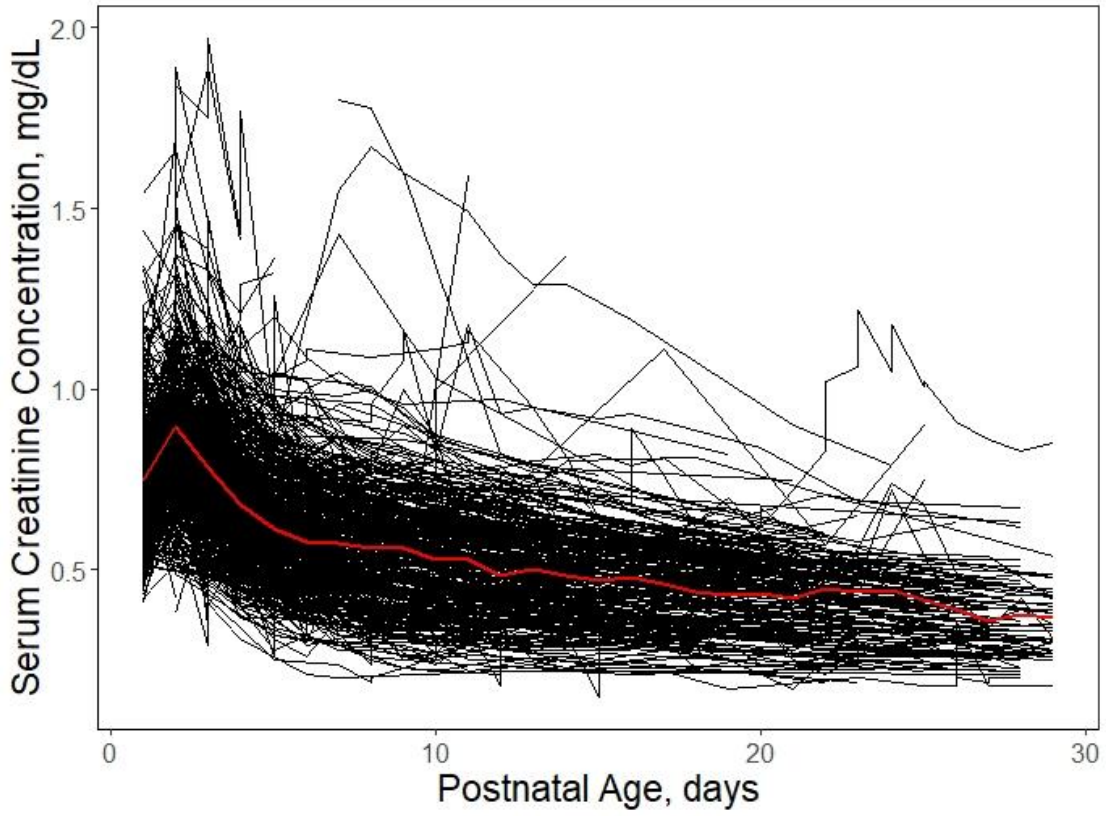
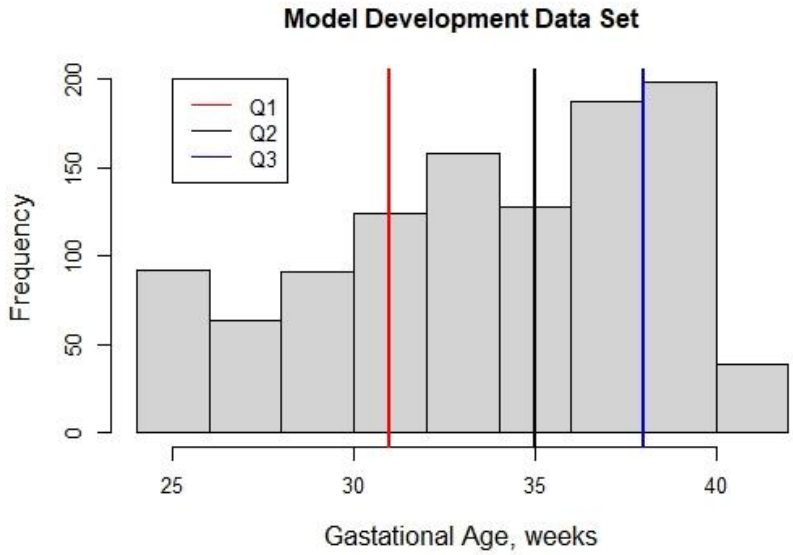
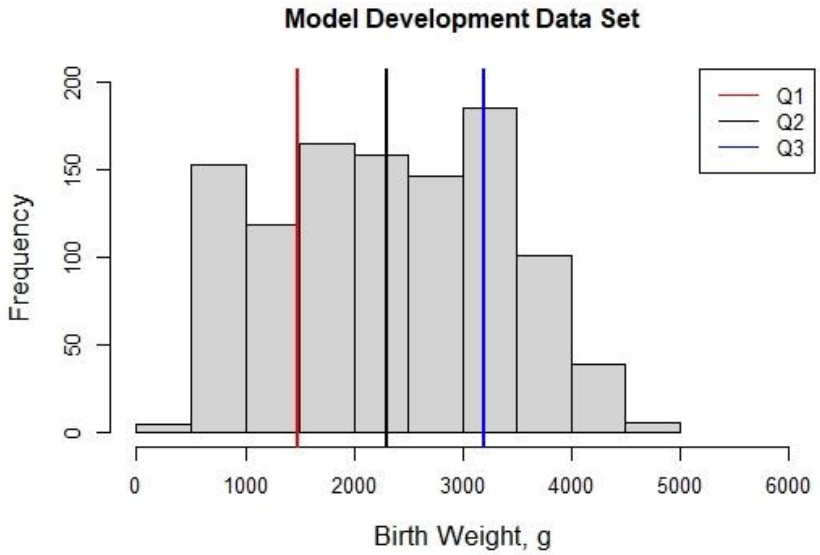
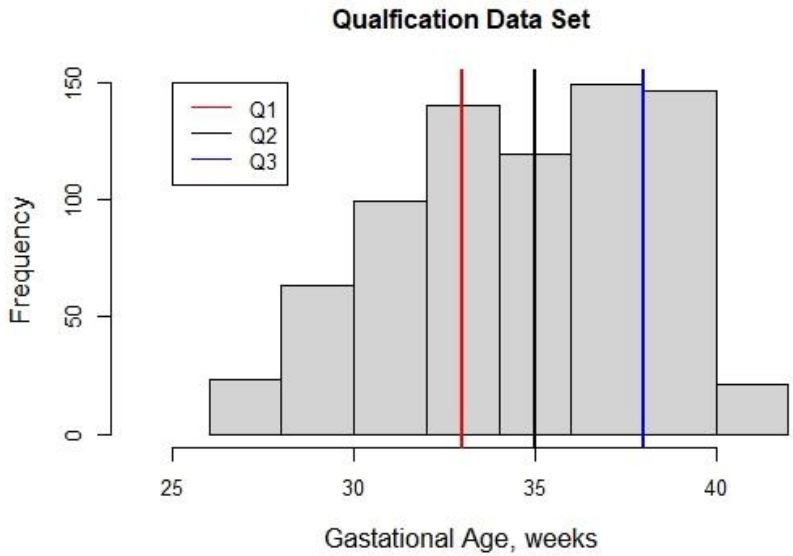

Serum Creatinine Concentration, mg/dL
2.0
1.5
1.0
0.5
0
10
20
30
Postnatal Age, days

Figure 1


Model Development Data Set
Frequency
Gastational Age, weeks
Q1
Q2
Q3
0
50
100
150
200
25
30
35
40


Model Development Data Set
Frequency
Birth Weight, g
Q1
Q2
Q3
0
50
100
150
200
0
1000
2000
3000
4000
5000
6000


Qualfication Data Set
Frequency
Gastational Age, weeks
Q1
Q2
Q3
0
50
100
150
25
30
35
40

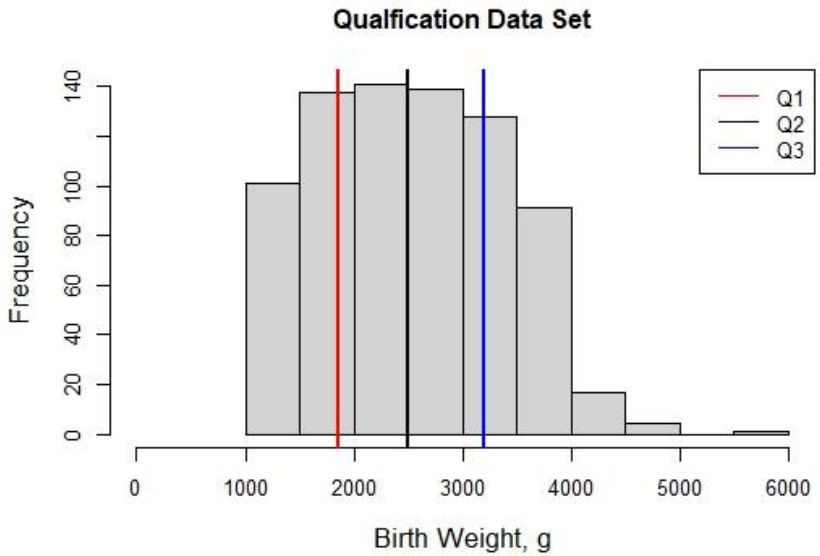

Qualfication Data Set
Frequency
Birth Weight, g
Q1
Q2
Q3
0
20
40
60
80
100
140
0
1000
2000
3000
4000
5000
6000

Figure 2

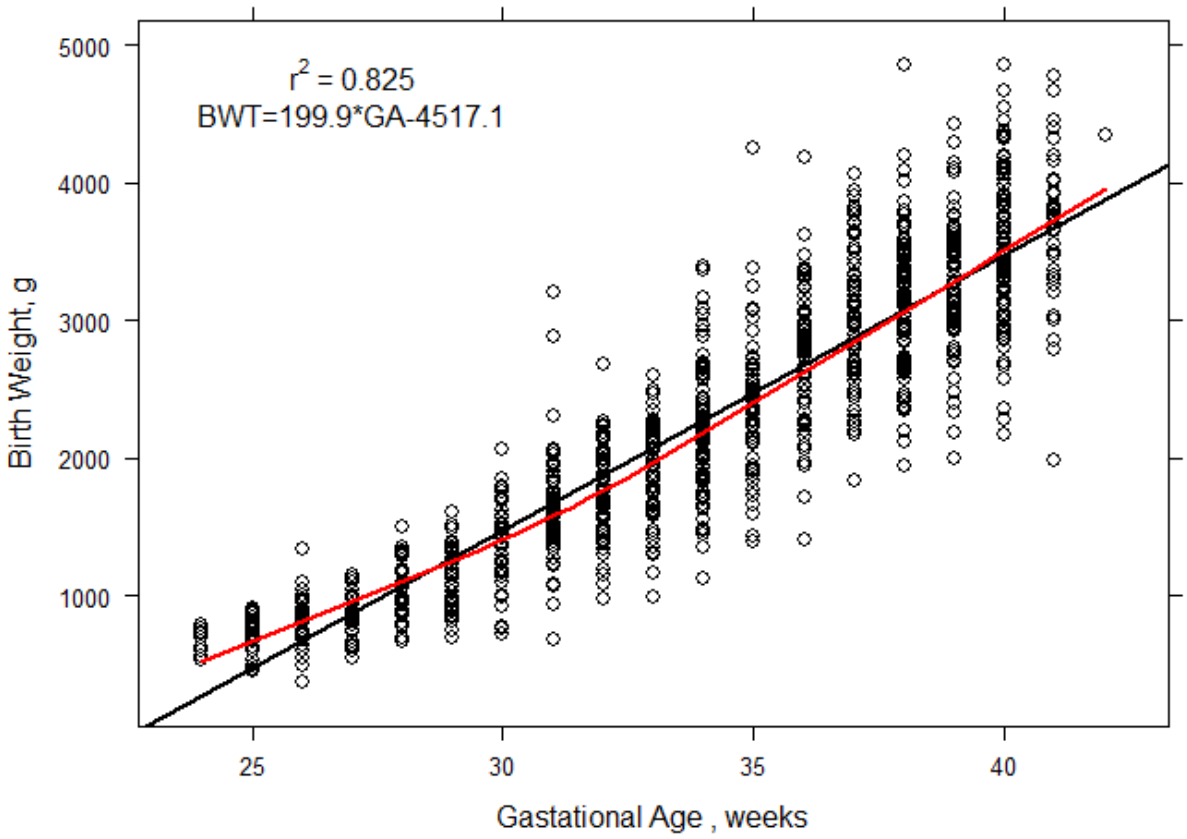

r^2 = 0.825
BWT=199.9*GA-4517.1
Birth Weight, g
5000
4000
3000
2000
1000
25
30
35
40
Gastational Age , weeks

Figure 3

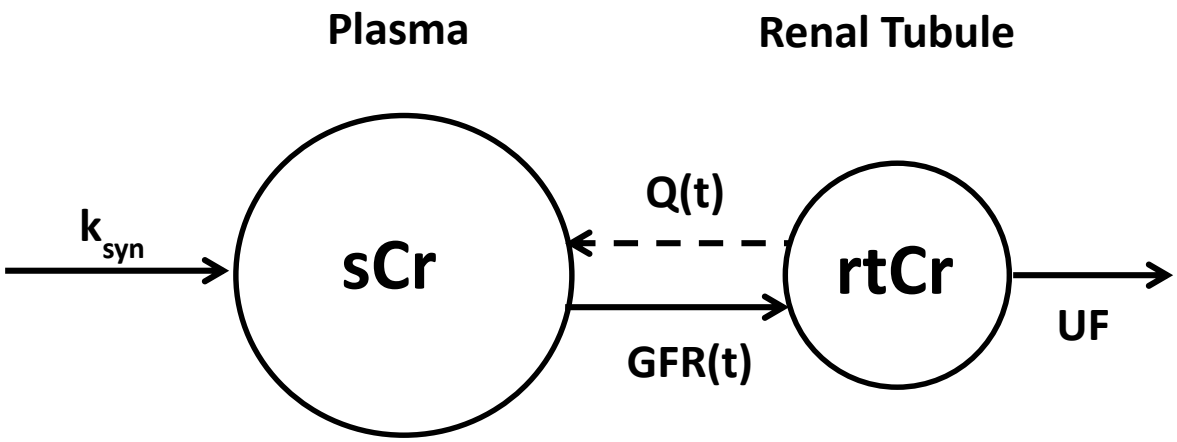
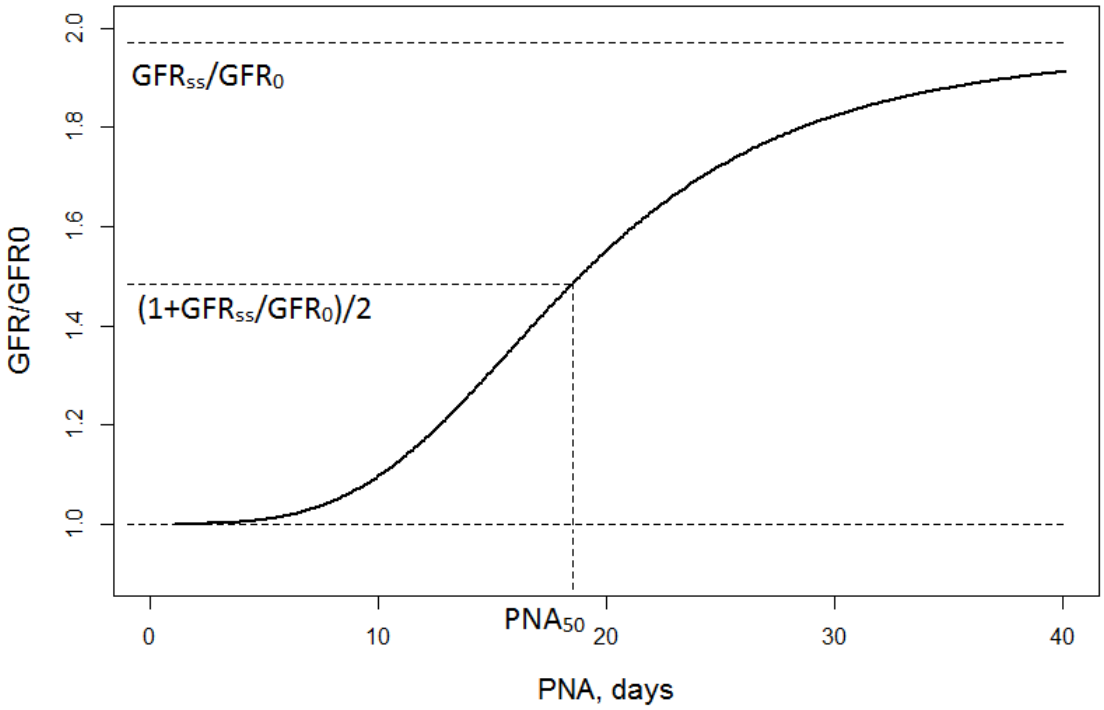


Figure 4


GFR/GFR0
2.0
1.8
1.6
1.4
1.2
1.0
GFR$_{ss}$/GFR$_0$
(1+GFR$_{ss}$/GFR$_0$)/2
0
10
PNA$_{50}$
20
30
40
PNA, days

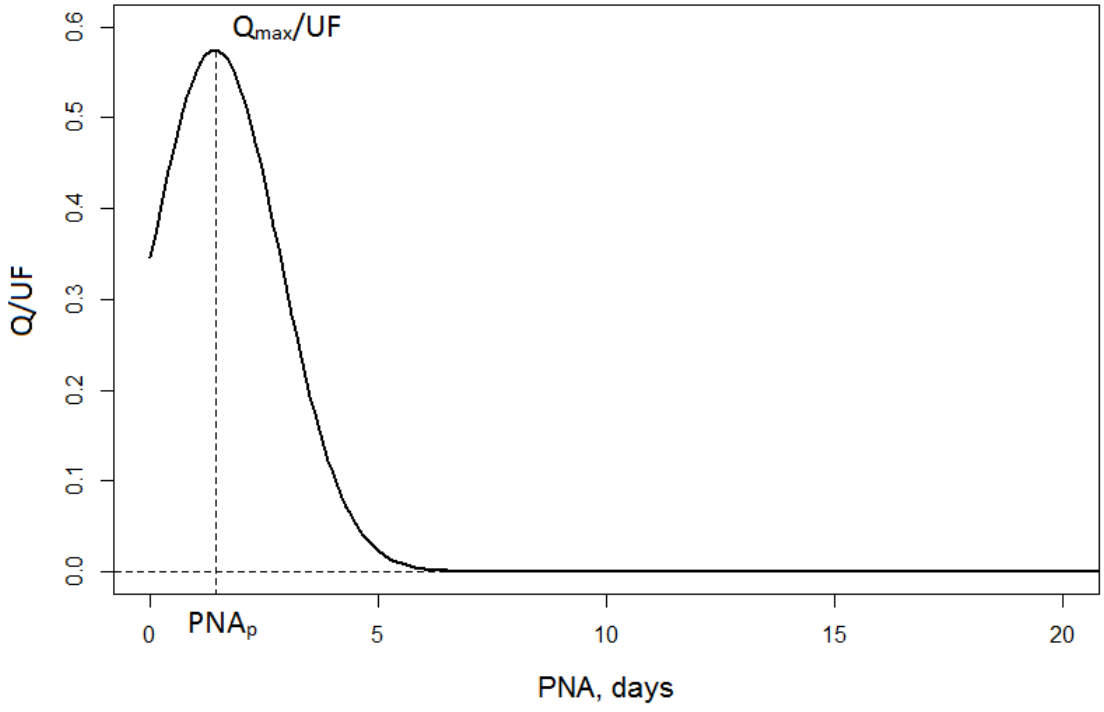

Q/UF
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Q$_{max}$/UF
0
PNA$_p$
5
10
15
20
PNA, days

Figure 5

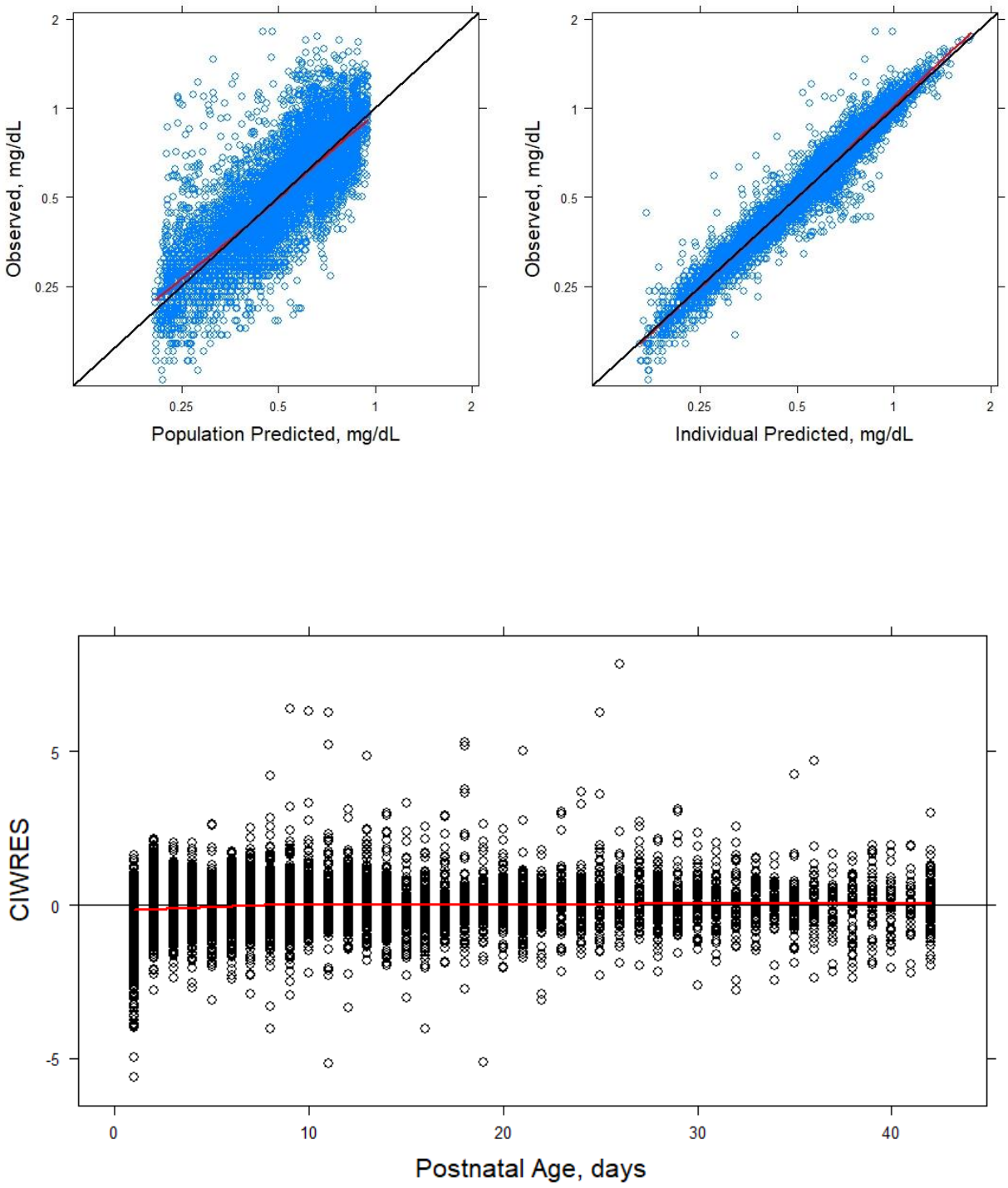

Observed, mg/dL
Population Predicted, mg/dL
Observed, mg/dL
Individual Predicted, mg/dL
CIWRES
Postnatal Age, days

Figure 6

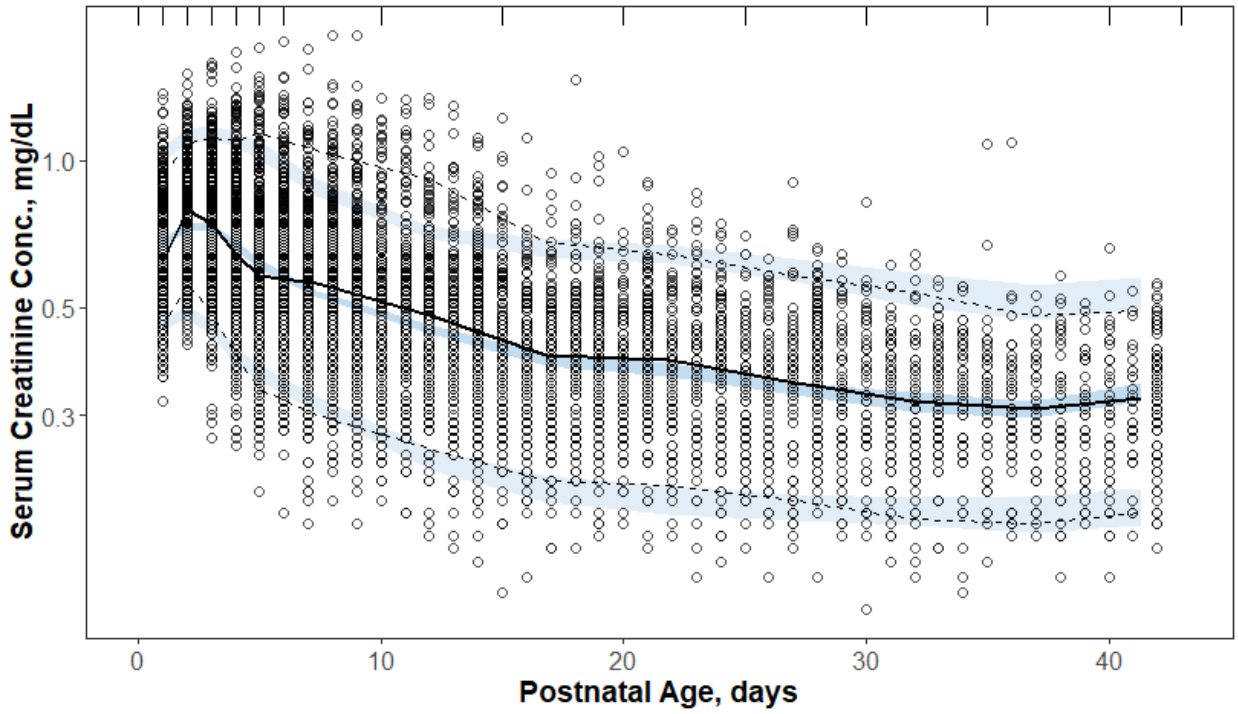

Serum Creatinine Conc., mg/dL
1.0
0.5
0.3
0
10
20
30
40
Postnatal Age, days

Figure 7

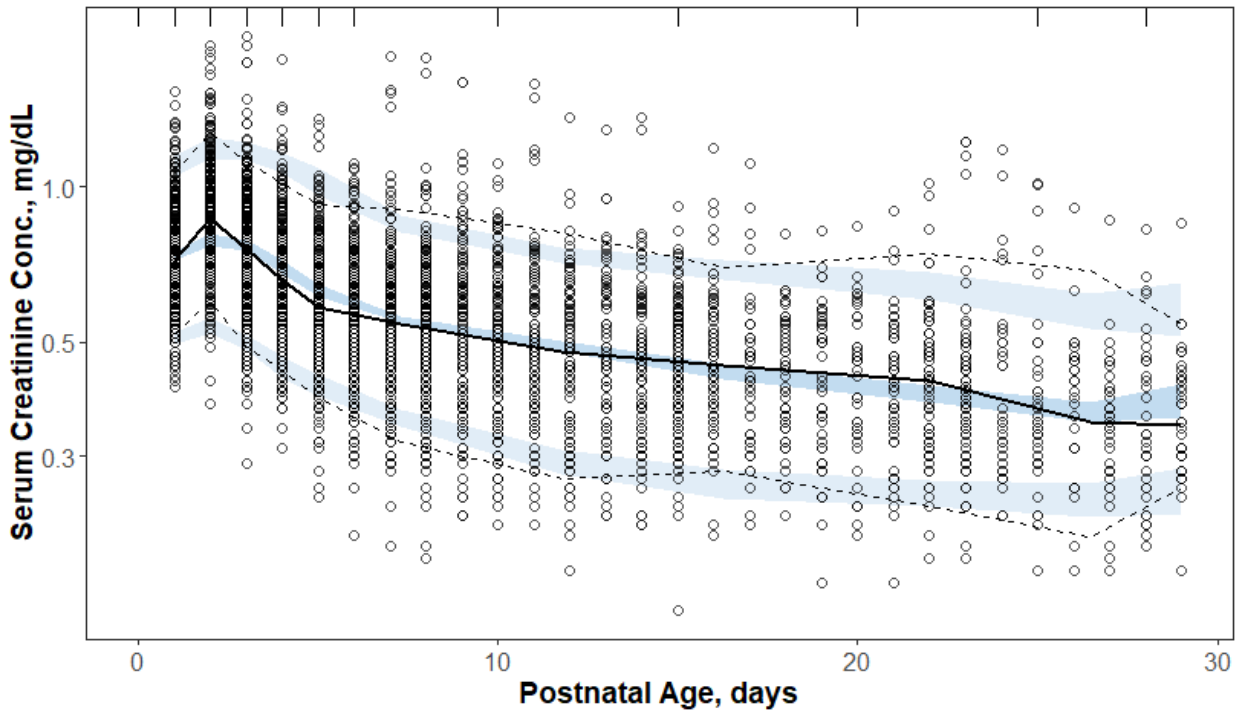
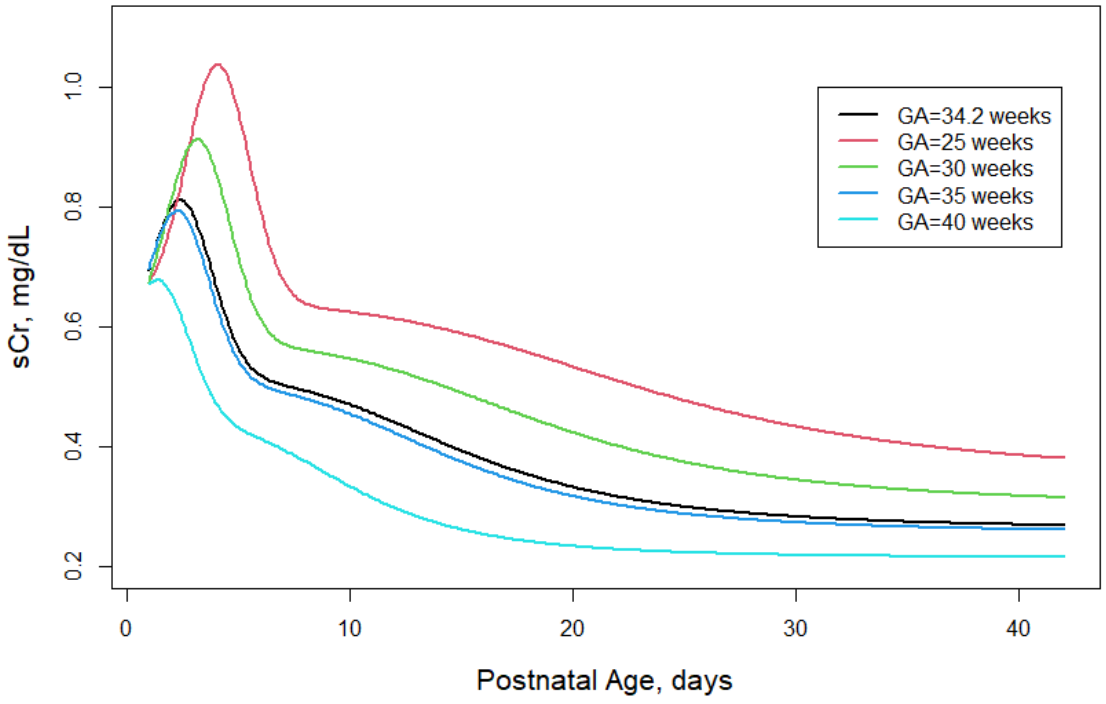

Serum Creatinine Conc., mg/dL
1.0
0.5
0.3
0
10
20
30
Postnatal Age, days

Figure 8


sCr, mg/dL
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
Postnatal Age, days
GA=34.2 weeks
GA=25 weeks
GA=30 weeks
GA=35 weeks
GA=40 weeks

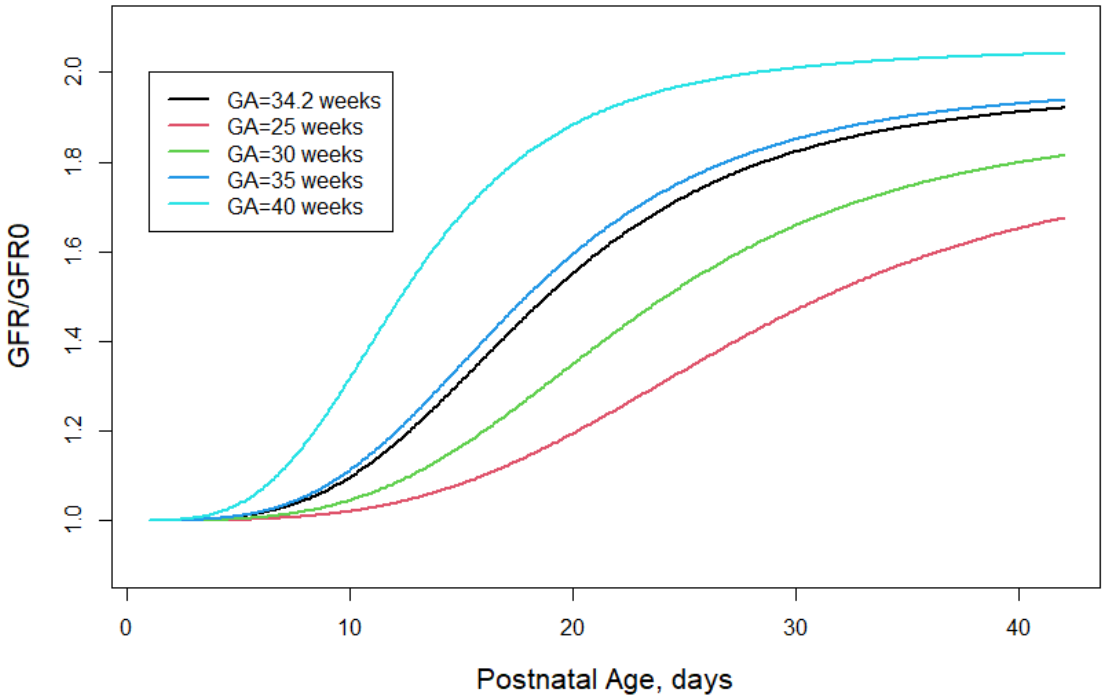

GFR/GFR0
1.0
1.2
1.4
1.6
1.8
2.0
0
10
20
30
40
Postnatal Age, days
GA=34.2 weeks
GA=25 weeks
GA=30 weeks
GA=35 weeks
GA=40 weeks

Figure 9

Supplementary Material

Population model of serum creatinine as time dependent covariate in neonates

Wojciech Krzyzanski, Anne Smits, John Van Den Anker, Karel Allegaert

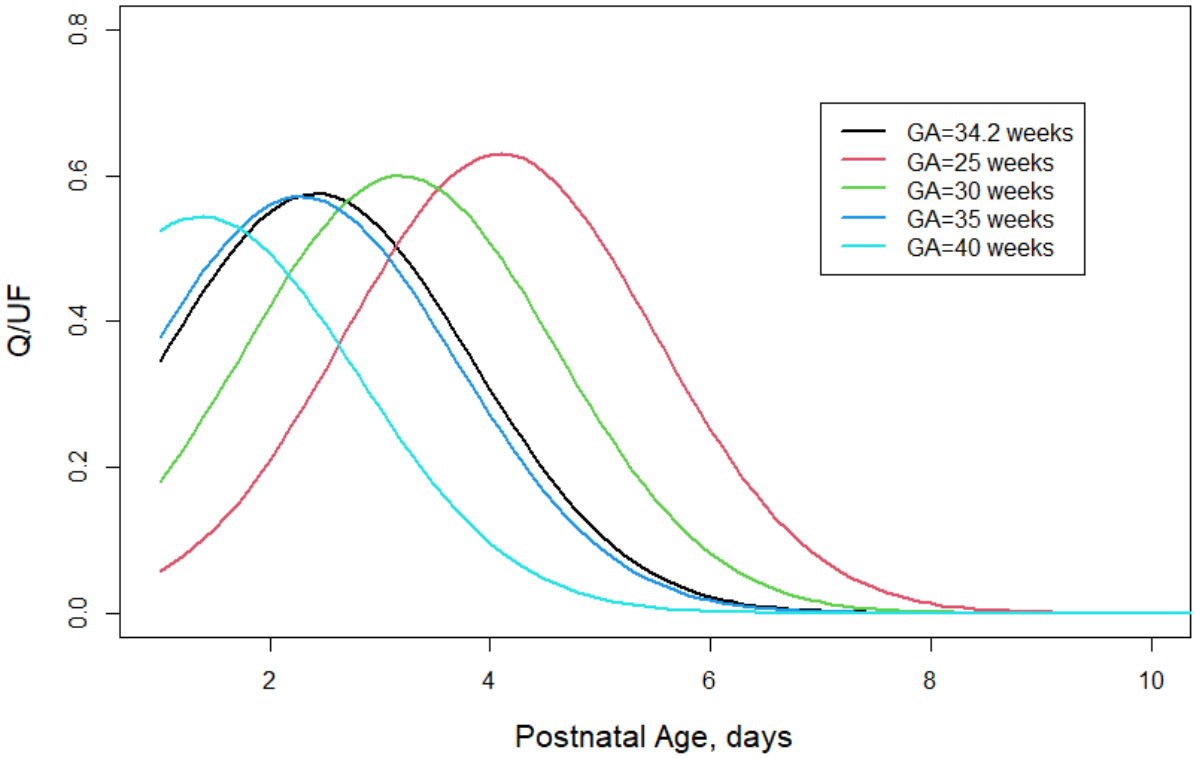


Fig. 1S. Simulated time courses of Q/UF for typical a patient of the indicated GA. Q is the back-flow and UF is the urinary flow. GA=34.2 weeks represents the population mean. The parameter values used for simulations are listed in Table 1.