Original Article

Predicting Neonatal Pharmacokinetics from Prior Data Using Population Pharmacokinetic Modeling†

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Abstract

Selection of the first dose for neonates in clinical trials is very challenging. The objective of this analysis was to assess if a population pharmacokinetic (PopPK) model developed with data from infants to adults is predictive of neonatal clearance, and to evaluate what age range of prior PK data are needed for informative modeling to predict neonate exposure. Two sources of pharmacokinetic data from 8 drugs were used to develop population models: i) data from all patients > 2 years of age, and ii) data from all non-neonatal patients aged >28 days. The prediction error based on the models using data from subjects > 2 years of age showed bias towards over prediction with median average fold error (AFE) for CLpredicted/CLobserved greater than 1.5. The bias for predicting neonatal PK was improved when using all prior PK data including infants as opposed to an assessment without infant PK data, with the median AFE 0.91. As an increased number of pediatric trials are conducted in neonates under FDASIA, dose selection should be based on the best estimates of neonatal pharmacokinetics and pharmacodynamics prior to the conduct of efficacy and safety studies in neonates.

Introduction

Conducting studies in the neonatal population during drug development remains a major challenge. Although approximately 200,000 neonates are admitted to a neonatal intensive care unit yearly as a result of prematurity, very few of the drugs that are used to treat neonates have been studied and approved for use in this pediatric population.[1] Drug development studies in sick newborns can be costly, risky, and have ethical or practical constraints.[2] Historically, few neonatal studies have been performed. Given these limitations, legislation was deemed necessary to include the neonatal population in drug development.

In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted in July, and renewed and made permanent the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). FDASIA also included several new provisions to stimulate pediatric drug development and to get pediatric information to providers and patients more quickly. The amendment specifically states that appropriate trials should be conducted for the neonatal population or justification should be provided for why this population is not included in the study. FDASIA states that the study reports for pediatric drugs or devices should include "the efforts made by the Secretary to increase the number of studies conducted in the neonatal population including efforts made to encourage the conduct of appropriate studies in neonates by companies with products that have sufficient safety and other information to make the conduct of the studies ethical and safe; and the results of such efforts".[3]

Another FDASIA section deals directly with the delay in pediatric drug development in comparison to the adult process. The delay in the submission of pediatric studies after a written request from the FDA can take as long as 8 years. FDASIA amends the Pediatric Study Plan (PSP) process so that the PSP must be submitted not later than 60 calendar days after the date of the end-of-Phase 2 meeting or such other time as may be agreed upon between the Secretary and the applicant. While speedier pediatric studies are a meaningful goal, having adequate information for safety and dose selection is critically important in the face of a 42% failure rate for efficacy trials in pediatric patients.[4] The specific reasons for the failed neonatal programs vary by product, and there are frequently multiple contributing factors. Issues with appropriate dose selection contribute to unsuccessful neonatal drug development programs.

Clinical pharmacology studies are pivotal for dose selection in pediatric drug development.[5] The developmental aspects of pharmacokinetics (PK) in neonates have been recognized for over 40 years.[6] Neonatal PK and pharmacodynamics (PD) studies often have a limited patient numbers in contrast to their extensive inter- and intra-subject variability.[7] Allometry is uncertain in neonates and infants since an additional role for organ functionality should be considered in the analysis. [8, 9] Given the potential limitations of studying the neonatal population, using a PK and PD modeling and simulation approach is important for dose selection and confirmation. A population PK (PopPK) approach has potential advantages in pediatrics in that it allows for use of sparse data, thus limiting blood sampling in individual patients. [10, 11]

During pediatric drug development, an age-staggered approach is often used, which is designed to adapt prior data from older pediatric patients and adults to inform the dose in younger patients in clinical trials.[12, 13] As such, PopPK models are developed based on the available data to predict the exposure and therefore inform the dose selection in a younger age group to be studied. The objective of this analysis was to determine the accuracy and precision of PopPK models in predicting drug clearance (CL) in neonates based on selected prior PK data.

Methods

Data Collection

The FDA website was searched for pediatric studies submitted between 2002 and 2013, and included (a) the pediatric labeling changes database,[14] and (b) medical, statistical, and clinical pharmacology reviews posted at Drugs@FDA to identify pediatric studies that included neonates. A prior review of drug labeling for neonates also provided a source of information.[15] A neonate was defined as <28 postnatal days of age per FDA guidance.[16] Drugs were included that had a pediatric labeling change approved by the FDA between 2002 and 2013, where clinical pharmacology information was available in the neonatal population and where the neonatal population was comprised of ≥ 5 neonates with at least 6 measured drug levels per neonate (Table 1). Additional information was collected including the indication for the drug, the number of neonates studied, all clinical PK studies, and the labeling pertaining to the neonatal clinical pharmacology studies.

Population PK Analysis

For each drug identified through the above procedure, a PopPK analysis was completed. The parameters in the population models were estimated using the NONMEM software program (Version 7.2, ICON Development Solutions, Ellicott City, MD). Interindividual variability in PK parameters was modeled as an exponentiation of random effects [$\exp(\eta_1)$] with residual variability modeled assuming a proportional and additive error model. The first-order conditional estimation method was used for estimation. The NONMEM objective function values and diagnostic plots were used to assess goodness of fit, to suggest covariates to add to the model, and to evaluate the model. The published FDA pharmacometric review for each drug provided the base model that described structural components (e.g. number of compartments). A standard forward selection and backward elimination procedure was used to evaluate the effects of subject covariates on PK parameters. The selection of baseline covariates was based on the statistical significance and clinical relevance. During forward selection, a covariate contributing at least a 3.84 unit change in the minimum value of the objective function (MVOF, α=0.05, one degree of freedom) and a decrease in IIV on the PK parameter of interest was considered statistically significant. During backward elimination, a covariate was considered significant if it contributed at least a 6.64 unit change in the MVOF (α=0.01, one degree of freedom) when removed from the model. Due to the proprietary nature of the specific drug information, this report will not focus on discussing specific modeling of particular drugs, as the raw data are not publically available.

Workflow

For each drug, two sources of time-concentration data were used to develop population models: i) data from all patients > 2 years of age including adults, ii) and data from all non-neonatal patients aged >28 days including adults. This allowed for an assessment of how the addition of infant PK data (>28 days to < 2 years) altered the prediction of neonatal clearance (CL). Using each final model, CL was predicted ($CL_{predicted}$) for every neonatal patient given their measured covariate values. The observed CL ($CL_{observed}$) value for each neonate was determined by non-compartmental analysis (NCA).

Scaling for size

The effect of body weight was modeled using two different scaling approaches as these are the most common methods used in pediatric pharmacokinetic modeling: i) power function with the exponent estimated based on the data (Model 1); and ii) allometric scaling to adults with a fixed exponent of 0.75 (Model 2).

$$F_{size} = \left(\frac{Weight}{Weight_{median}}\right)^{PWR} \quad \text{[Model 1]}$$

$$F_{size} = \left(\frac{Weight}{Weight_{std}}\right)^{0.75} \quad \text{[Model 2]}$$

PWR is an empirically derived scaling exponent, $Weight_{median}$ is the median body weight in the PK dataset used for population analyses. $Weight_{std}$ is the adult weight of 70 kg.

Scaling for age

The relationship between CL and age was explored using a sigmoid E_{max} model.

$$F_{age} = \frac{Age^{HillCL}}{Age^{HillCL} + MATCL_{50}^{HillCL}}$$

Age is postnatal age in days, weeks or years depending on the dataset, *HillCL* is the Hill coefficient for CL and $MATCL_{50}^{HillCL}$ is the age at which clearance is 50% of the typical CL value. For drugs that included infants who were born prematurely, postmenstrual age (PMA) was explored for age and/or a categorical covariate was explored (i.e. preterm vs. term). Preterm was defined as less than 37 weeks of gestational age.

Other covariates

In the case of Drug b, creatinine clearance (CrCL) was included in the final models based on our step-wise covariate analyses and was estimated using Counahan-Barratt method.[17] As a result, CrCL was explored as a covariate based on,

$$F_{CrCL} = \left(\frac{CrCL}{CrCL_{std}}\right)^{PWR}$$

PWR is estimated by the model and $CrCL_{std}$ is the adult CrCL of 80 ml/min.

Data Analysis

The bias and precision of clearance prediction were assessed through calculation of average fold error (AFE) and absolute average fold error (AAFE) [18] using the following:

$$AFE = 10^{\frac{1}{N}\sum \log(\frac{CL_{predicted}}{CL_{observed}})}$$

$$AAFE = 10^{\frac{1}{N}\sum |\log(\frac{CL_{predicted}}{CL_{observed}})|}$$

where *N* denotes number of neonates in the neonatal trial. An AFE greater than one suggests a bias towards over prediction and an AFE less than one suggests a bias towards under prediction. An AAFE equal to 1 suggests high precision. In addition, the percentage of drugs with predicted CL values within two-fold and 20% from the observed CL values was derived.

Simulation Check

To assess the a priori likelihood of the model deriving the observed neonatal CL values, the most globally accurate model was used to simulate the expected CL distribution in neonates.

Based on the distribution of age and weight from the neonatal patients, a selection of 1000 virtual neonates using Monte Carlo methods was created and clearances were predicted. The percentage of observed neonatal clearances from each of the eight drug trials was compared to the simulated 90th percentile.

TIBCO Spotfire S+® Version 8.1 (Palo Alto, CA) was used for graphic analyses. WinNonLin® *Version* 6.0 (Pharsight Corporation, USA) was used for non-compartmental analyses.

Results

A total of 301 drugs had pediatric review summaries or full reviews posted on the FDA website from 2002 to 2013. Among a total of 446 pediatric labeling changes during this time period, only 26 included neonatal labeling (Figure 1). Thirty-three drugs had studies that included neonates, and fifteen studies conducted PopPK analyses (Figure 1). In these PK studies, the number of neonatal subjects varied from 1 to 46. There were eight drugs that met the pre-specified criteria for further analysis. In these studies, the number of neonates ranged from 10 to 46 (median: 16) with a total number of PK samples ranging from 49 to 198 (median: 156). For comparative studies in infants, the

number of infants ranged from 9 to 331 (median: 25) with a total number of PK samples ranging from 59 to 690 (median: 30). All eight drugs were small molecules, administered intravenously or orally with various elimination pathways (Table 2).

Table 3 presents the neonatal CL predictive performance based on two models (Model 1 vs. Model 2) using prior data. The final models are presented in Supplemental Table 1. PMA was a significant covariate in a number of cases whereas the categorical covariate of preterm vs. term was never significant (Supplemental Table 1). The evaluation of each model was done using standard techniques as listed above. No major deviations were identified in the age groups for which the models were developed.

Predicting neonate clearance using data from subjects >2 years

The prediction error based on the models using data from subjects > 2 years of age are presented in Figure 2 (individual data) and Figure 3 (pooled data). Regardless of the model used, there was bias towards over prediction (7 of 8 drugs; Figure 3) with median AFE values greater than 1 (Model 1: 1.62; Model 2: 1.95). The precision of the CL prediction for the 8 drugs in neonates was better using Model 1 as compared to Model 2 although the median AAFE was high for both models (Model 1: 1.72; Model 2: 2.00) (Table 3).

Predicting neonate clearance using data from subjects > 28 days

The prediction error based on the models using data from subjects > 28 days of age is presented in Figure 2 (individual data) and in Figure 3 (pooled data). With Model 1, there was a low median bias (4 of 8 drugs – Figure 3) with AFE values ranging between 0.31-1.98 (median: 0.91). The precision of the CL prediction for the 8 drugs in neonates ranged from 1.15-3.20 (median 1.69) (Table 3).

When using the fixed scaling exponent of 0.75 for body weight (Model 2), there was bias toward under prediction (5 of 8 drugs; Figure 3) with AFE values ranging between 0.20-2.29 (median: 0.76). The precision of the CL prediction for the 8 drugs in neonates ranged from 1.38-4.9 (median 1.75) (Table 3).

Preterm vs. term neonates

Among the eight drugs, there were four studies that included PK sampling in preterm neonates. The difference in prediction accuracy between preterm versus term neonates was explored (Figure 4). With the exception of Drug d, where preterm neonates had a greater AFE than term neonates, the differences in AFE between preterm vs. term neonates were relatively small (Figure 4).

Simulations

Simulations were conducted with the final models developed under Model 1 using data from all individuals >28 days of age (least globally bias and most globally precise method). If the model is predictive of neonatal clearance and clearance variability, the expectation is that 90% of the observed neonate clearances will fall within the simulated 90th percentile. Only 2 of the 8 models had >90% of the observed values within the 90th percentile (Drug f and Drug g – Table 4) although these showed 100% of observed values within the 90th percentile. This finding suggests that the variability in the model was over predicted. For the remaining drugs, there was a trend towards over or under prediction as previously demonstrated in Figure 3.

Discussion

Challenges in the design and conduct of clinical trials in neonates as well as ethical constraints have resulted in the neonatal population being excluded from many drug development programs. Conditions such as primary pulmonary hypertension of the newborn, hypoxic-ischemic encephalopathy, intraventricular hemorrhage, respiratory distress syndrome, and necrotizing enterocolitis are major conditions encountered in the neonatal population. Unfortunately, drug development studies are lacking for drugs used to treat these conditions in neonates. Up to 90% of drugs administered to neonates are used off-label.[19] A recent review demonstrated that only 35% of the most commonly used medications in the neonatal intensive care unit are approved for use by the U.S. Food and Drug Administrations for infants. [20]

The enactment of FDASIA has guaranteed that the neonatal population will be considered during drug development and the FDA review process. Whether FDASIA leads to more neonatal studies is uncertain at present. However, drugs that can be studied in neonates should be studied as expediently as possible. Safety and drug dosing studies are essential for the successful development of a drug for neonatal use. Since simple allometric scaling is not appropriate for determining doses

in neonates, then relying on the prior experience with PK in other populations is the common method of determining first-in-neonate dosing.

Clinical pharmacology studies in neonates are needed to provide the effective and optimal dose regimen in this vulnerable population. However, many pediatric clinical trials have difficulty recruiting neonates and infants, and previous trials often had to be terminated or deferred. In addition, PK/PD sampling in neonates is adversely impacted by limited blood sampling, incorrect timing of sampling and lack of availability of sensitive drug concentration assays for small volume specimens.[15] Therefore PopPK has become the favored approach to obtaining PK information in neonates, and numerous examples have been published.[21-24] There are important study design considerations for a PopPK study in pediatric patients [25], and neonatal sample size varied considerably in our review of PopPK studies in drug development.

In pediatric drug development, an age-staggered approach is used to guide the dose selection in younger patients based on the information available from adults and older pediatric patients. For example, initially a pediatric dose in an older age group (6– 17 years) can be defined by allometric scaling based on the adult dose. Following the availability of PK data in the 6–17 age group, modeling and simulation can be used to describe exposure as a function of age and body size and to propose dose recommendations for subsequent younger age groups.[26] The PK model can then be updated as PK data from each group becomes available. To assess the accuracy of the PopPK models that include older age cohorts for the prediction of CL in neonates, we used two sets of prior information. The first was adults plus children over the age of two years, and the second was adults plus children over the age of 28 days. Two models were employed with Model 1 using an estimated power function and Model 2 employing the 0.75 power function that is commonly used to account for size. Estimation of the power function (Model 1) using data from all cohorts (>28 days) appeared to produce results with the lowest bias and highest precision (Table 3). While the inclusion of infant data greatly reduced the median bias for both Model 1 and Model 2, the magnitude of the range of fold errors was similar regardless of the prior data used for model building. The use of data >2years generally led to over prediction of CL in neonates. However the use of data >28 days led to an equal probability of over vs under prediction to a similar magnitude as not using infant data. The precision of the CL estimates were generally low regardless of the method used (Table 3), but the use of infant data using Model 1 appeared to produce slightly more precise neonatal CL estimates.

In our analysis, we used the age cut-off value from the current FDA draft guidance for pediatric pharmacokinetic studies. It should be noted that in pediatric drug development, other cut-offs, such as >1 year of age, might be used during an age-staggered enrollment. However, our study demonstrated a large inter-patient and inter-drug variability in prediticion even using data above > 1 month, indicating a significant challenge to using these approaches for predicting neonatal clearance.

While the fold error calculations were used to assess bias and precision of observed CL values, the probability of the model to estimate those observed CL values was assessed through simulation. Clinical trial simulation relies on the estimates of variability from a model to derive estimates of the expected variability in a future sample population. Using the most precise and least biased method (Model 1 with all age cohorts), 4 of the 8 drugs have at least 80% of the observed values within the predicted 90th percentile. However, the remaining 4 had either the majority of observed CLs under predicted (2/8) or over predicted (2/8). In summary, there is limited confidence that the most precise and least biased method of predicting neonatal CL will produce reliable results.

An alternative approach for determining doses in neonates in clinical trials that could be performed without knowledge of PK in the infant population would be to use physiologically-based PK (PBPK) modeling and simulation. Extrapolation to a younger age group from a PBPK model developed in adults requires alteration of the organism specific inputs while assuming that the drug specific inputs are age independent. As a result, growth (e.g. organ size) and maturation (e.g. enzyme concentration/gram organ) are inherently accounted for within the model and are not driven by PK data as in PopPK models. Development of pediatric PBPK models is discussed in detail in Maharaj and Edginton.[27] One recent study used a PBPK model in newborn and adult animals to move to adult and newborn humans successfully for an antiviral agent.[28] This study developed a PBPK model for oseltamivir in monkeys, and adapted that model to adult humans and neonates. A number of refinements to the model were necessary to adequately characterize the observed concentrations of oseltamivir and its carboxylate metabolite. More recently, a PBPK model for acetaminophen was developed that was able to retrospectively predict clinical PK data in neonates[29], and another for rivaroxaban was used prospectively to plan pediatric clinical trials.[30]

One potential limitation in our analyses is that there are only 8 dugs with sufficient pre-specified neonate PK data from our databases. As a result, the final model includes body size, age and CRCL as covariates, but other potential covariates, such as genetic variants, could not be evaluated in our analyses. Another limitation is that the premature neonatal data are very limited. Therefore, further analyses on premature neonates are warranted when more data are available. While this discussion has focused on PK assessment in neonates, drug development in neonates must consider the PD effect and the exposure-response relationship. For example, neonates were found to have a higher sensitivity to QTc interval prolongation compared with older patients when treated with sotalol.[31] Integration of the dose-exposure and the exposure-response relationship to derive neonatal doses is desirable.

In conclusion, an assessment of PopPK studies in neonates submitted to the U.S. FDA demonstrated considerable variability in the numbers of patients and samples that were used in the assessment. When re-evaluating the Pop-PK models for the drugs that had sufficient data available, the bias of neonatal PK predictions was improved when using all prior PK data. However, the precision did not greatly improve. As a result, there is limited confidence in the extrapolation of PopPK modeling for the purposes of neonatal PK prediction, which is also supported by large inter-drug variability in relation to prediction accuracy. As an increased number of clinical trials may be conducted in neonates under FDASIA, dose selection should be based on the best estimates of PK and PD in neonates prior to the conduct of efficacy and safety studies in this pediatric patient population. Further studies are warranted for better predicting neonatal pharmacokinetics to inform appropriate dose selection.

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Figure Legends

Figure 1. (A) Neonatal labeling changes and (B) Population pharmacokinetic (PopPK) studies that included neonates under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act during 2002-2013. PK=pharmacokinetic; PD=pharmacodynamic

Figure 2. Predictive performance of clearance in neonates using population pharmacokinetic models. The left (A and C) plots represent the results when using maturation function and scaling with the exponent estimated from prior data, and the right (B and D) plots represent the results when using maturation function and scaling with the fixed exponent 0.75. The upper (A and B) panels represent the prediction with data from >28 days of age. The lower (C and D) panels represent the prediction with data from >2 years of age. The colors represent the eight different drugs (titled a – h). The circles represent term neonates and the triangles represent preterm neonates.

Figure 3. Prediction accuracy for clearance (CL) in neonates using a population pharmacokinetic model estimate using prior data from subjects >28 days of age (upper panels, A and B) or using subjects >2 years of age (lower panels, C and D). The effects of body weight on CL were modeled using two different approaches: (i): power function with the exponent estimated based on the data (A and C); or (ii) allometric scaling to adults with fixed exponent of 0.75 (B and D). The dotted lines represent 0.5 and 2-fold for the ratio of model predicted neonatal clearance relative to the observed value.

Figure 4**.** Prediction accuracy for clearance (CL) in preterm and term neonates using a population pharmacokinetic estimate using prior data from subjects >28 days of age. The effects of body weight on CL were modeled in two different approaches: (A): power function with the exponent estimated based on the data (Model 1); (B) allometric scaling to adults with a fixed exponent 0.75 (Model 2). The dotted lines represent 0.5 and 2 fold difference of predicted clearance relative to the observed value. Open circles represent the average fold error (AFE) value in term neonates and closed circles represent preterm neonates. The lines represent 95% geometric confidence intervals. Each pair of predictions is from four different drugs.

Table 1. Pharmacokinetic samples collected for the population analyses

Drug	Neonates		Infants		Children		Adolescents		Adults	
	N*	Samples	N	Samples	N	Samples	N	Samples	N	Samples
a	46	163	32	338	25	407	22	352	0	0
b	10	67	33	196	51	338	11	80	26	910
c	20	187	18	288	32	455	27	297	0	0
d	30	148	51	249	81	427	11	90	1	9
e	13	53	120	655	48	424	21	241	0	0
f	16	49	331	690	143	344	21	285	122	3124
g	14	198	9	167	29	506	41	793	53	985
h	15	182	9	322	40	345	39	361	0	0

* number of individuals

Table 2. Routes of administration and elimination pathways for modeled drugs

Drugs	Route of Administration	Major Elimination Pathways
a	IV	Primarily metabolized in liver by multiple pathways; <5% renal elimination
b	IV	Primarily renal elimination
c	Oral	Primarily renal elimination
d	IV	Primarily metabolized in liver (65%) by unknown pathways, with a minimal contribution by CYP3A4; renal elimination (35%)
e	Oral	Primarily metabolized by CYP2C19 and some CYP3A4; 18% found in feces
f	Oral	Almost exclusively metabolized in liver via non-enzymatic reduction with some CYP3A and CYP2C19 metabolism
g	IV	Primarily hepatic elimination
h	Oral	Primarily renal elimination

Table 3. Predictive performance of the neonatal clearance using two models with different prior data

	Model 1 > 28 days	Model 2 > 28 days	Model 1 > 2 yrs	Model 2 > 2 yrs
Median AFE [range]	0.91 [0.31 - 1.98]	0.76 [0.2 – 2.29]	1.62 [0.66 -5.19]	1.95 [0.54 - 4.94]
AFE within 0.5-2 (%)*	74.3	79.3	66.8	59.1
AFE within 0.8-1.25 (%)	23.2	13.6	17.1	8.33
Median AAFE [range]	1.69 [1.15 – 3.20]	1.75 [1.38 - 4.9]	1.72 [1.18 – 5.19]	2.00 [1.64 - 4.94]

*Percentage of neonates with a fold error (FE) between 0.5 and 2, indicating a 2 fold difference from the observed CL

Table 4. Percentage of neonates in the trial with observed CL inside or outside the simulated 90th percentile of clearances by simulations using the PopPK model Scenario 1 (Model 1 with > 28 days data) with percentage of overpredicted or underpredicted clearances.

Drug	Number of neonates in trial	% within simulated 90th percentile	% below 5th percentile (over predicted)	% above 95th percentile (under predicted)
a	46	80	20	0
b	10	20	0	80
c	20	80	0	20
d	30	37	63	0
e	13	60	0	40
f	16	100	0	0
g	14	100	0	0
h	15	27	9	64

Figure 1

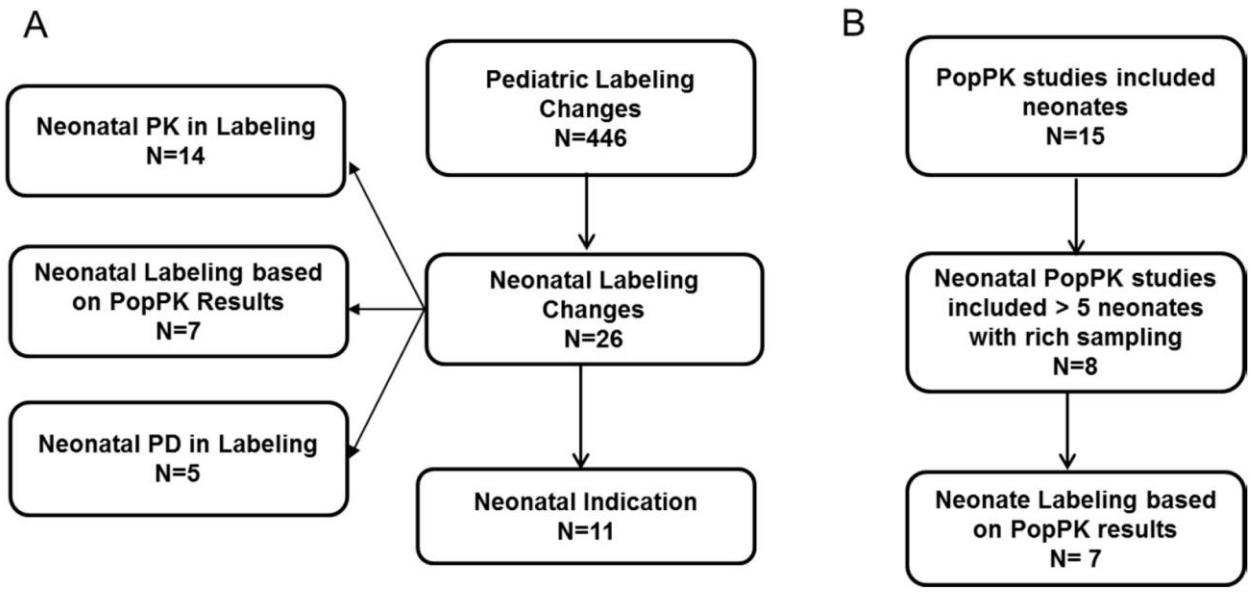

Figure 2

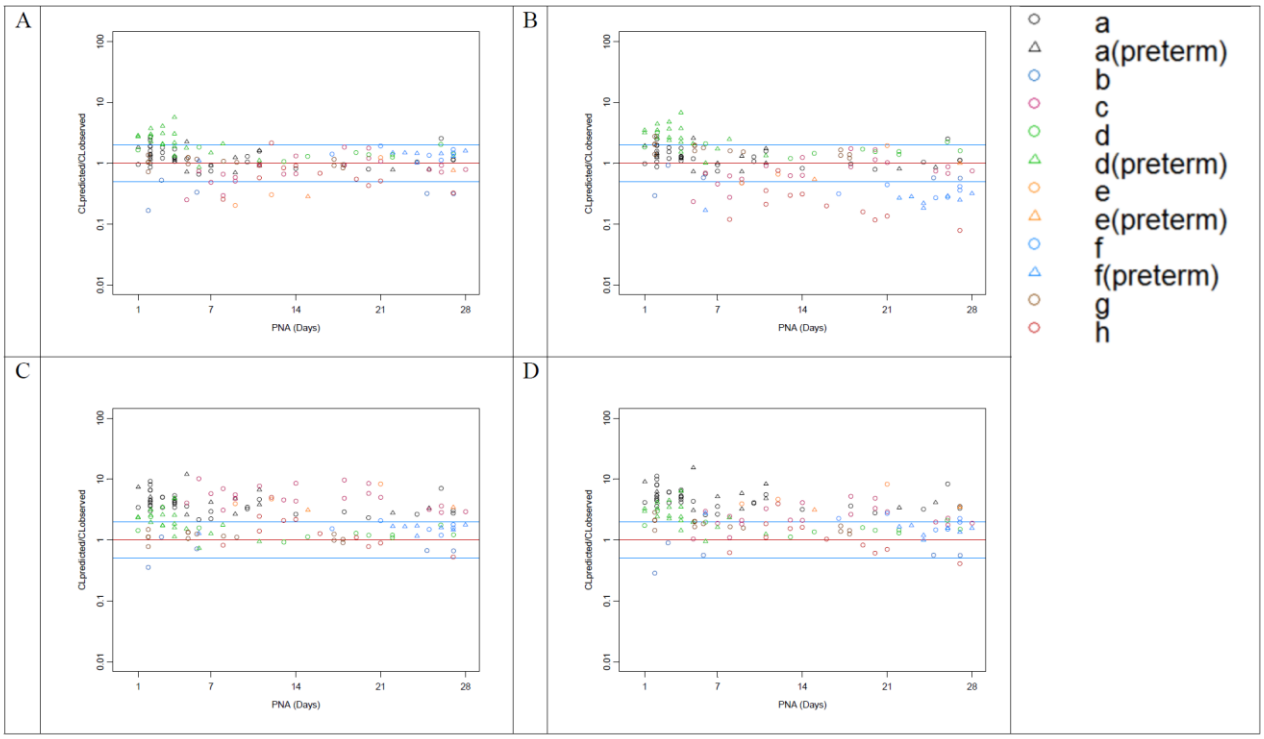

Figure 3

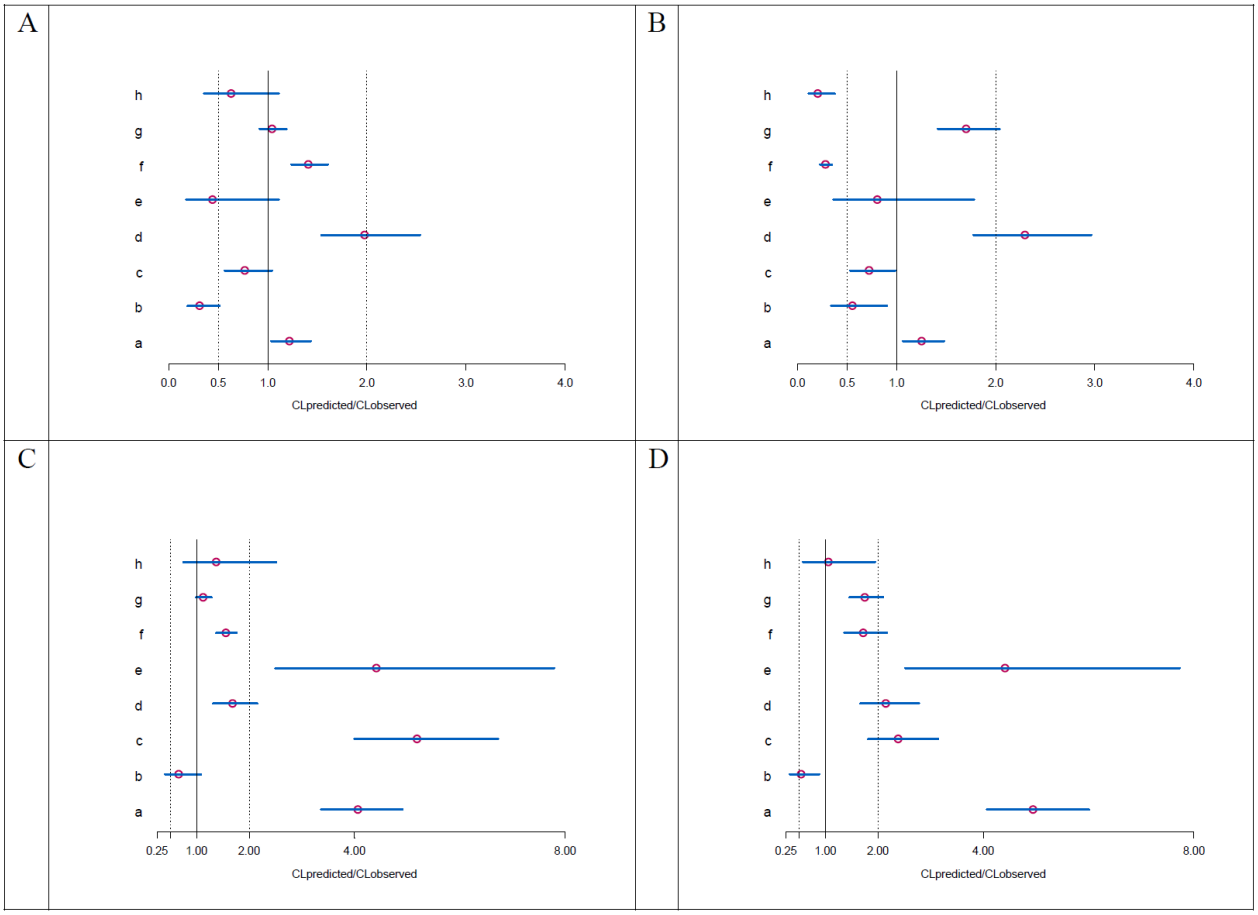

Figure 4