

Modelling of urea clearance in pediatric and young adult patients on chronic hemodialysis

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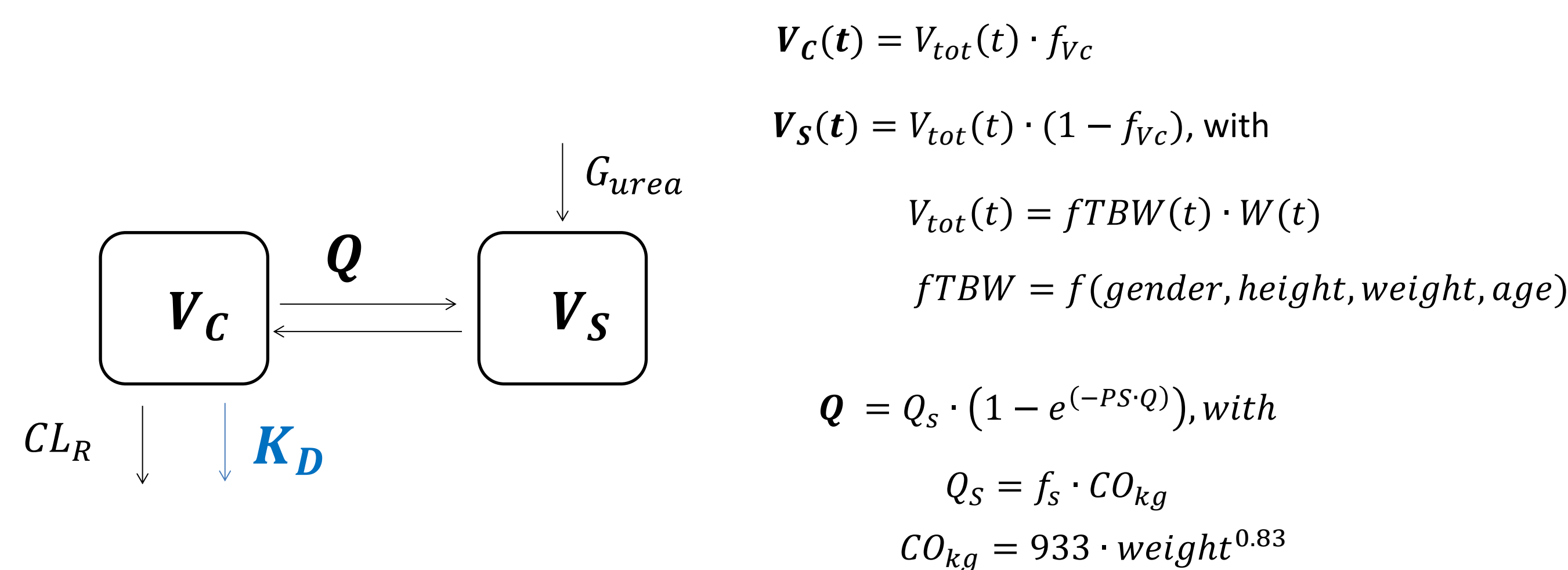
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Introduction

- **Urea dialytic clearance (K_D)** can be predicted with a mechanistic equation in adult patients on chronic hemodialysis[1,2], from prescribed:
 - blood flow (Q_B)
 - dialytic flow (Q_D) and
 - *in vitro* mass-transfer coefficient for urea of the filter (KoA) (Eq. 1)
- It has been suggested that eq. 1 underpredicts K_D in pediatric hemodialysis patients[3], most likely due to different Q_B and Q_D prescribed than in adults, leading to greater difference (bias) between *in vitro* determined and *in vivo* observed KoA in pediatric patients.

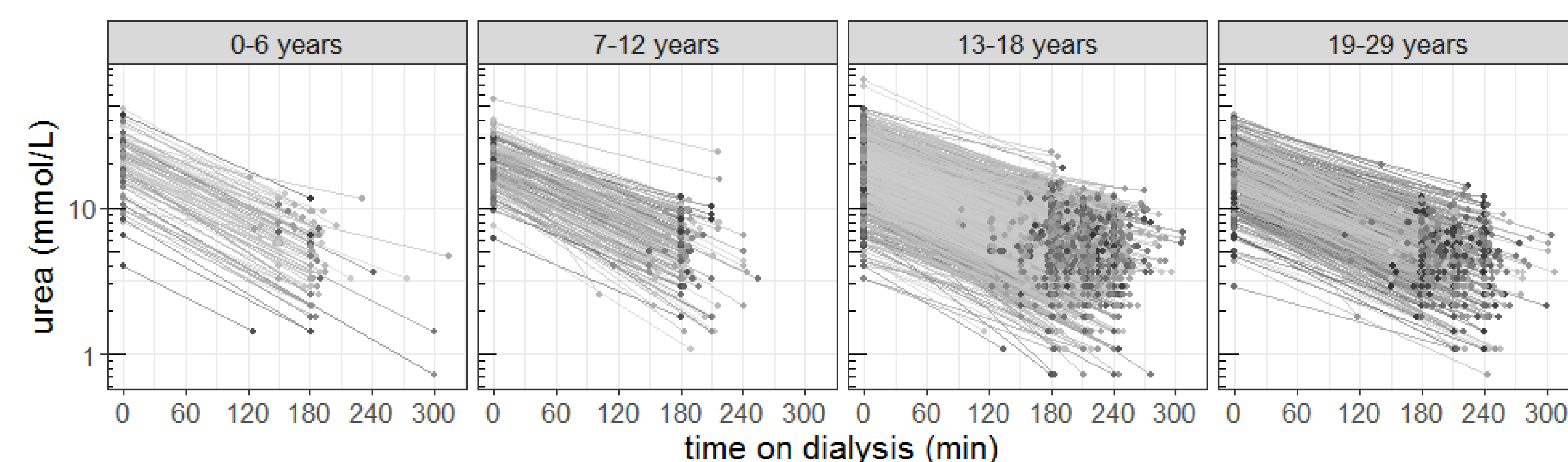
Methods

1. A two-compartment urea kinetic model previously developed in adults [2] was scaled based on physiologic understanding of kinetic parameters to pediatric patients, with between-subject variability (BSV) assigned to KoA.



Structural two-compartment urea kinetic model (left) and scaling approach (right). K_D , urea dialytic clearance (see. eq. 1). V_C/V_S central and slowly equilibrating peripheral distribution volumes. $V_{tot}(t)$: total distribution volume (decreasing with ultrafiltration over time t), assumed to equal the product of fraction of total body water (fTBW) and weight (W). fTBW is a function of gender, height, weight and age [6]. Q : inter-compartmental clearance, scaled using weight-specific cardiac output (CO_{kg}) [7,8]. f_S : fraction of flow to slowly perfused tissues, PS: capillary permeability-coefficient surface area product for urea. G_{urea} : urea generation rate from protein catabolism, calculated from pre- and post urea concentration samples. CL_R : residual urea clearance.

2. The model was fitted using NONMEM (FOCE with interaction) to a dataset comprising pre- and post urea concentration samples of 923 pediatric and young adult patients aged 1-29 years (2676 HD sessions in total, with a maximum of 3 hemodialysis sessions (occasions) per patient):



3. Stepwise covariate model building was used to evaluate the association and relationship of prescription parameters with individual *in vivo* KoA estimates. Nested models were compared by the likelihood ratio test, based on the decrease in objective function value (ΔOFV , $\alpha=0.05$). The mean relative prediction error (MrPE) in post-HD urea concentrations was further calculated with 95% confidence intervals to assess the bias in population predictions for age groups 1-6, 7-12, 12-18, and 19-29 years.

References

- [1] Michaels et al. *Trans Am Soc Artif Intern Organs* 1966
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- [3] Gotta et al. (submitted)
- [4] Depner et al. *ASAIO* 2004
- [5] Leyppelt et al. *ASAIO* 2006
- [6] Cheek et al. *Am. J. Dis. Child* 1966
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- [8] Odeh et al. *Clin. Pharmacol. Ther.* 1993

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Objective

- To further improve the prediction of *in vivo* KoA and thus K_D in children on chronic hemodialysis

$$K_D = Q_B \cdot \frac{e^{(z-1)}}{\left(e^z - \frac{Q_B}{Q_D}\right)}, \text{ with } z = \frac{KoA_{in vivo}}{Q_D} \cdot \left(1 - \frac{Q_B}{Q_D}\right)$$

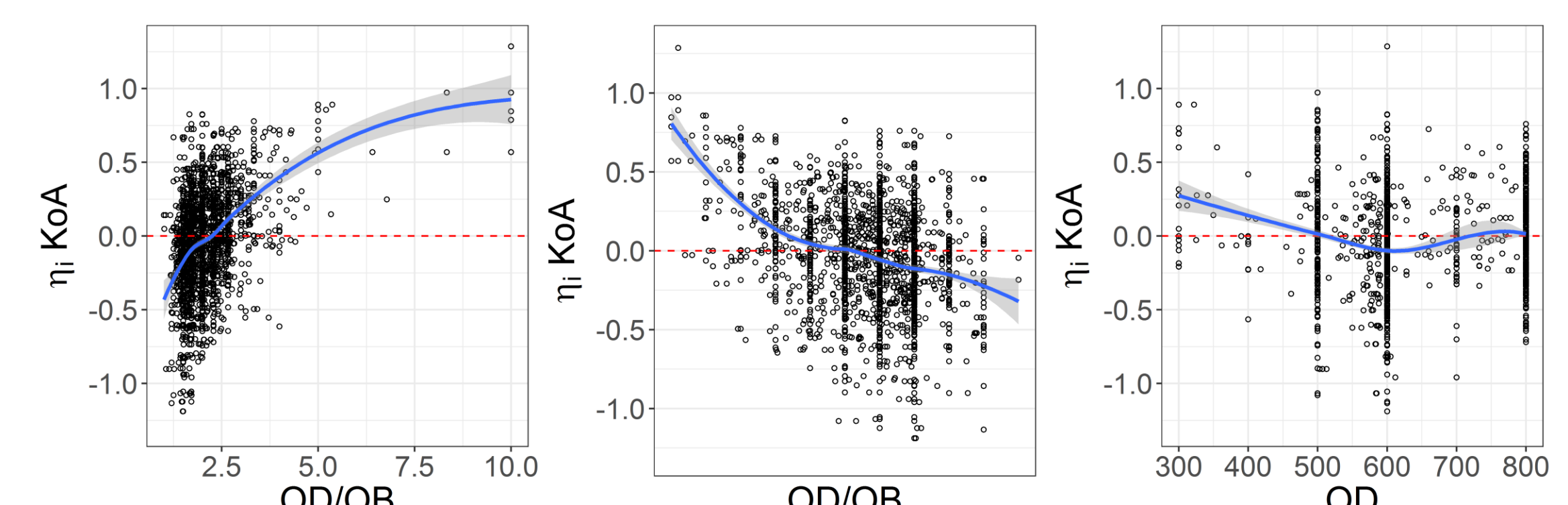
$$KoA_{in vivo} = KoA_{in vitro} \cdot f_{c,KoA}$$

Equation 1. Mechanistic prediction of urea dialytic clearance, K_D (counter-current blood and dialysate flow, Q_B and Q_D), based on *in vitro* determined filter mass-transfer coefficient for urea (KoA) [1]. Bias between reported *in vitro* KoA of the filter and individual estimated *in vivo* KoA was modeled in this work as a fraction ($f_{c,KoA}$).

Results

Scaled baseline model

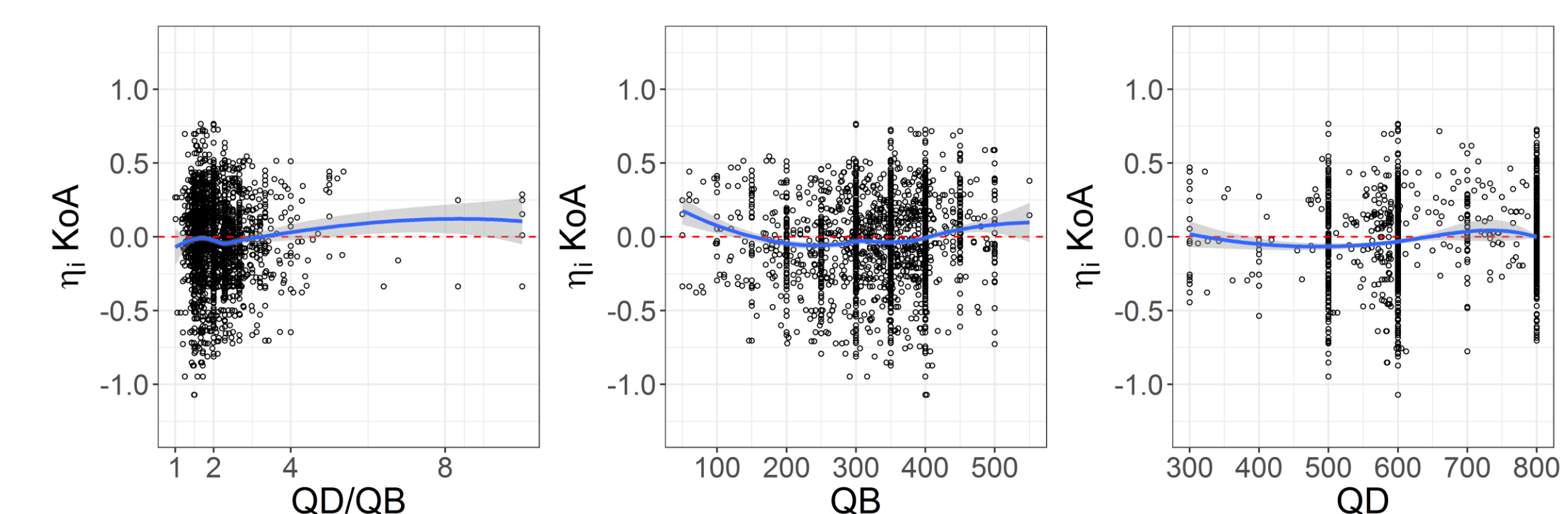
- Q_D/Q_B ratio was the parameter most strongly associated with a bias between reported *in vitro* KoA of the filter and individual estimated *in vivo* KoA (ΔOFV : -359)



Distribution of individual random effects (baseline model) versus main considered covariates QB: blood flow, QD: dialysate flow. QD/QB ratio.

Covariate model

- Inclusion of Q_D/Q_B ratio as a covariate removed bias observed with Q_B and Q_D , and reduced the MrPE in post-HD concentrations largely in children (decrease from 58% (35-81%) to 6% (-9-22%) in children 1-6 years).
- Inclusion of session duration, low-flux vs high-flux filter use, and ultra-filtration rate could further improve the model fit.



Distribution of individual random effects (covariate model) versus main considered covariates QB: blood flow, QD: dialysate flow. QD/QB ratio.

Conclusions

- Blood to dialysate flow rates (Q_D/Q_B) are higher in pediatric patients than in adults, and are associated with higher *in vivo* efficiency of filters than predicted from *in vitro* KoA, especially in infants and children <6y, where highest Q_D/Q_B ratios are used → Improved knowledge is needed to improve safety of HD therapy in children when over or underdialysis needs to be avoided.
- Our developed model can help to predict urea dialytic clearance from prescription parameters in pediatric patients, and may also help to predict drug clearance in pediatric hemodialysis patients.