Personalizing hemodialysis (HD) treatment in pediatric patients with end-stage renal disease (ESRD) – *application and integration of quantitative pharmacology with machine learning*

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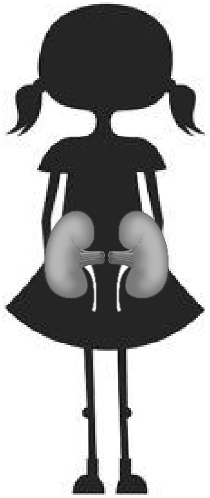
PAGE Meeting, Sep 6, 2021

Clinical Applications – Integrating Machine Learning and Quantitative Pharmacology

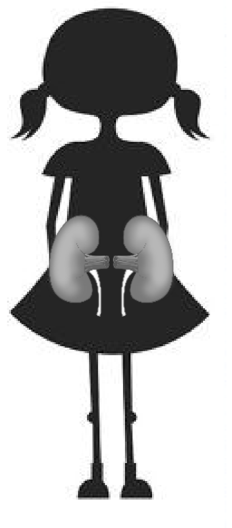
Pediatric Endstage Renal Disease (ESRD)

- Mortality ≥30x ↑ compared to healthy children
- Rare condition



Hemodialysis (HD)

=Mode of initial renal replacement therapy in ~ 50% of patients



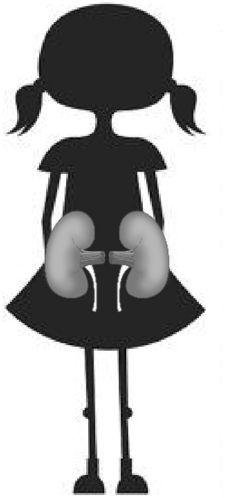
Hemodialysis (HD)

=Mode of initial renal replacement therapy in ~ 50% of patients

Adult targets:

– Urea dialyzer clearance (**K_D**): Weight-normalized **K**t/V ≥ 1.4

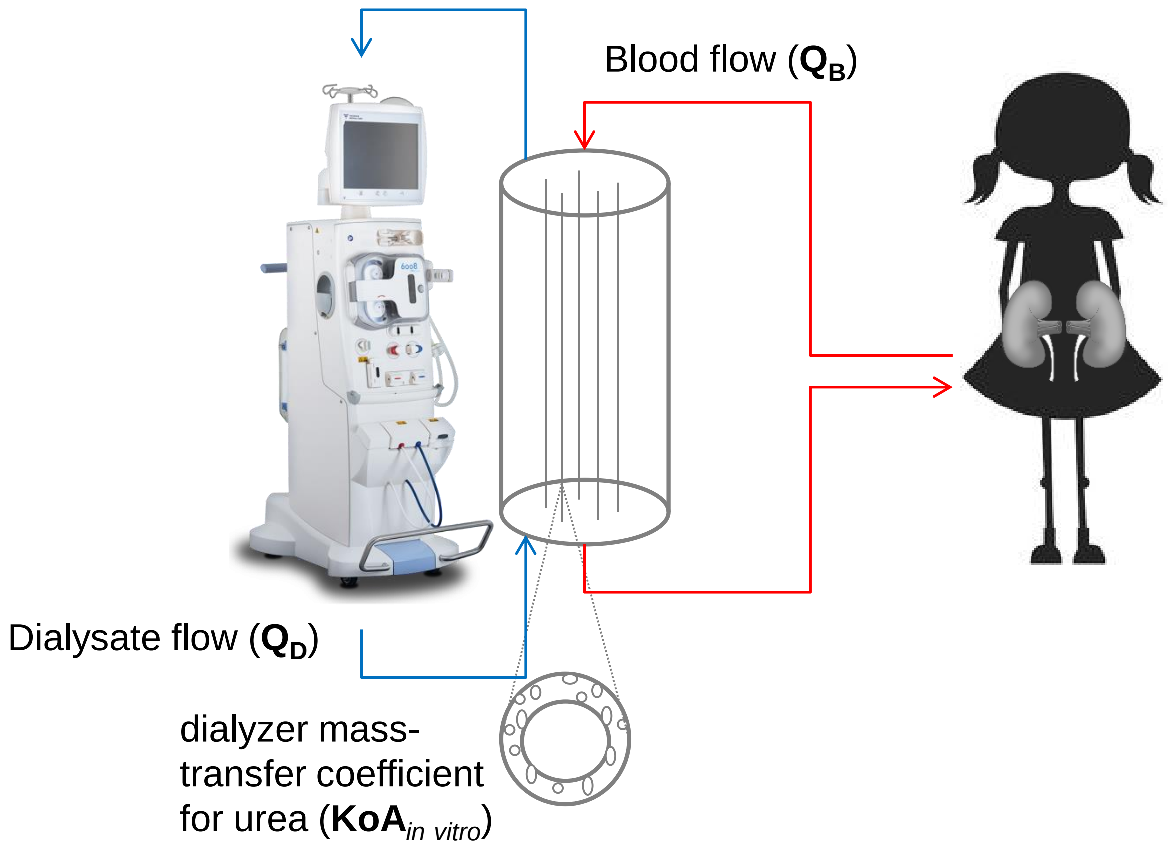
– Fluid removal rate: < 10-12 ml/kg/h (Ultrafiltration, **UFR)**



Urea dialyzer clearance K_D

mechanistic prediction (mass balance) – needs in vivo correction

$\mathbf{K_D} = f(Q_D, Q_B, \boldsymbol{KoA}_{\boldsymbol{in\ vitro}})$[1]



[1]Michaels *Am Soc Artif Intern Organs* 1966

HD corrects only part of ESRD problems…

Other disease-related problems require additional intervention strategies

– Uremia

– Fluid overload

– Anemia

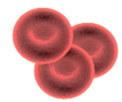
– Cardiovascular disease

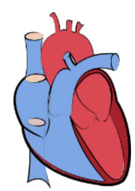
– Hypertension

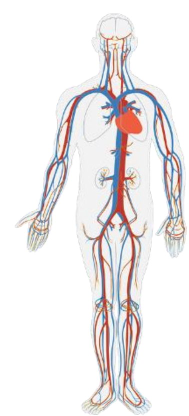
– Mineral and bone disorder

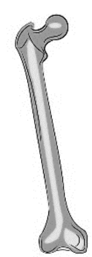
– Malnutrition

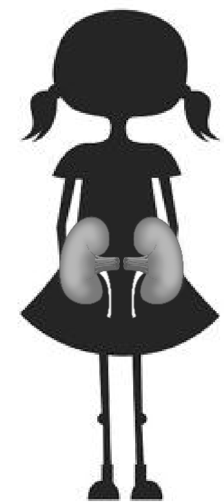
– …











Aim: To develop scientific evidence for personalized HD treatment *in children*

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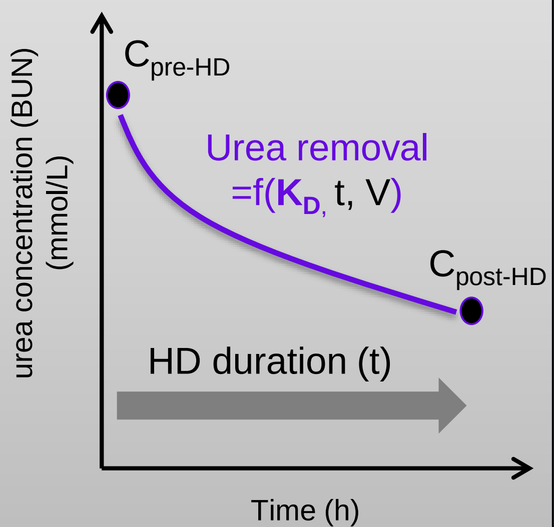
Predict *in vivo* urea dialyzer clearance (K_D)



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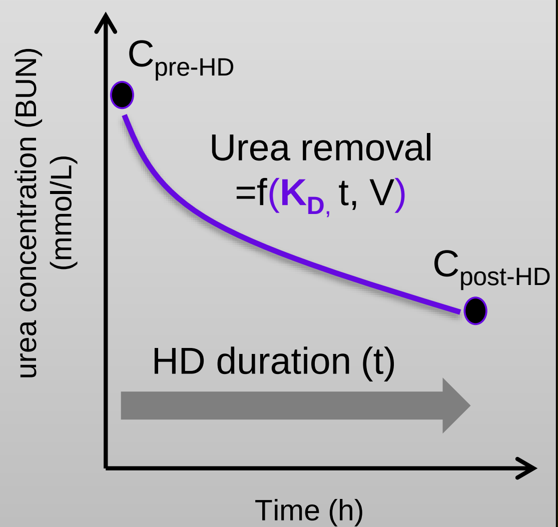
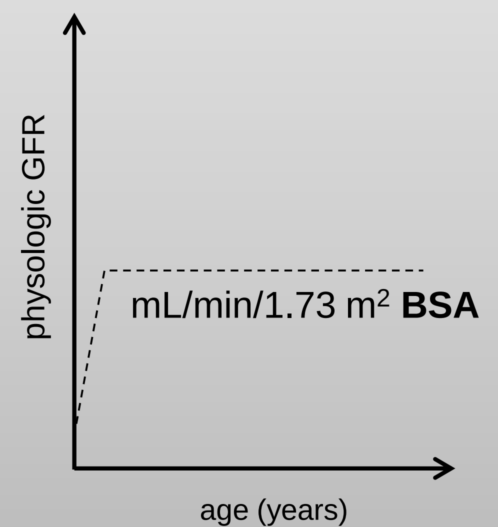


Best HD dose (Kt/V) and scaling (Kt/BSA)?



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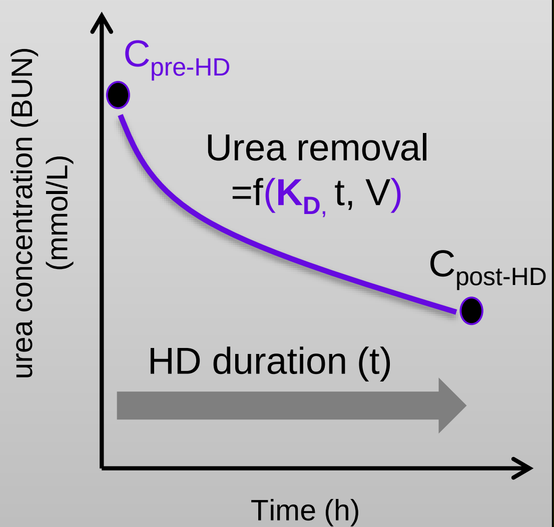

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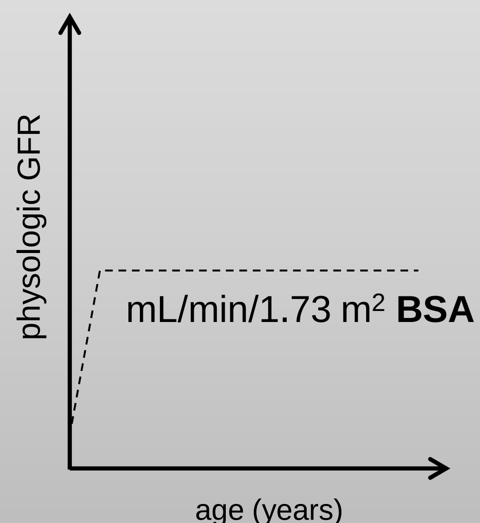
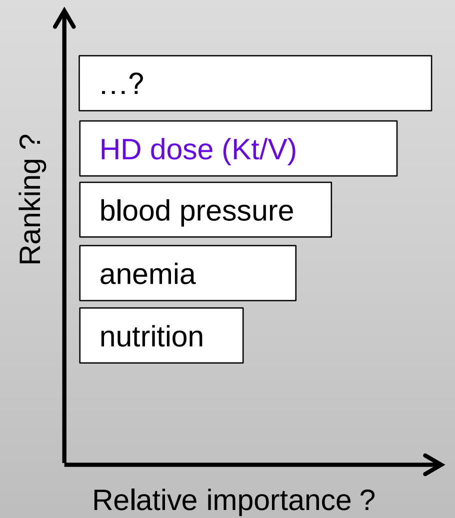


Importance of HD dose (Kt/V) compared to other factors?



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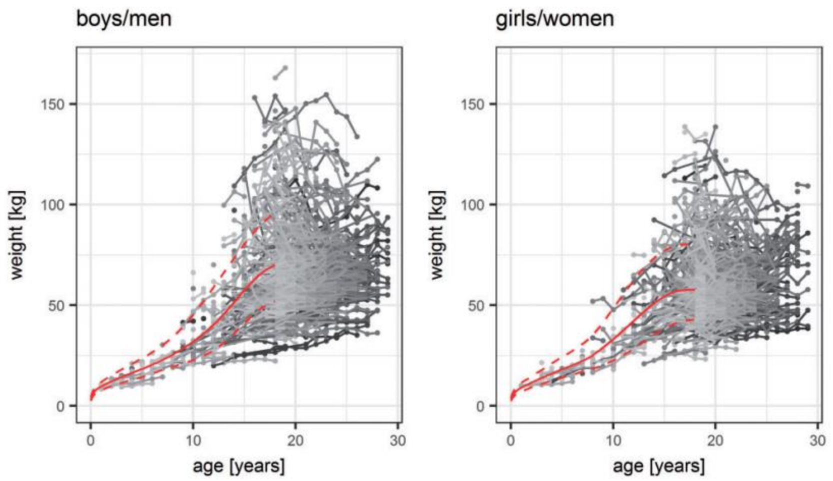
Data used for retrospective analysis

Cohort of 1852 patients

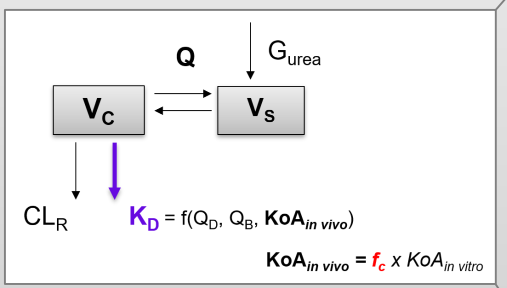
- ✓ on chronic HD since childhood (<19 years)
- ✓ HD 3x/week
- ✓ <30 years (2004-2016)



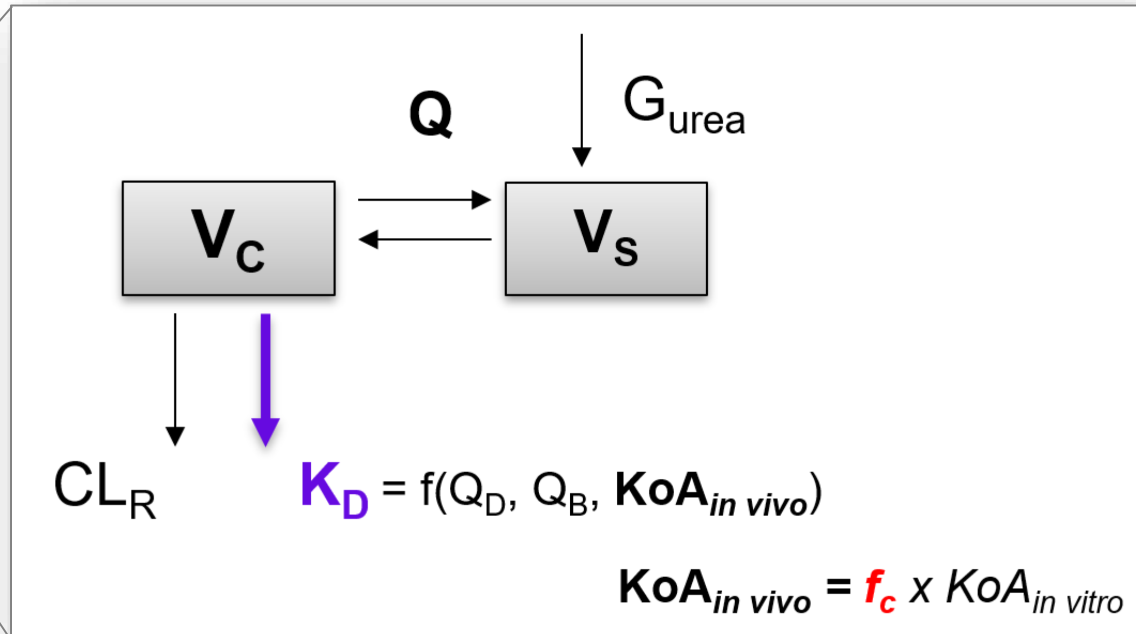
Gotta et al. *Nephrol Dial Transplant* 2018
Gotta et al. *Hemodialysis International* 2019

Methods

Pharmacometic (PMX) modeling of K_D



- Physiologic scaling of distribution parameters (perfusion-limited)
- Mechanistic K_D prediction from $\mathbf{KoA}_{in\ vitro}$
- Covariate analysis: factors associated with *in vivo* correction factor f_c



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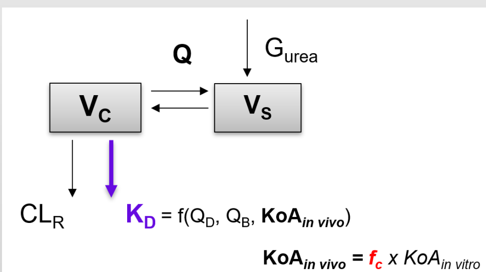

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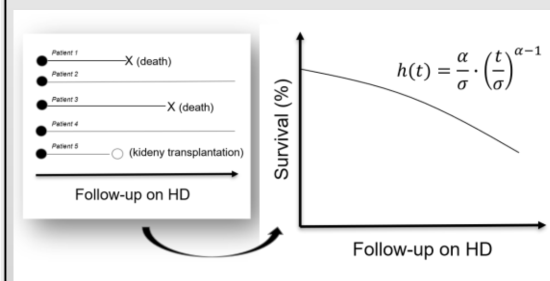
Parametric time to event (TTE) survival modeling



- Weibull accelarated failure time (AFT) model
- mean **K**t/**V** versus **K**t/**BSA** as predictors of log hazard

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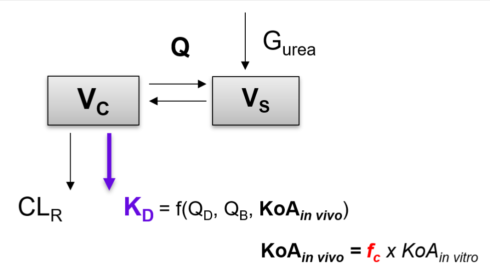

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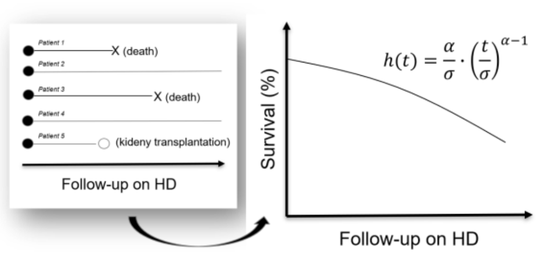

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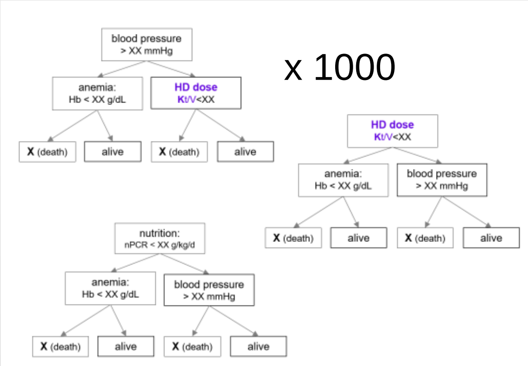
Machine learning (ML) 5-year mortality



- Random forest
- **HD dose (Kt/V)** and > 100 other potential predictor variables (features)

Gotta V, et al. PAGE 2021

Results

Included data

N=1852 patients (53903 HD treatments)

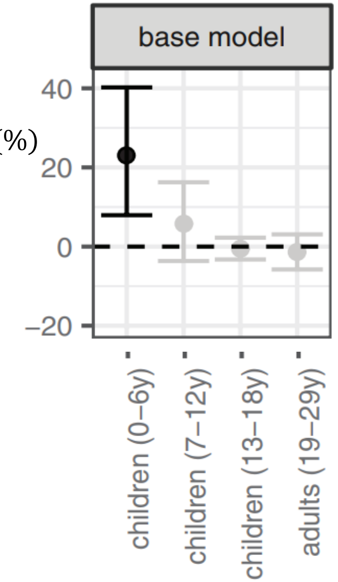
Pharmacometic (PMX) modeling of K_D	Parametric time to event (TTE) survival modeling	Machine learning (ML) 5-year mortality
N=1691 patients (923+768 for model development+evaluation)	N=1493 patients	N=363 patients

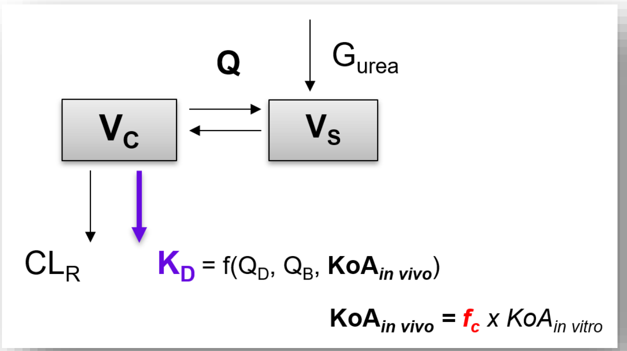
Gotta V et al. *ASAIO* 2019
Gotta V et al. *Ped Nephrol* 2021
Gotta V and Tancev G et al. *NDT* 2020

PMX modeling of K_D

***Base model**: $C_{post\text{-}HD}$ underpredicted in children <6 years*

$$\textbf{Mean prediction error}\ (\%) = \frac{C_{IPRED} - C_{OBS}}{C_{OBS}} \cdot 100$$





f_c = 1.2 (RSE: 1.6%)

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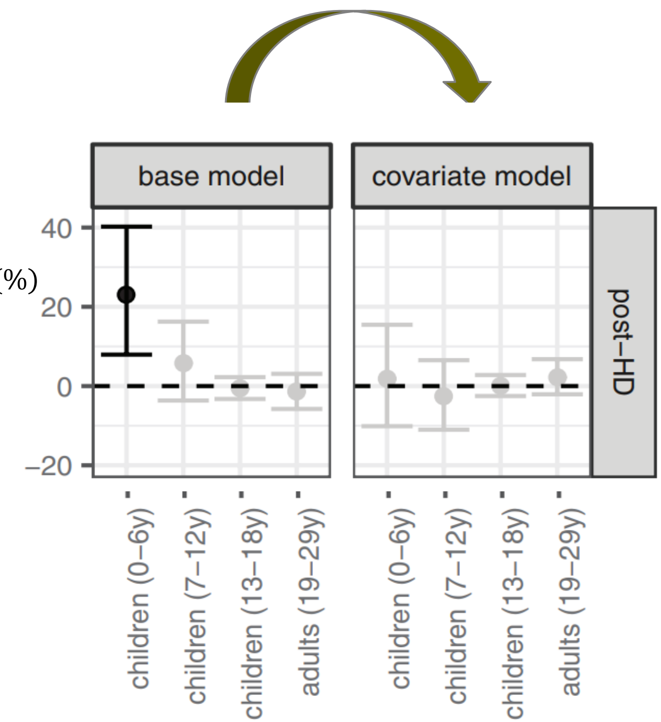
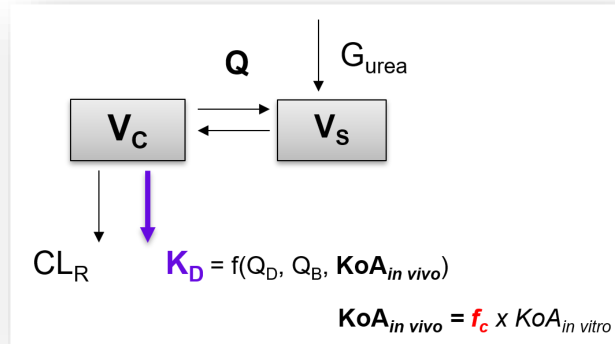
PMX modeling of K_D

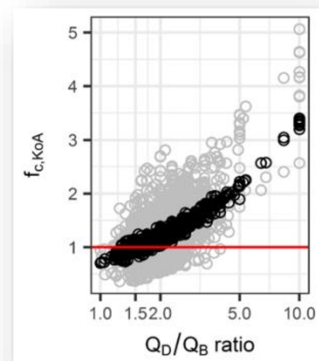
***Covariate model**: accounting for high Q_D/Q_B corrects bias in children <6 years*

$$\textit{Mean prediction error}\ (\%) = \frac{C_{IPRED} - C_{OBS}}{C_{OBS}} \cdot 100$$





$f_c = f(Q_D/Q_B$ ratio$)$



Population predictions
Indiviudal predictions

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PMX modeling of K_D

Covariate model*: other factors for personalized in vivo HD clearance prediction*

- ✓ Q_D/Q_B ratio
- ✓ Type of filter (low-/high-flux)
- ✓ Predicted true Q_B
  (lower than nominal Q_B > 200 mL/min)

Typical adult prescription

Prescription

Blood flow (Q_B)	500	mL/min
Dialysate flow (Q_D)	800	mL/min
filter mass-transfer-area coefficient for urea (KoA *in vitro*)	800	mL/min
Low-flux filter use	0	1=yes, 0=high-flux

Calculated values

*Calculated in vitro urea dialyzer clearance (K_D) without correction**	*274*	*mL/min*	
*Calculated true Q_B ***	*457*	*mL/min*	
Calculated Q_D/Q_B ratio	*1.60*		
Calculated KoA correction factor for Q_D/Q_B ratio and filter flux	*0.66*		
Caclulated corrected *in vivo* urea dialyzer clerance (K_D)*:**	**198**	**mL/min**	**=72.1% of *in vitro* K_D^***

Pediatric prescription

100	mL/min
500	mL/min
300	mL/min
0	1=yes, 0=high-flux
44	*mL/min*
100	*mL/min*
5.00	
2.06	
68	**mL/min =156% of *in vitro* K_D^***

Gotta V et al. *ASAIO* 2019

PMX modeling of K_D

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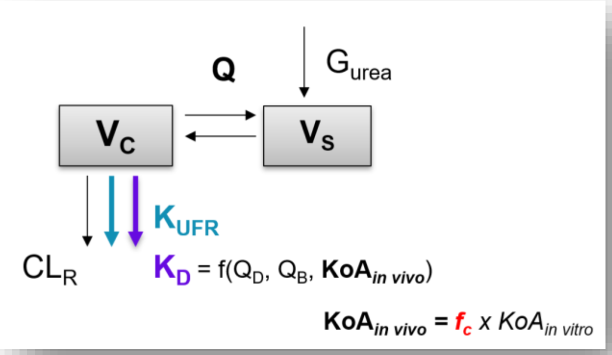
- ✓ **Ultrafiltration rate (K_{UFR})**: adds as convective clearance to diffusive K_D



$CL_{tot} = CL_R + K_D + K_{UFR}$

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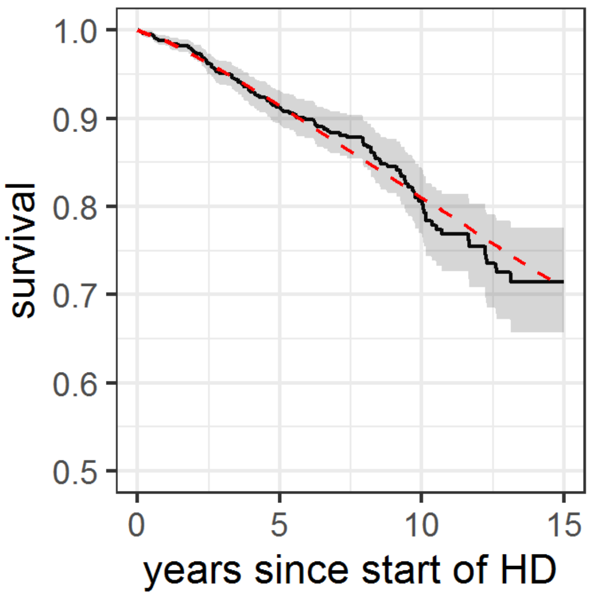
Parametric TTE modeling

Weibull model predicts baseline hazard well



- - - Weibull model predictions (unadjusted)

- Scale σ = 35.4 years
  (time when predicted survival = 40%)
- Shape α = 1.23
  (indicating with α > 1 increasing hazard of death over time)

___ Kaplan Meier curve (95% CI)

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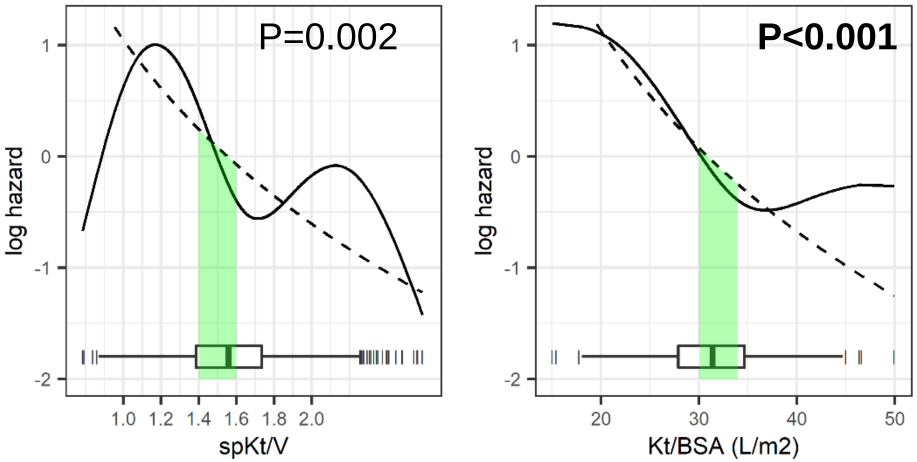
Parametric TTE modeling

BSA-based HD dose (Kt/BSA) better predictor of survival than weight-based Kt/V



- - - Weibull model prediction (log-linear relationship with log hazard)

___ prediction from flexible non-linear spline model

Parametric TTE modeling

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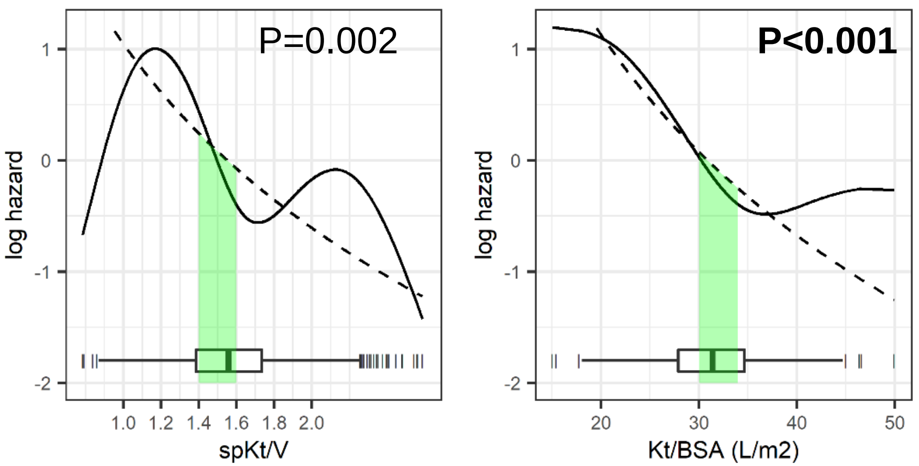

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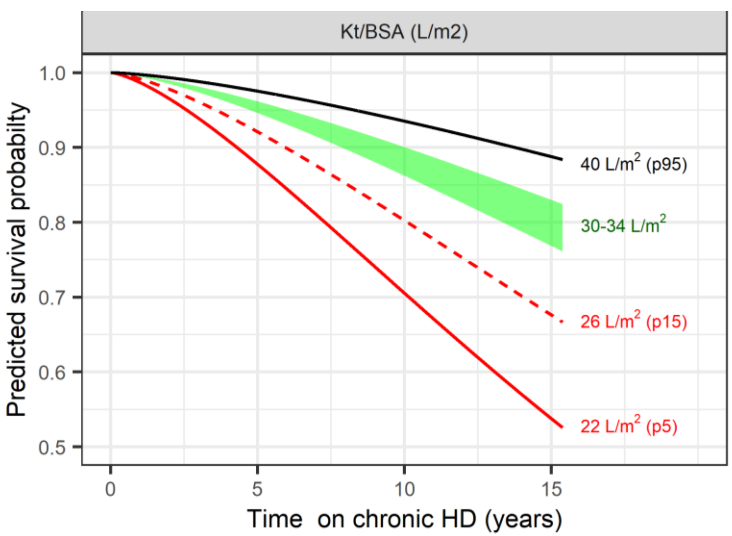
___ prediction from flexible non-linear spline model

Kt/BSA >30 L/m² corresponds to

– Kt/V >1.4 (>12 years / adults)

– **Kt/V >1.6 (<12 years)**



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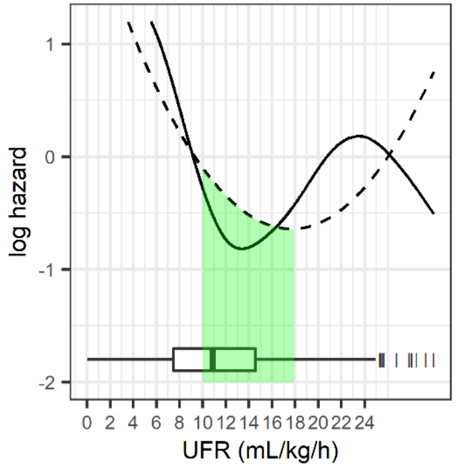
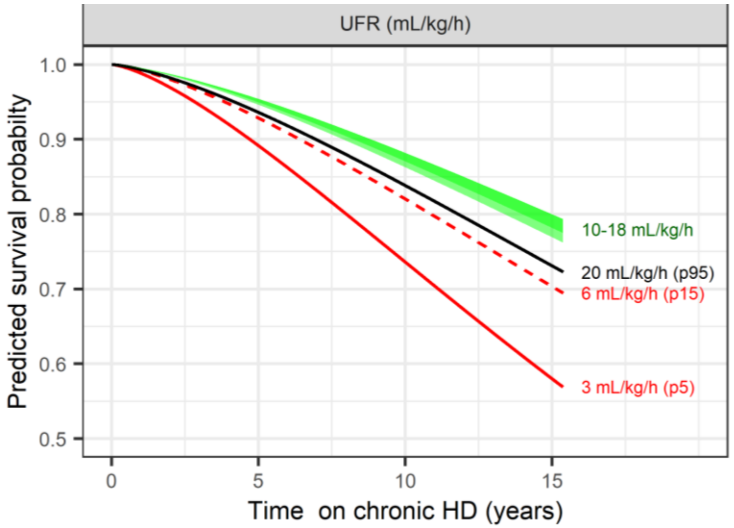
Parametric TTE modeling

Ultrafiltration (UFR) associated with survival in U-shaped relationship





- - - Weibull model prediction (quadratic relationship with log hazard)

___ prediction from flexible non-linear spline model

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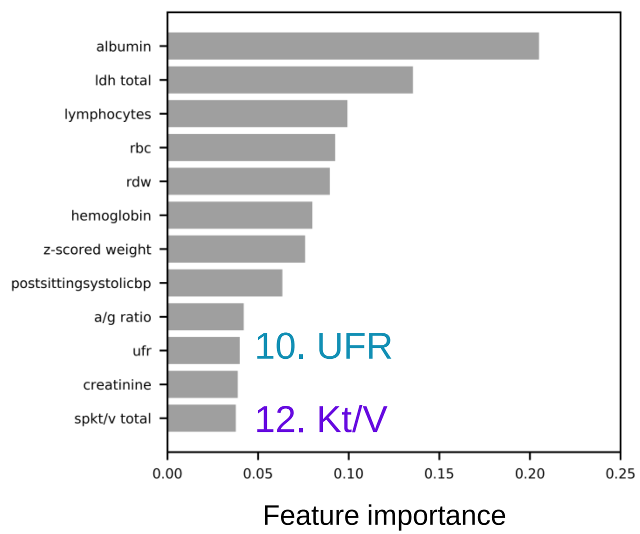
Machine learning (Random forest)

***12 predictors** related to nutrition, inflammation, anemia and HD dose (Kt/V, UFR)*

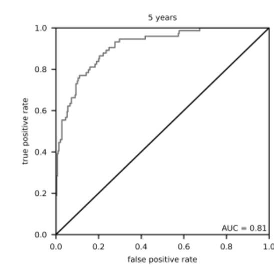
105 potential predictor variables («features»)

- Demographics
- HD treatment
- Laboratory measurements (monthly)

Final ML model: n=12 features retained



AUC_{ROC}: 0.81



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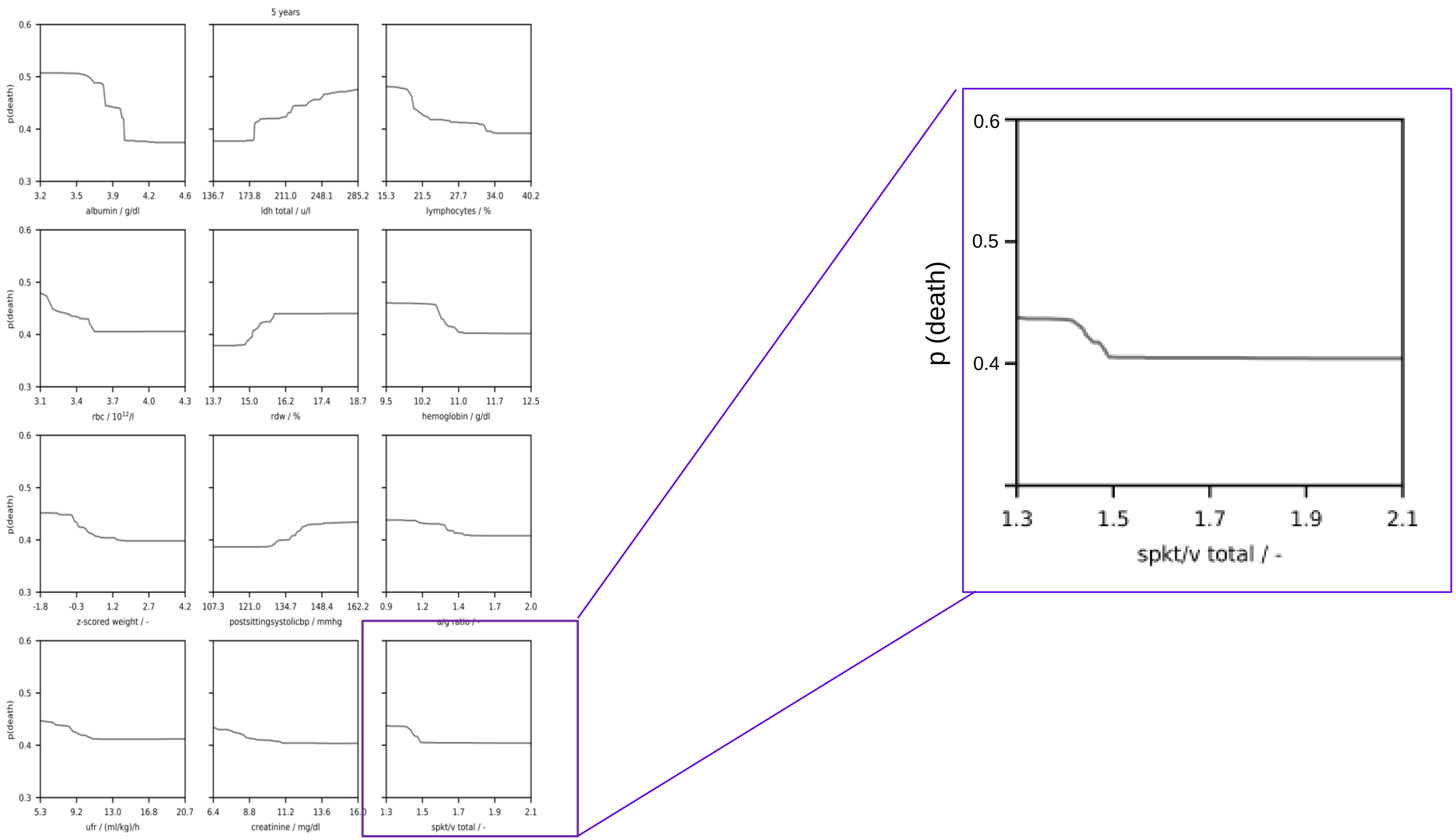
Machine learning (Random forest)

***Partial dependence plots**: Increased mortality with low Kt/V < 1.5*



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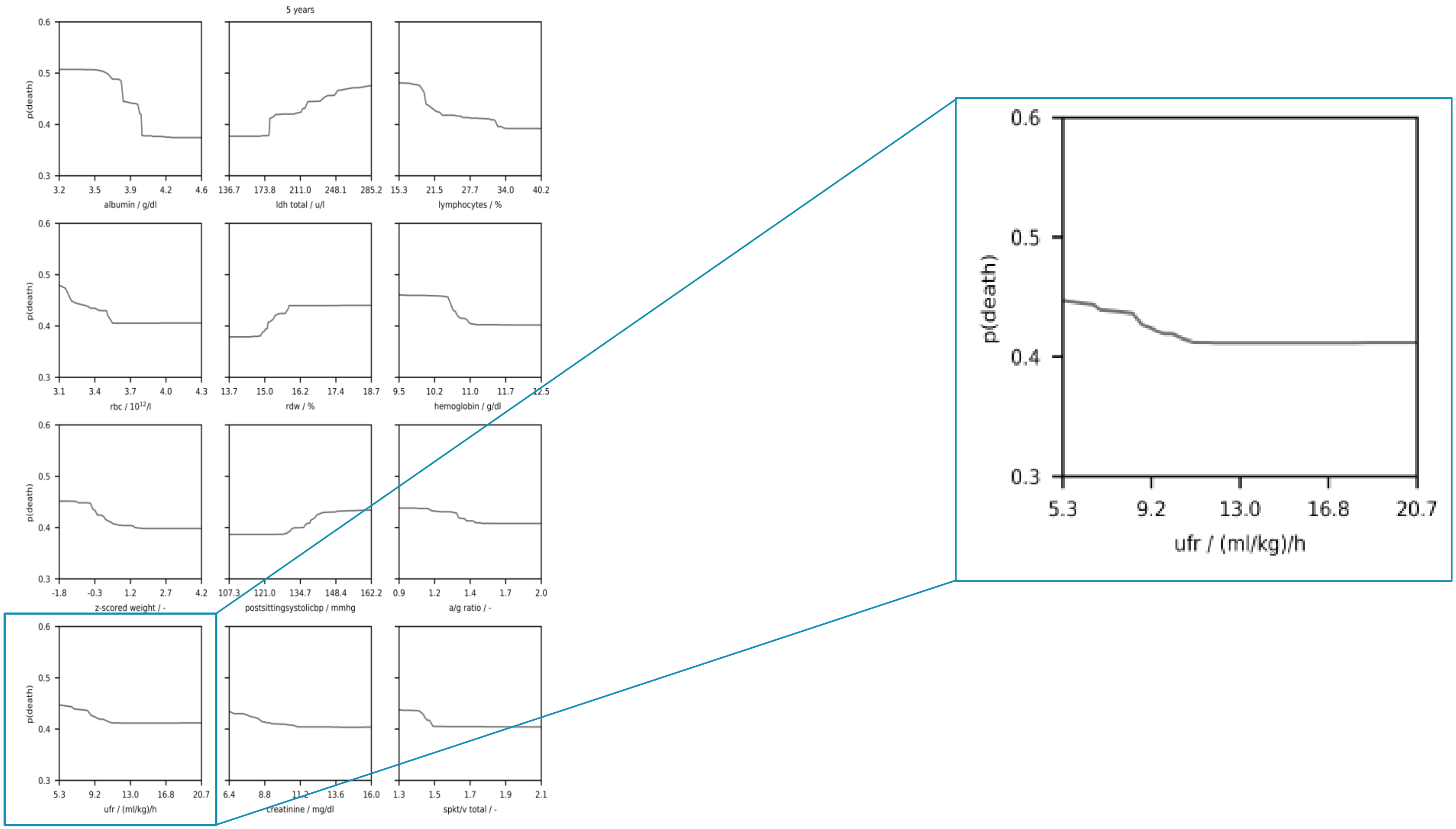
Machine learning (Random forest)

***Partial dependence plots**: Increased mortality with low UFR < 10 mL/kg/h*



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Conclusion: Quantitative pharmacology and ML approaches can help to personalize HD treatment in children

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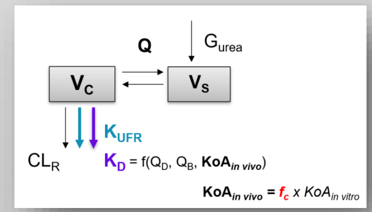
PMX: Scaling/predicting urea dialyzer clearance (K_D) from adult to pediatric HD patients



TTE/ML: Intense HD prescription in children needed for best long-term survival

Conclusion: Quantitative pharmacology and ML approaches can help to personalize HD treatment in children

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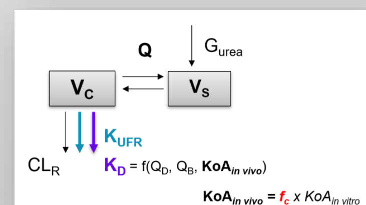
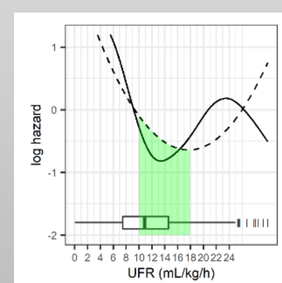
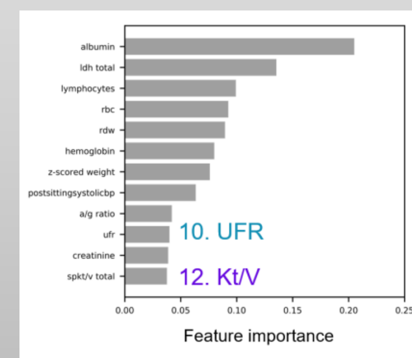


TTE/ML: Intense HD prescription in children needed for best long-term survival

- Kt/**BSA** > Kt/**V** (alternatively: age-dependent Kt/V)
- UFR: U-shaped relationship (increased mortality <10 and >18 mL/kg/h)



- Importance of other disease-related factors besides HD dose (Kt/**V**) / UFR



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Thank you for your attention!


Prof. Marc Pfister


Dr. Andrew Atkinson

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Universität Basel Forschungsfonds


Prof. Olivera Marsenic Coloures

Stanford Children's Health | Lucile Packard Children's Hospital Stanford


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