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Pharmacokinetics of cefotaxime in intensive care patients: exploration of the sources of variability with a population model

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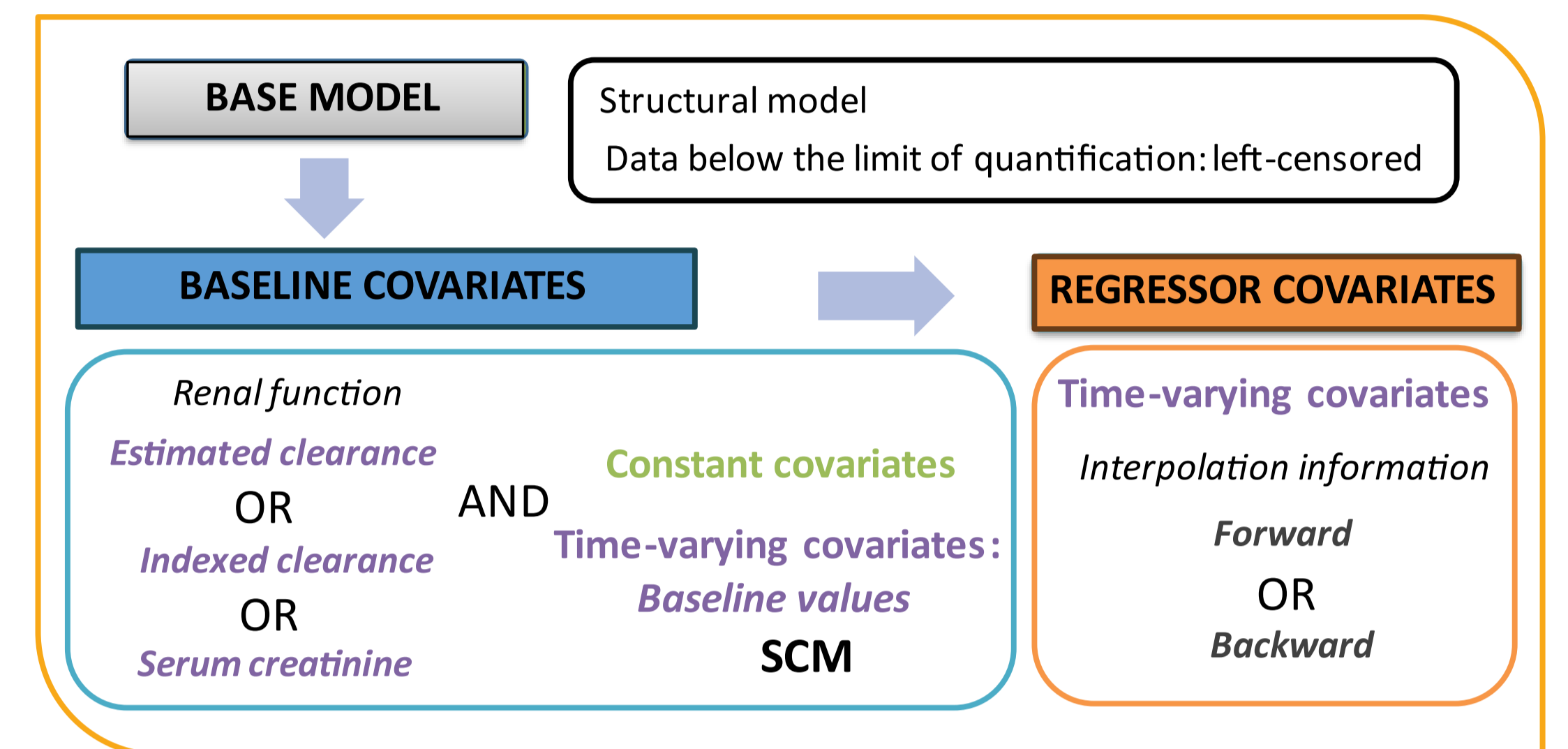
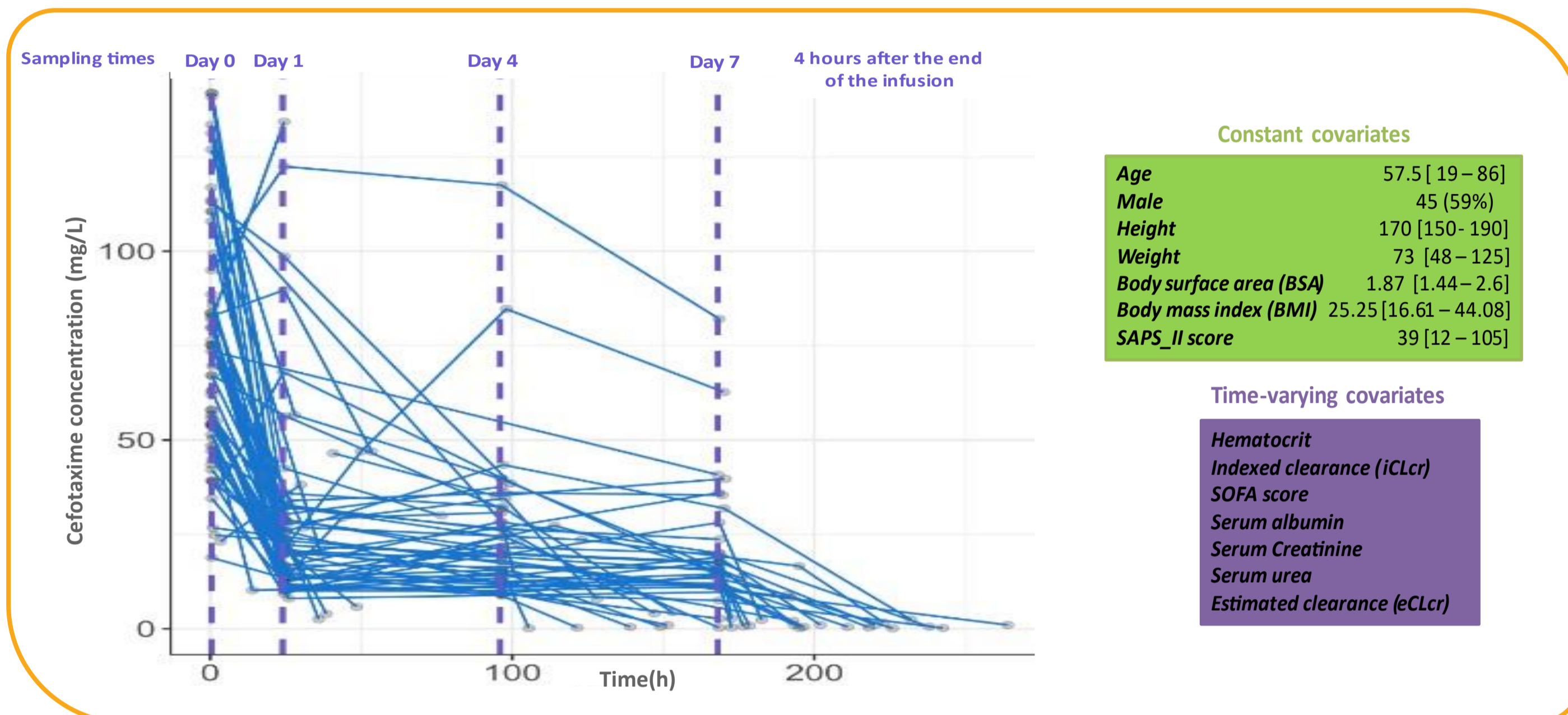
BACKGROUND

- Beta-lactam antibiotics commonly used in intensive care unit (ICU)
- Patho-physiological modifications → High inter- and intra-individual pharmacokinetic (PK) variability
- ➔ Supra or sub-therapeutic concentrations ➔ Need for a personalized drug dosing regimen

Aim: To perform cefotaxime a priori dosing adjustment based on a population PK approach encompassing time-varying physio-pathology

METHODS

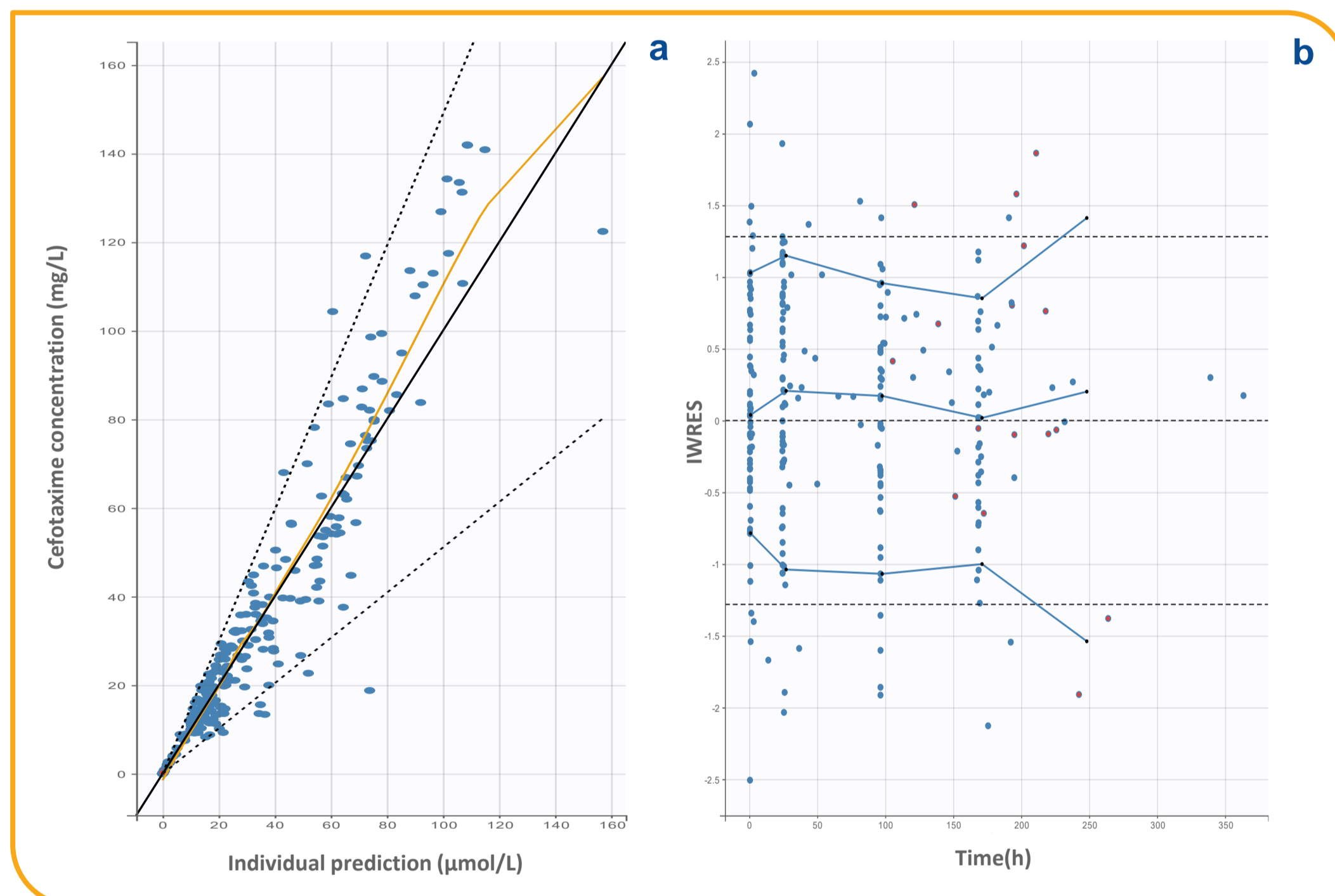
- Prospective, multicenter, observational study (October 2015 - May 2017) conducted in ICUs of Marseille
- Dosing regimen: Loading dose (2g-4g/0.5h) followed by continuous infusion (1-24g/24h) over 7 days
- Population PK analysis: MONOLIX 2023R1 software



Analysis plan SCM: stepwise covariate model procedure with forward ($\alpha=0.05$) and backward steps ($\alpha=0.01$), power and exponential relationships tested

Collected data BSA: body surface area determined using the Dubois and Dubois formula, eCLcr: estimated creatinine clearance determined using the Cockcroft and Gault formula, iCLcr: indexed clearance creatinine: $iCLcr = \frac{1.73}{BSA} \times \left(\frac{Urine\ creatinine \times Urine\ volume}{Serum\ creatinine} \right)$, Severity score: SAPS-II Simplified Acute Physiology Score 2; SOFA: Sepsis-related Organ Failure Assessment, Data are number (%) or median, minimum and maximum

RESULTS



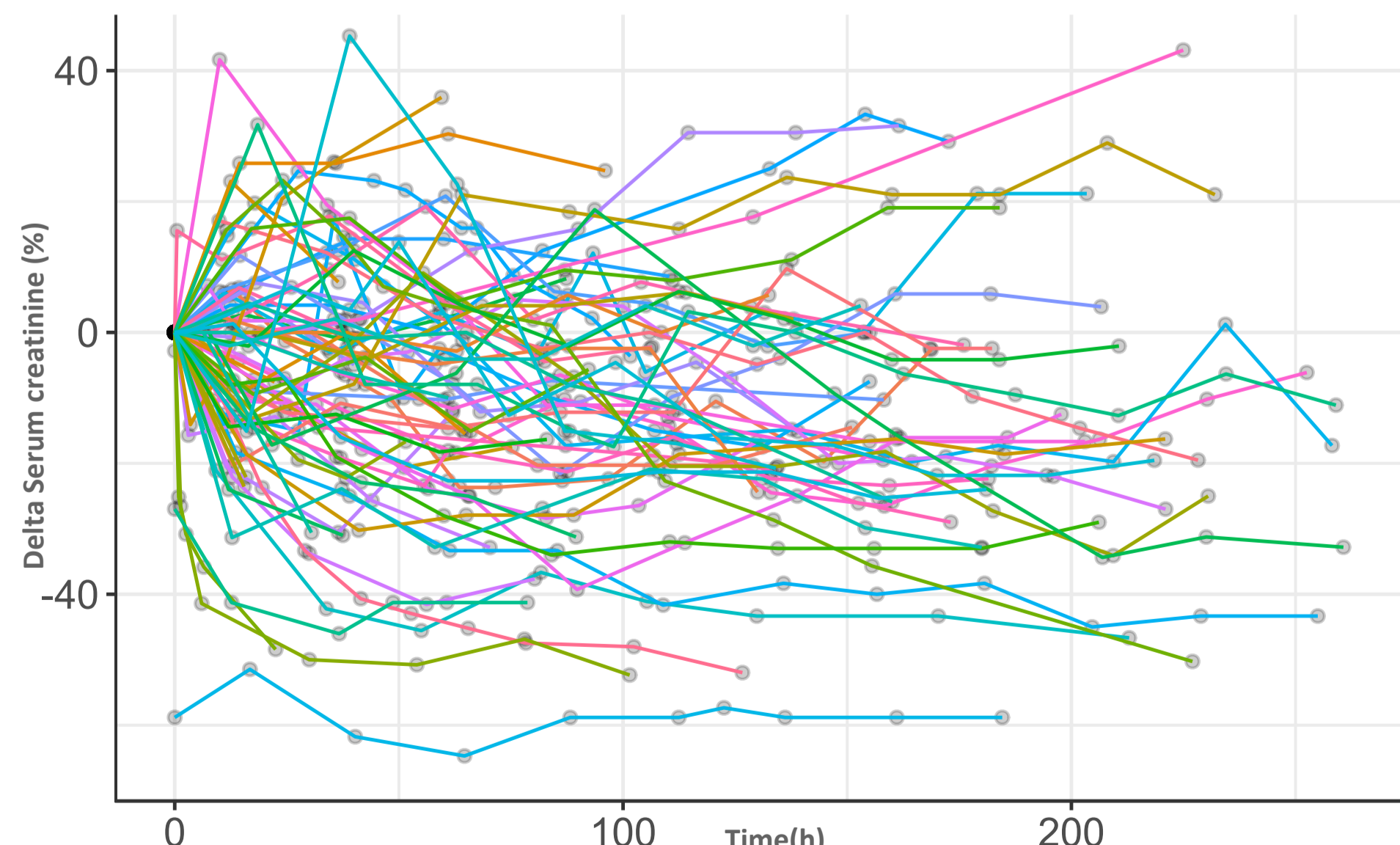
Goodness of fit plots a: orange line: spline, dashed black line: 90% prediction interval, b: IWRES: individual weighted residuals, dashed line: theoretical mean and predicted percentiles, blue line: empirical percentiles

- One-compartment model with proportional residual error

Model	Δ BICc
Baseline covariates	-10.16
Regressor covariates	-6.41
Forward interpolation	
Regressor covariates	-15.45
Backward interpolation	

Model building BICc: Corrected Bayesian Information Criteria, Δ : difference from base model (w/o covariate)
Forward interpolation: last observation carried backward
Backward interpolation: next observation carried backward

- ➔ Power law relationship
- ➔ Constant covariates: Age and BSA
- ➔ Time-varying covariates : Serum creatinine



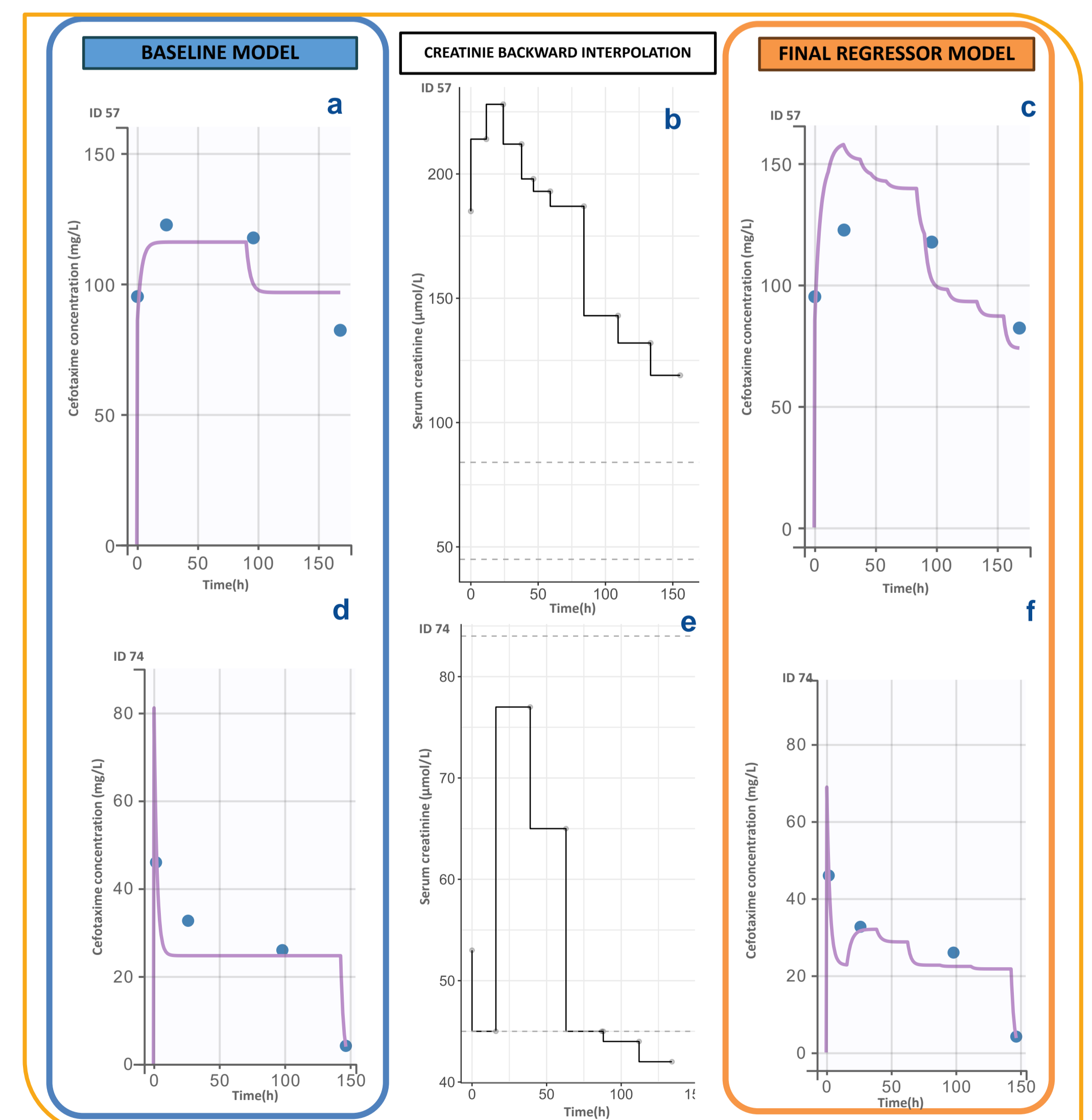
Serum creatinine intra-variability
Lines: One color per individual, grey dot: observed data
 $\Delta Serum\ creatinine = \left(\frac{Serum\ creatinine_t - Serum\ creatinine_{baseline}}{Serum\ creatinine_{baseline}} \right) \times 100$

➔ High intra-variability

Parameter	Estimates	RSE (%)	[SHR](%)
Fixed effects			
CL (L/h)	10.44	4.56	
V (L)	23.02	5.89	
Covariate effects			
β_{CL_Age}	-0.62	18.3	
β_{CL_BSA}	1.53	24.0	
$\beta_{CL_creatinine}$	-0.64	14.7	
Random effects			
IIV CL	0.31	11.4	[-7.82]
IIV V	0.37	14.8	[3.56]
ϵ	0.3	6.66	

Final Parameter estimates
RSE relative standard error, SHR shrinkage, CL clearance, V distribution volume, IIV inter-individual variability, ϵ proportional residual error
Green: constant covariates effect on CL, Purple: time-varying covariate effect on CL

➔ Regressor explains part of the intra-individual variability



Representative individual fits with interpolation of creatinemia a,d,f,g: purple line: prediction using the estimated individual, blue dot: observed data b,e: black line serum creatinine in backward interpolation, grey dot: observed data, dashed grey line: normal values

CONCLUSION

- High inter- and intra-variability of cefotaxime PK in ICU patients was partly explained by time-varying creatinine covariate
- A creatinine biomarker model will be developed to anticipate serum creatinine variations and consequences on PK

Contact

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