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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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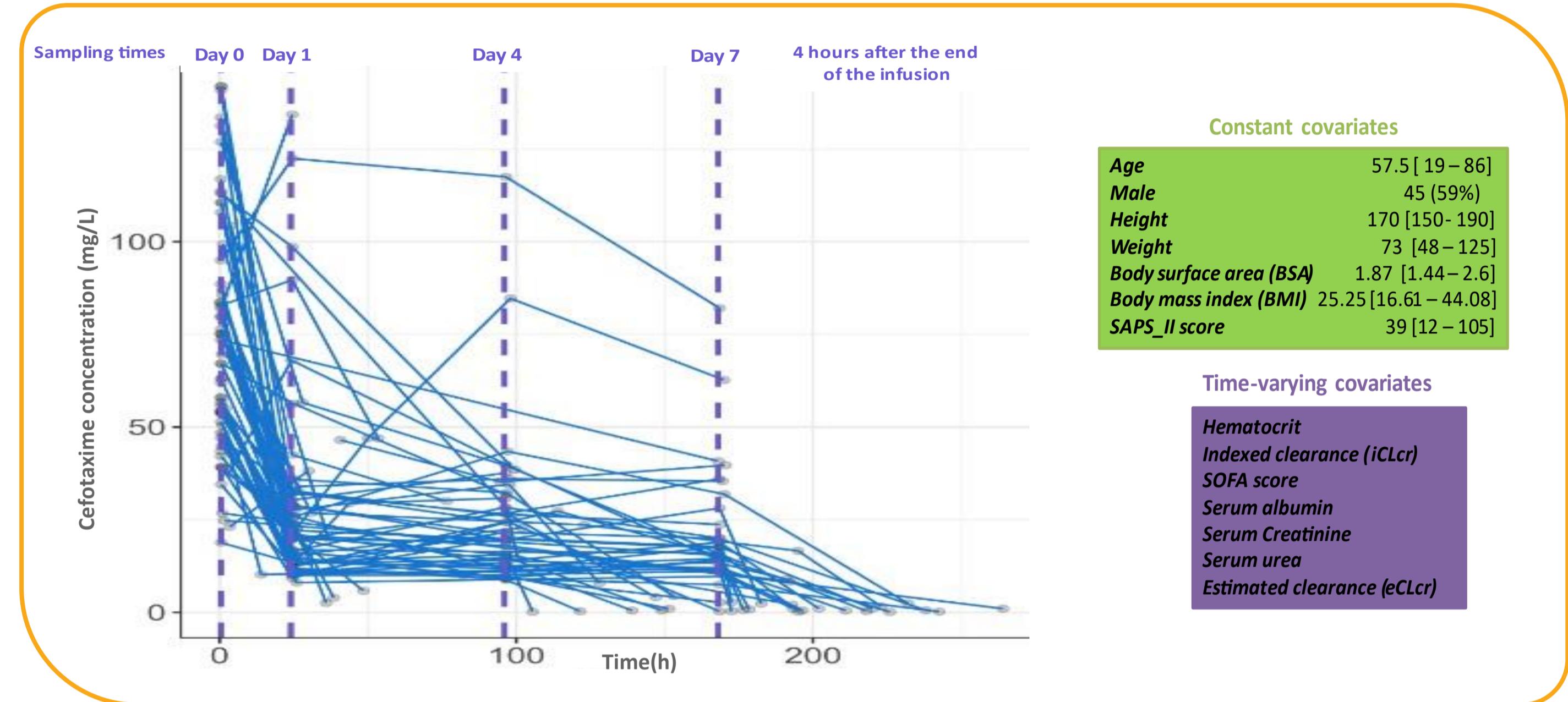
BACKGROUND

- 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

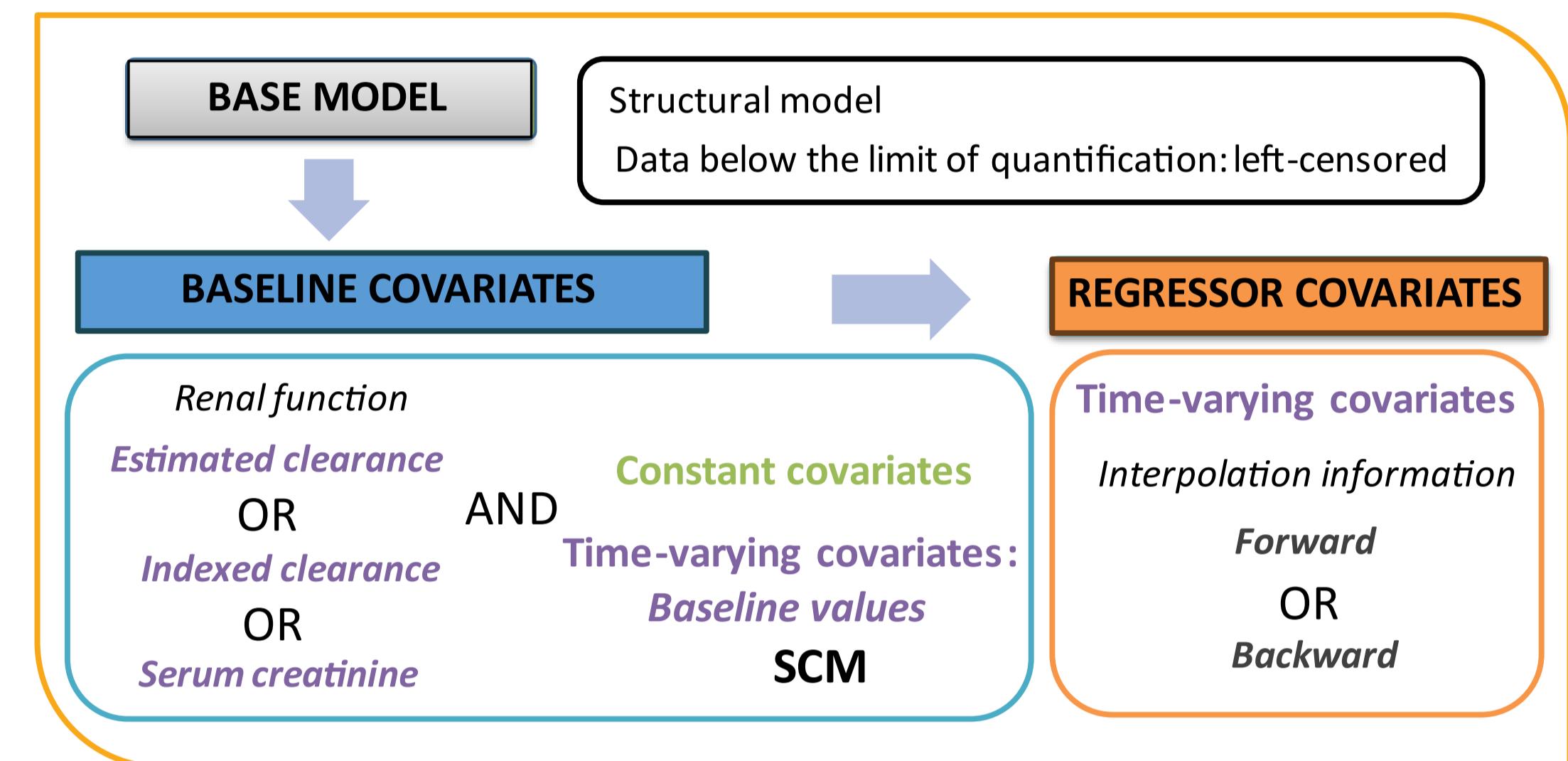
Aim: To perform cefotaxime *a priori* dosing adjustment based on a population PK approach encompassing time-varying physio-pathology

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

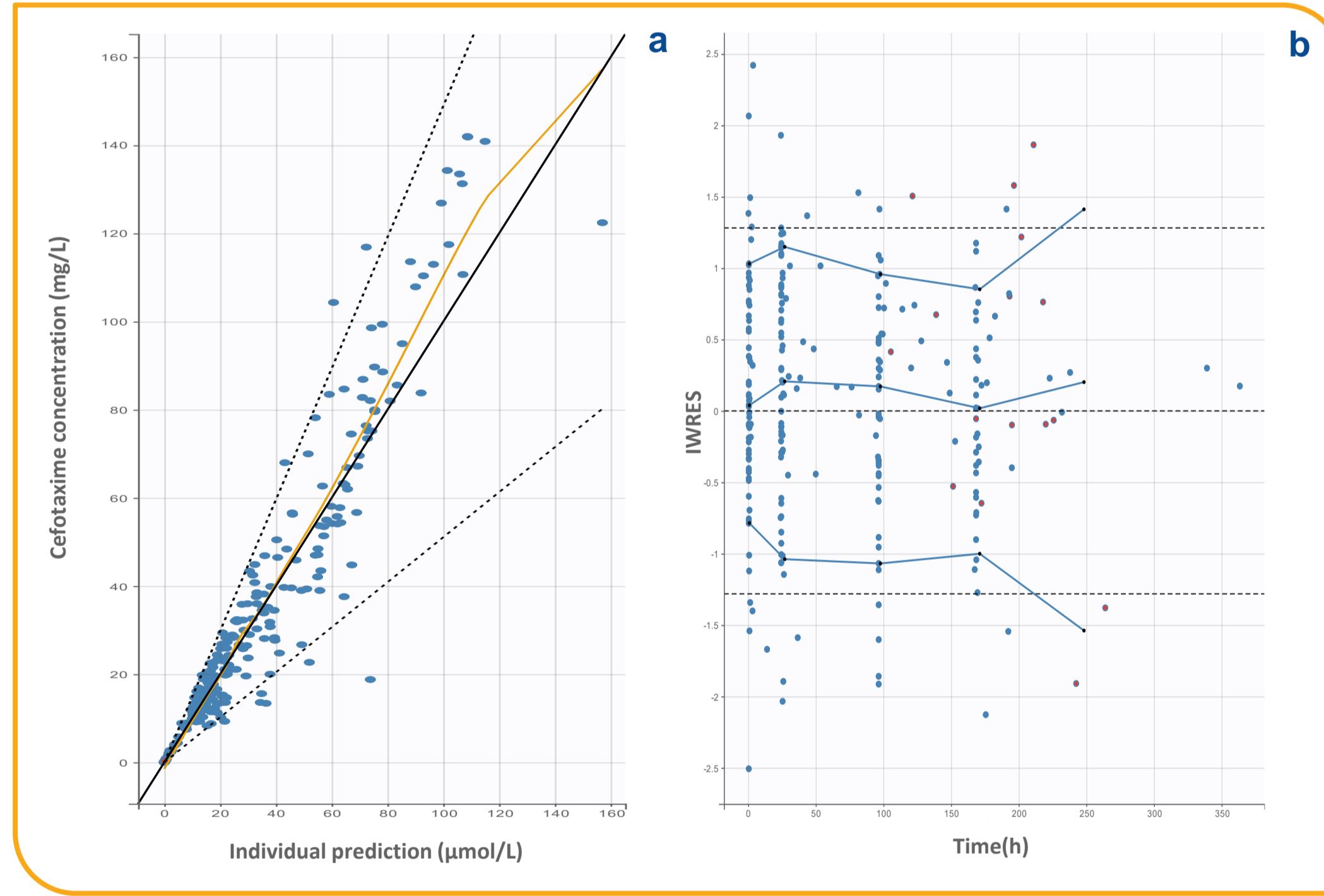


Collected data BSA: body surface area determined using the Dubois and Dubois formula, eCLcr: estimated creatinine clearance determined using the Cockcroft and Gault formula, iCLcr: indexed clearance creatinine: $iCLcr = \frac{1.73}{BSA} \times \frac{(Urine\ creatinine \times Urine\ volume)}{Serum\ creatine}$,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



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

RESULTS

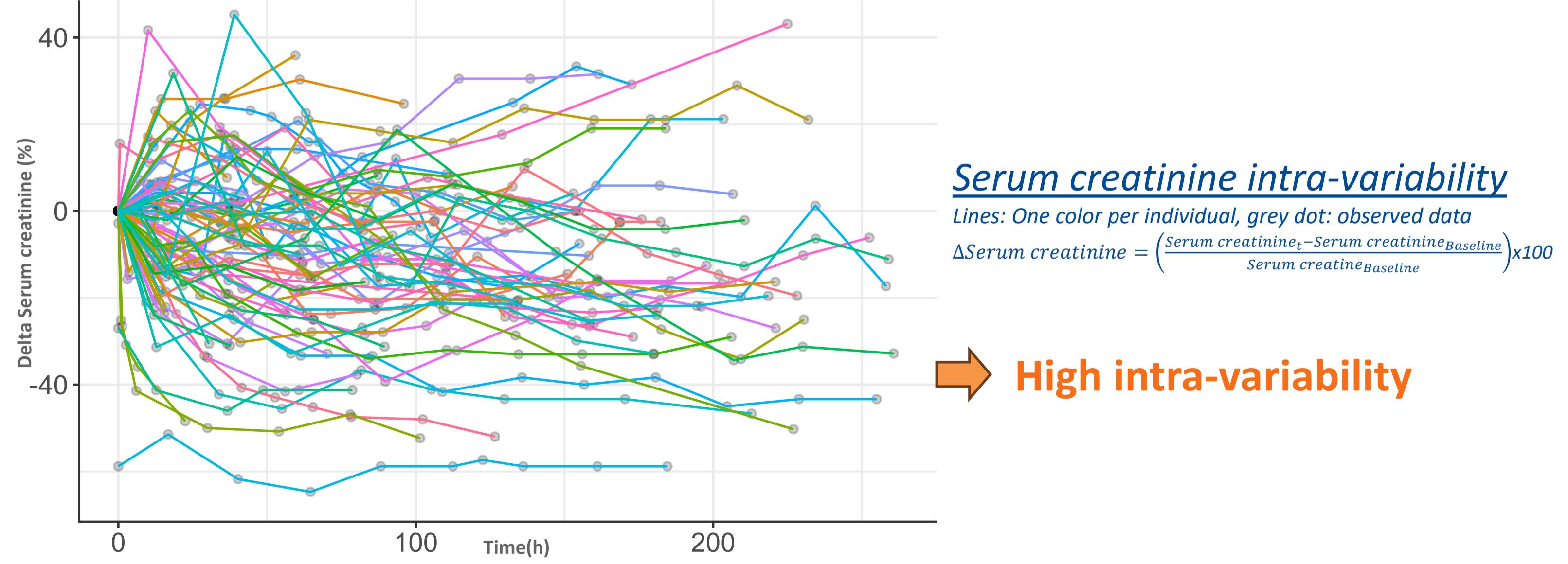


Goodness of fit plots a: orange line: spline, dashed black line: 90% prediction interval, b: IWRES: individual weighted residuals, dashed line: theoretical mean and predicted percentiles, blue line: empirical percentiles

- One-compartment model with proportional residual error

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

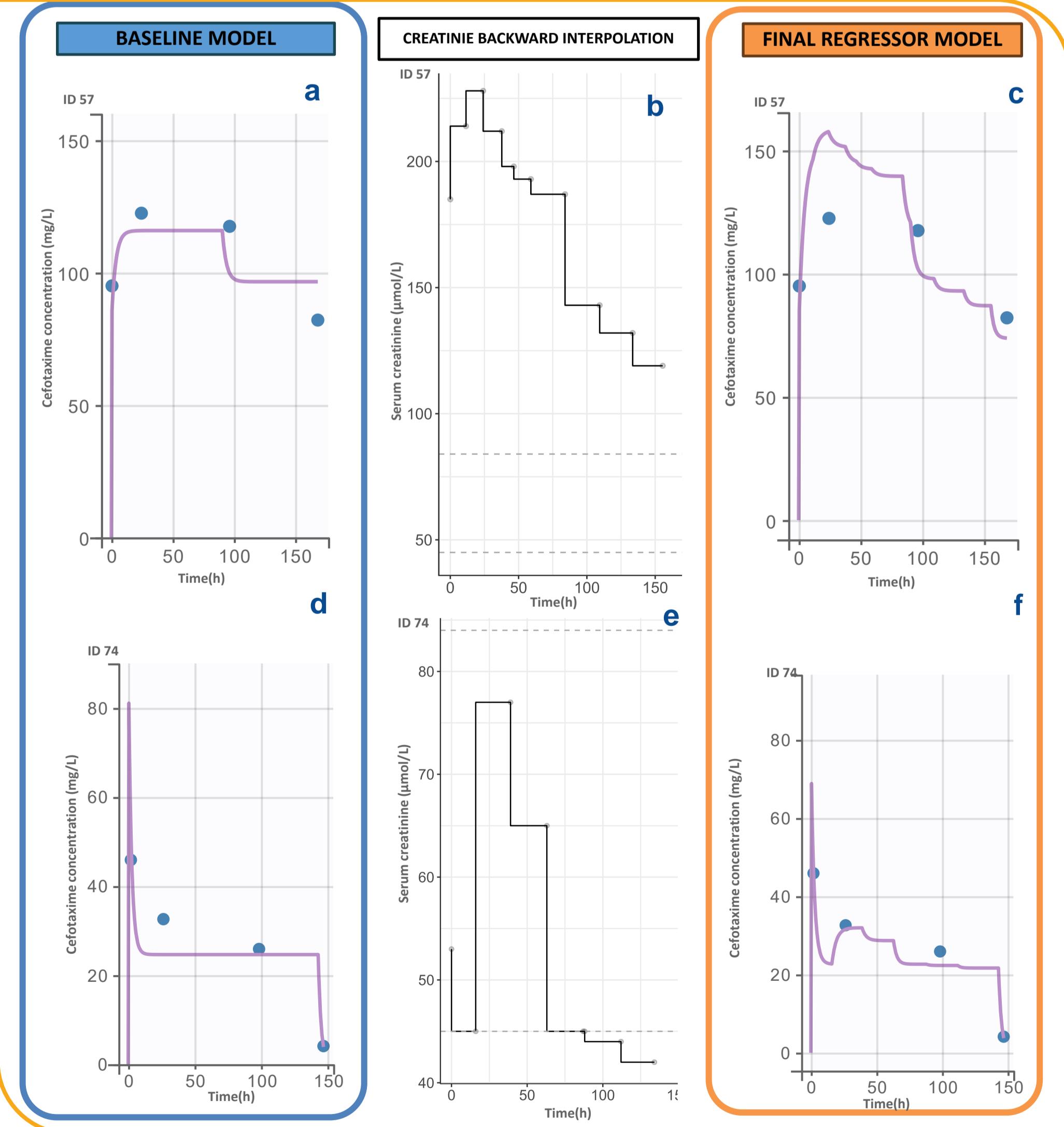
- Power law relationship
- Constant covariates: Age and BSA
- Time-varying covariates : Serum creatinine



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

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