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Population pharmacokinetic model of cefotaxime encompassing time-varying physiopathology: exploration of intra-individual variability of the renal function

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BACKGROUND

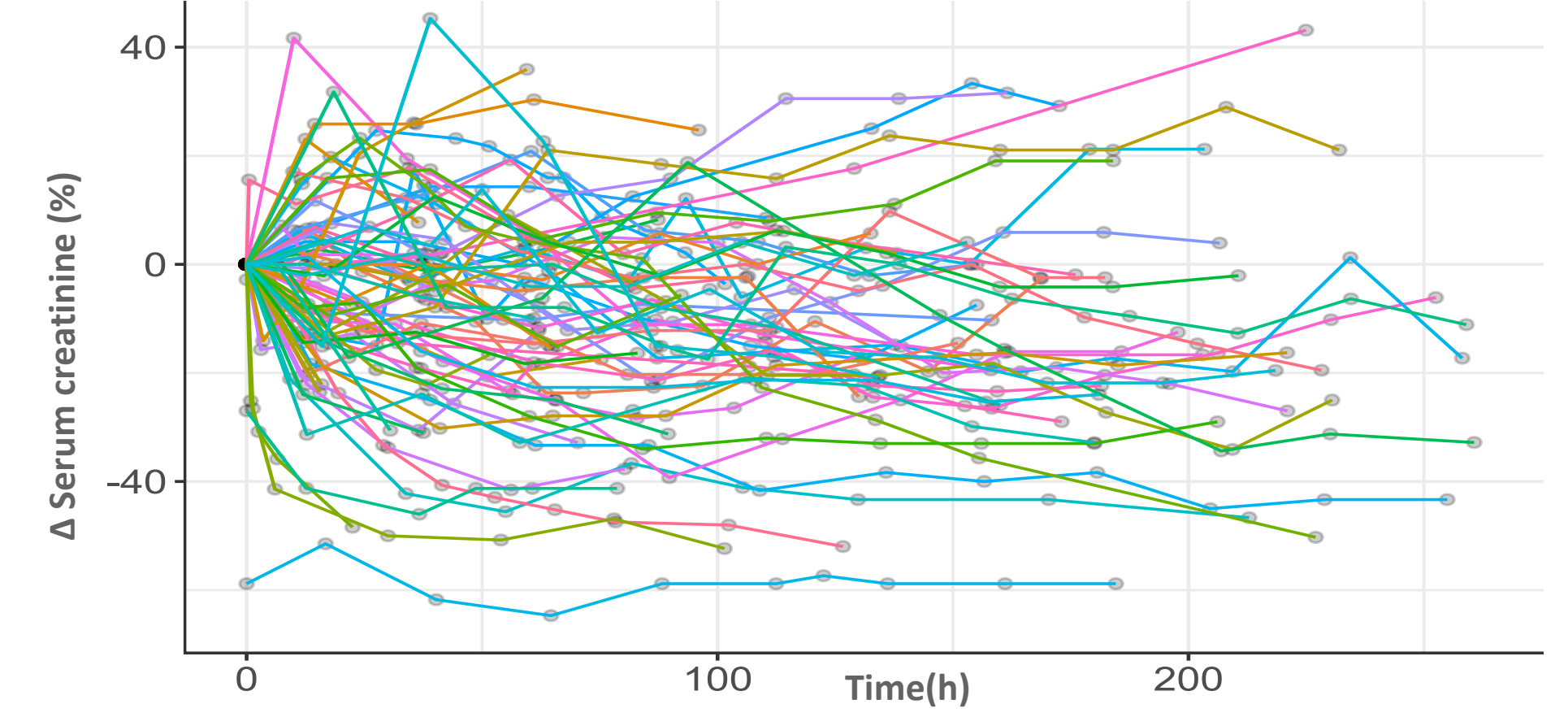
Critically ill patients → Patho-physiological modifications

→ High inter- and intra-individual pharmacokinetic (PK) variability

→ Supra- or sub-therapeutic concentrations^[1]

→ Need for a personalized drug dosing regimen

Aim: To perform a priori dosing adjustment of cefotaxime based on a biomarker model of renal function

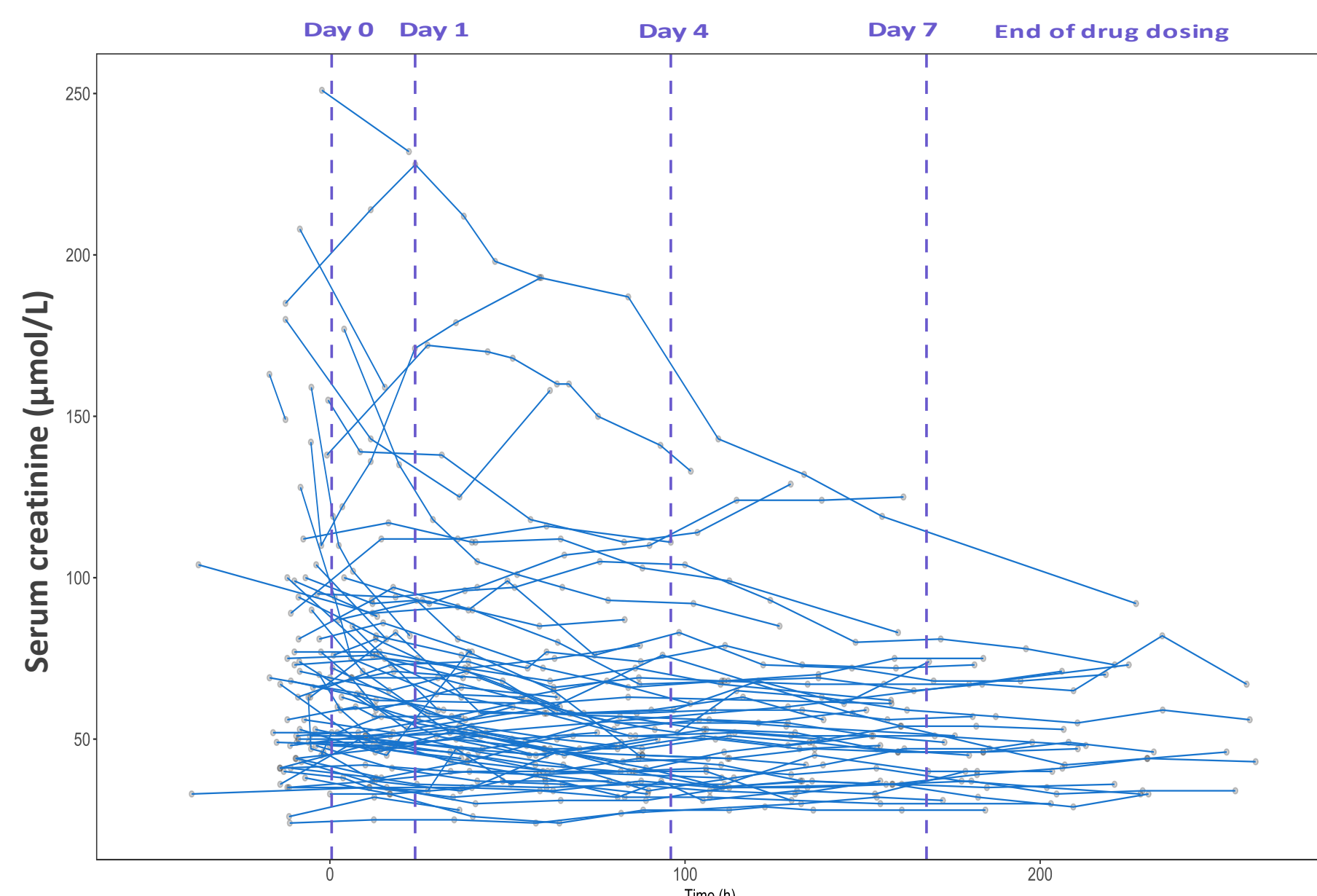


Serum creatinine evolution $\Delta \text{Serum creatinine} = \left(\frac{\text{Serum creatinine}_{\text{Time}} - \text{Serum creatinine}_{\text{Baseline}}}{\text{Serum creatinine}_{\text{Baseline}}} \right) \times 100$
Grey dots: observed data. Lines: One color per individual

METHODS

STUDY DESIGN

- Prospective, multicenter, observational study (Oct. 2015 - May 2017) in Intensive Care Units (ICU) of Marseille.
- Cefotaxime dosing regimen: loading dose (2g-4g/0.5h) followed by continuous infusion (1-24g/24h) over 7 days



Constant covariates: median [Range] or number

Age (years)	57 [19 – 86]
Male/Female	45/31
Height (cm)	170 [150 – 190]
Weight (kg)	73 [48 – 125]
Body surface area (BSA, m ²)	1.87 [1.44 – 2.60]
Body mass index (BMI, kg/m ²)	25.25 [16.61 – 44.08]
SAPS_II score	39 [12 – 105]

Time-varying covariates

Hematocrit
Indexed clearance (iCLcr)
SOFA score
Serum albumin
Serum Creatinine
Serum urea
Estimated clearance (eCLcr)

Covariates: Constant covariates collected at inclusion; Time-varying covariates collected every 24h

BSA: body surface area determined using the Dubois and Dubois formula, Severity score: SAPS_II Simplified Acute Physiology Score 2; SOFA: Sepsis-related Organ Failure Assessment, estimated creatinine clearance determined using the Cockcroft and Gault formula, indexed clearance creatinine: $iCLcr = \frac{1.73}{BSA} \times \left(\frac{\text{Urine creatinine} \times \text{Urine volume}}{\text{Serum creatinine}} \right)$

POPULATION PK ANALYSIS PLAN

251 cefotaxime concentrations

BASE MODEL Structural model (without covariates)
Data below the limit of quantification: left-censored

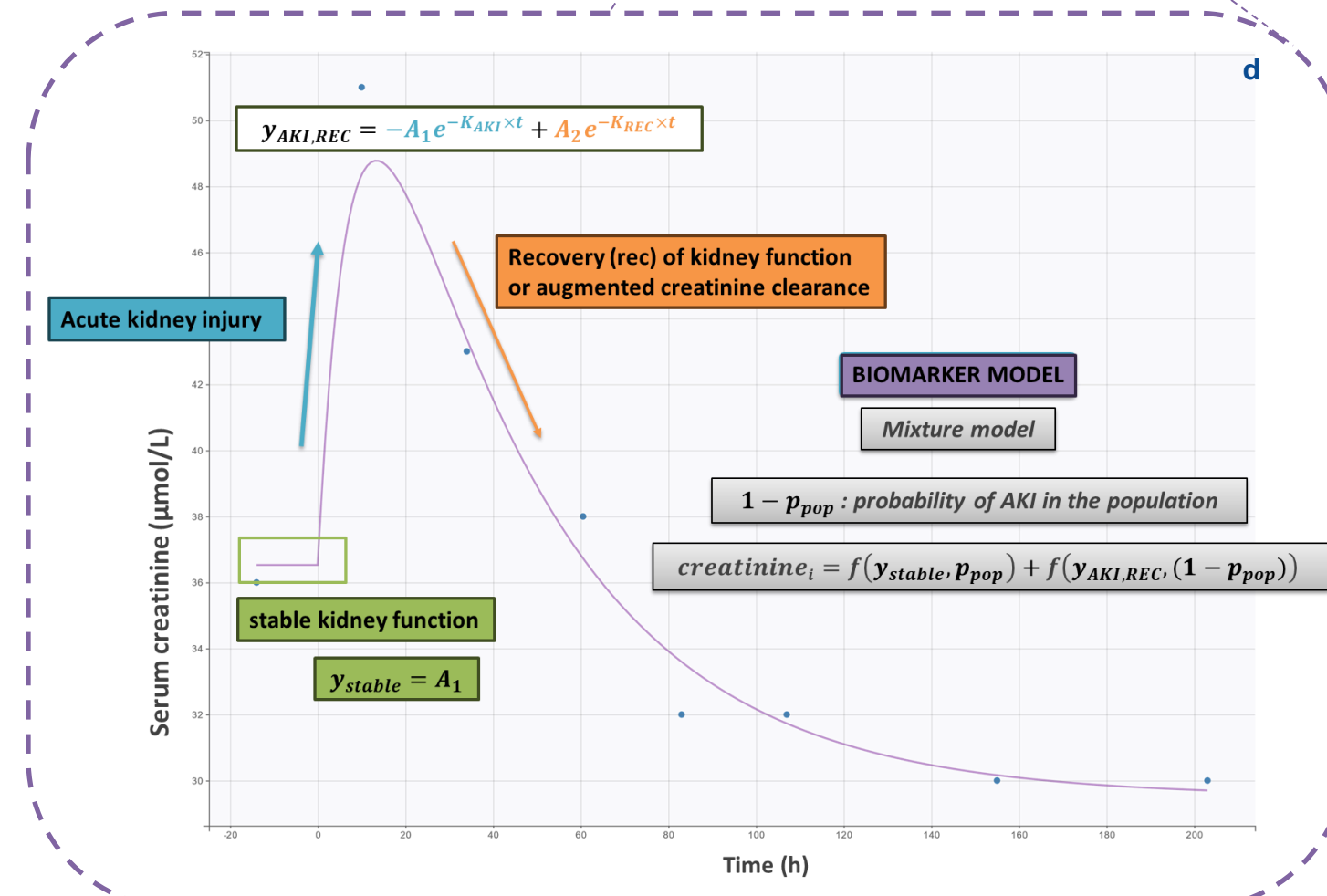
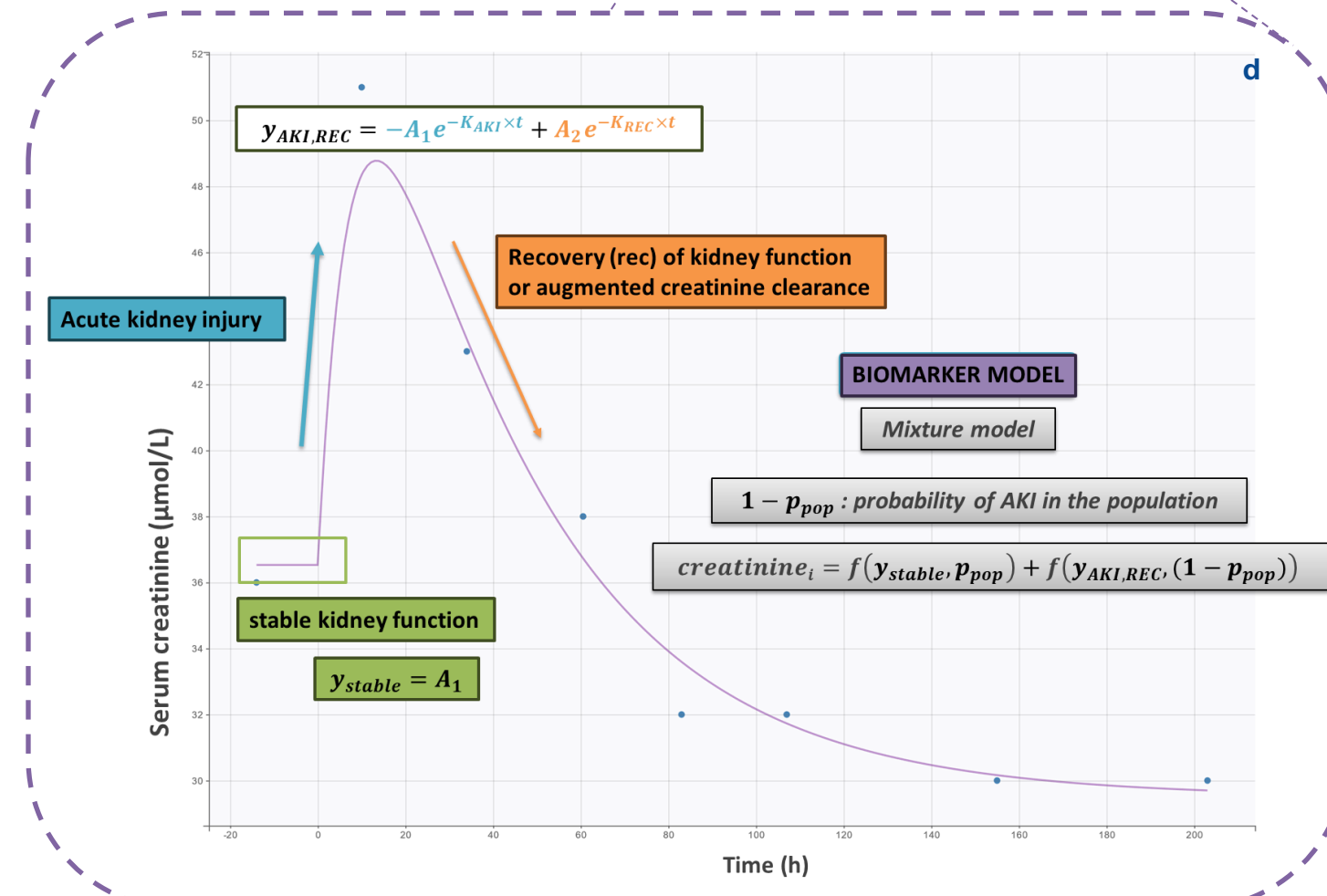
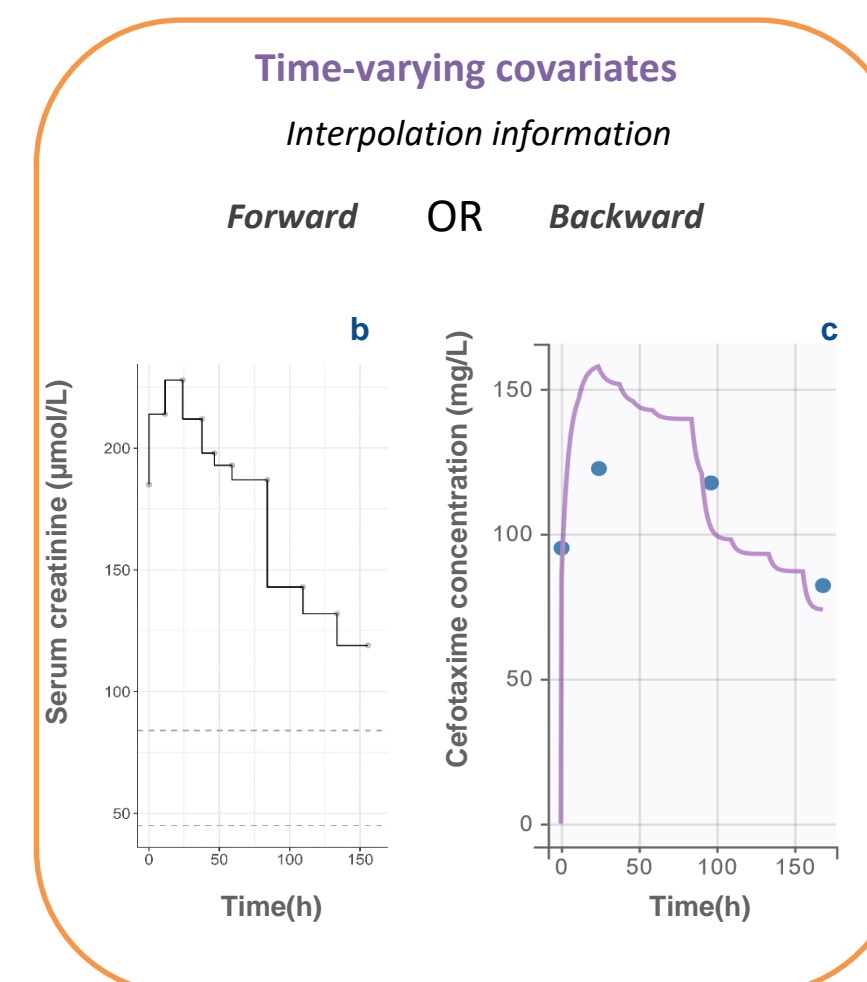
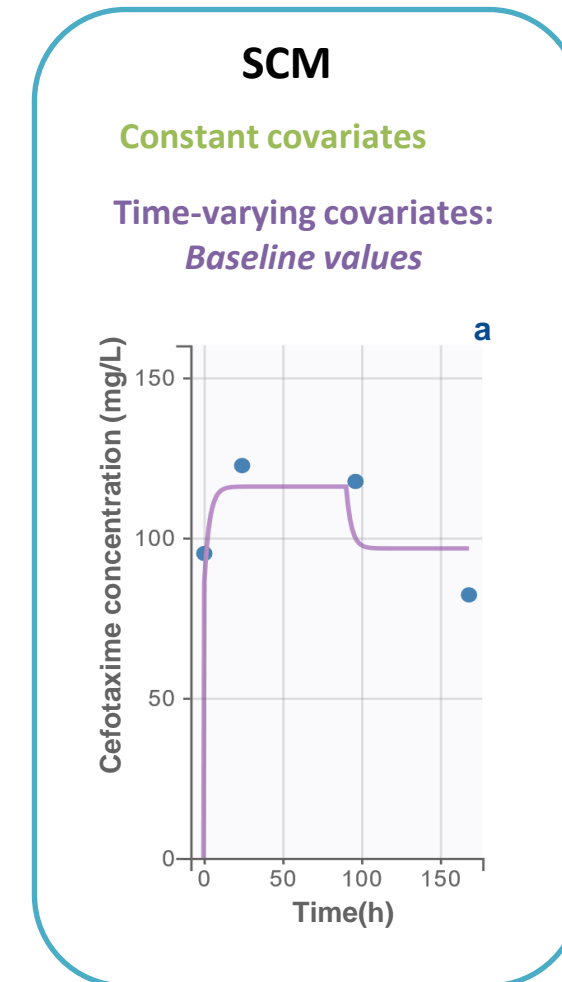
BASELINE COVARIATES

REGRESSOR COVARIATES

BIOMARKER MODEL

523 serum creatinine concentrations

Time-varying covariates
Biomarker V_d CL_R
PK V CL



Analysis: MONOLIX® 2023R1 software. a) Cefotaxime concentrations: representative individual fit with baseline serum creatinine. b) Serum creatinine: representative individual fit with backward interpolation. c) Cefotaxime concentrations: representative individual fit with backward interpolation. d) Serum creatinine: representative individual fit with a biomarker model

SCM: stepwise covariate model procedure with forward ($\alpha = 0.05$) and backward steps ($\alpha = 0.01$), power and exponential covariate relationships tested
Purple line: individual prediction, blue dot: observed data, black line: backward interpolation, blue dot: observed data, dashed grey line: normal values

RESULTS

POPULATION PK MODEL OF CREATININE

Parameter	Base model		Final model	
	Estimates	RSE (%) [SHR](%)	Estimates	RSE (%) [SHR](%)
Fixed effects				
A_1 (μmol/L)	72.7	6.09	75.67	4.88
A_2 (μmol/L)	114	10.8	105	7.28
K_{AKI} (1/h)	0.021	30.7	0.025	22.1
K_{REC} (1/h)	0.022	18.7	0.023	13.9
P_{pop}	0.77	2.08	0.73	2.47
Covariate effects				
βA_{1_urea}			0.39	24.1
βA_{2_urea}			0.91	14.8
Random effects				
IIV A_1	0.41	11.4 [-9.01]	0.35	11.4 [-6.4]
IIV A_2	0.81	10.4 [3.24]	0.51	10.4 [0.406]
IIV K_{AKI}	1.47	19.3 [11.7]	1.1	19.3 [13.6]
IIV K_{REC}	0.99	18.2 [7.37]	0.84	18.2 [-7]
IV P_{pop}	0.26	16.1 [3.59]	0.28	16.1 [-5]
ϵ	0.075	4.23	0.075	4.49

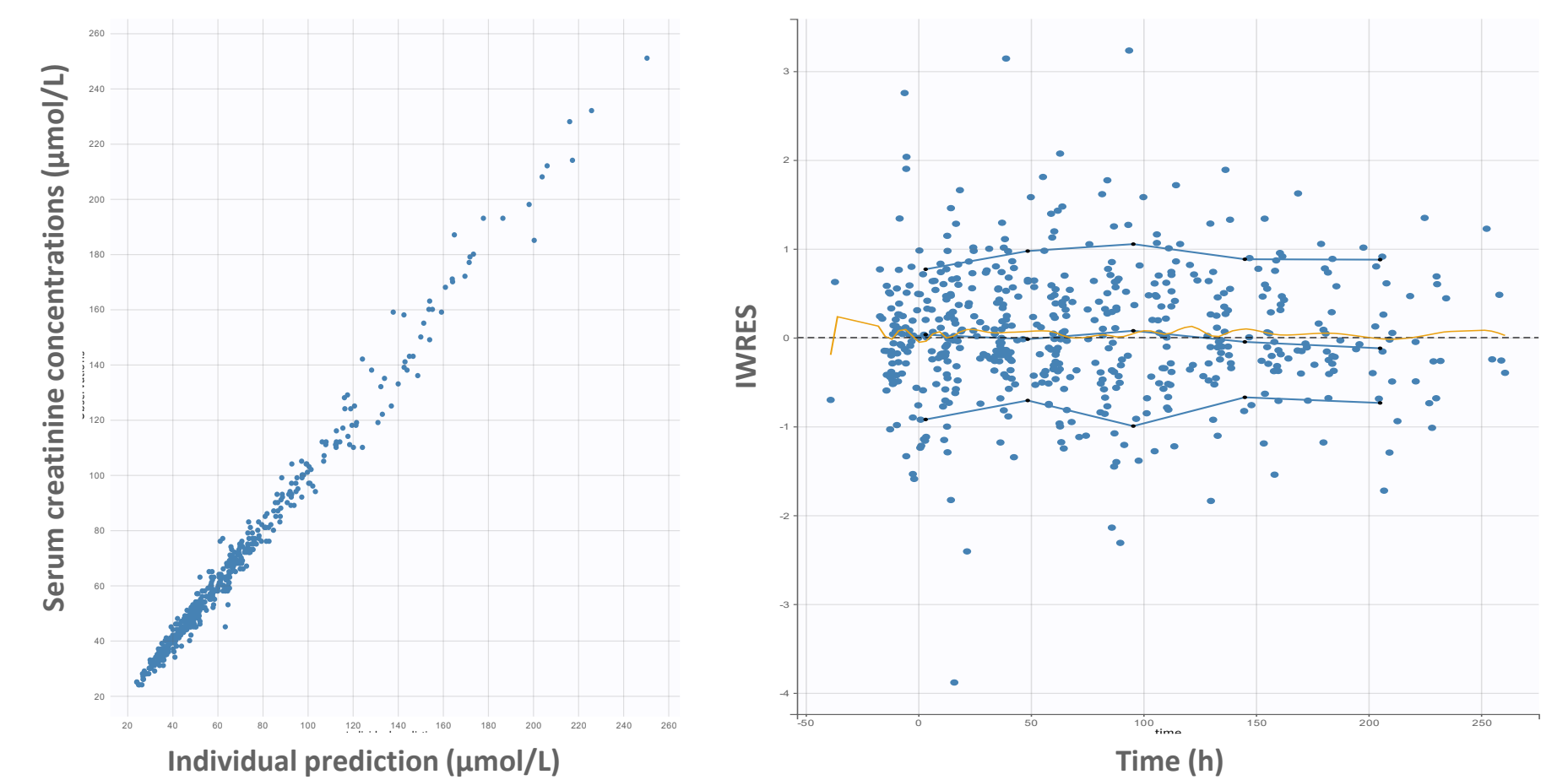
Parameter estimates

RSE relative standard error
SHR shrinkage
AKI: Acute kidney injury
REC: recovery of kidney function
Green: baseline covariates
IIV inter-individual variability,
 ϵ proportional residual error

Goodness of fit plots

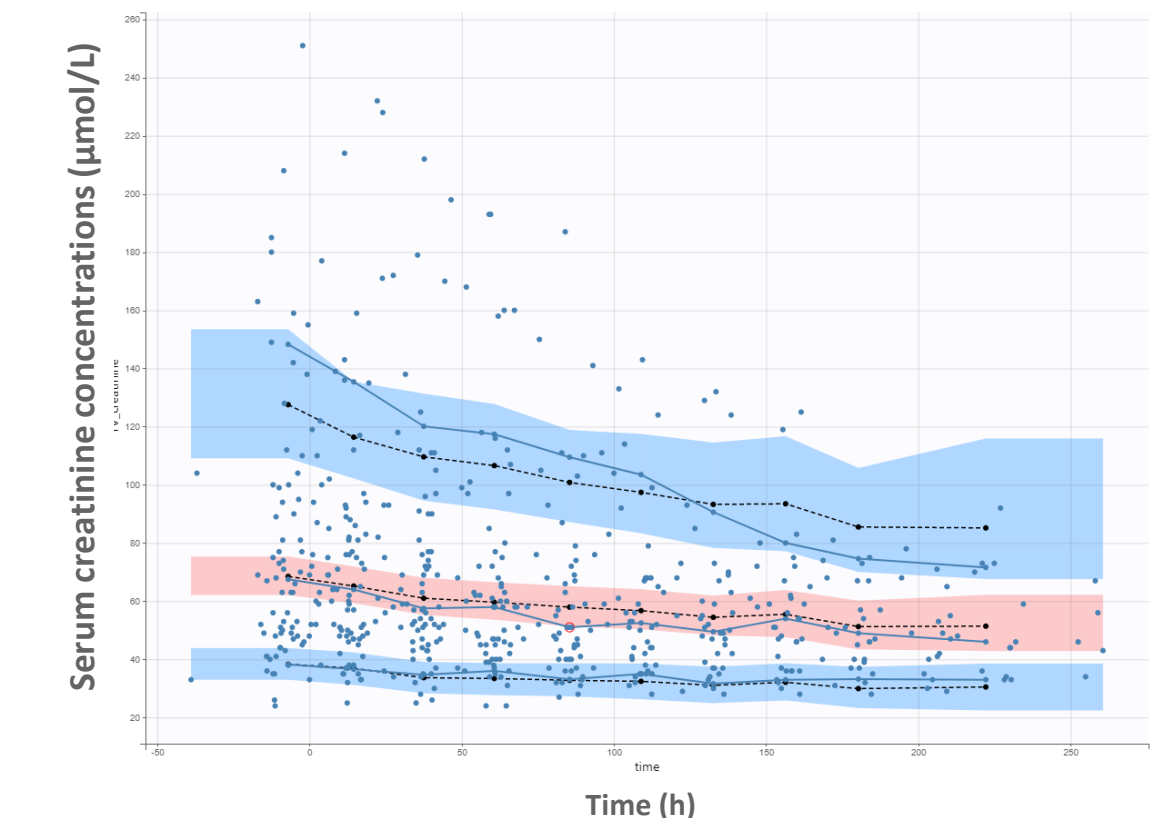
Orange line: spline, dashed black line: 90% prediction interval, IWRES: individual weighted residuals, dashed line: theoretical mean, blue line: empirical percentiles

MODEL EVALUATION



Visual Predictive Check

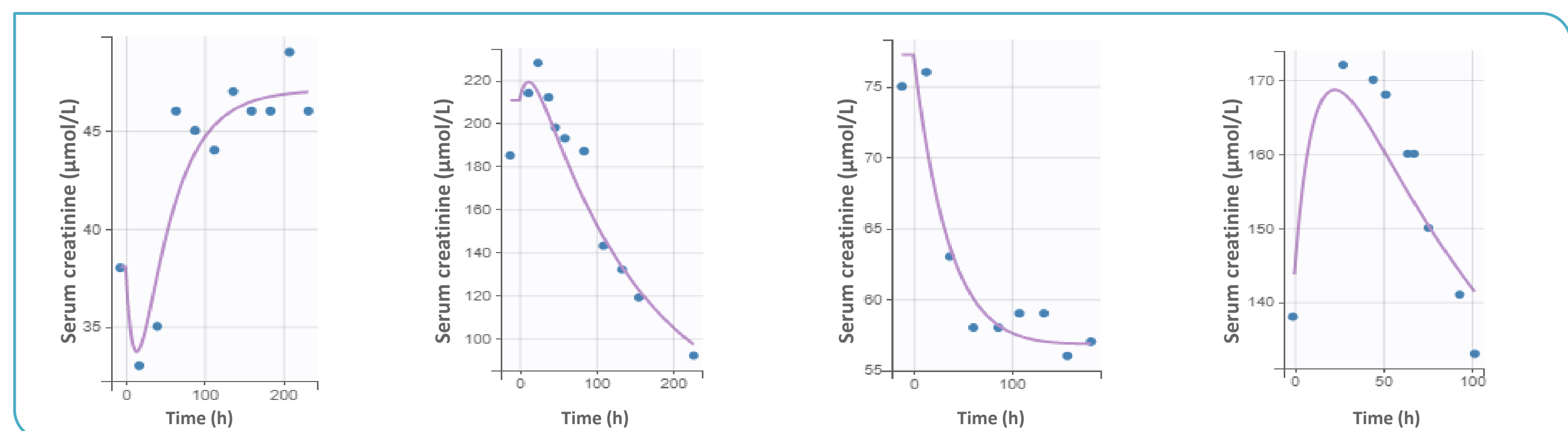
blue solid lines: 5th, 50th and 95th percentiles of observed data, shaded areas: 95% confidence interval of the simulated 50th (red), 5th and 95th (blue) percentiles respectively



→ Intra-individual variation of probability of constant or first order model

- Detection of changes between normal renal function and AKI
- Detection of changes between AKI and recovery of renal function

→ Serum urea concentration explains part of the IIV of creatinine levels



Representative individuals for creatinine with biomarker model

a,b,c,d: purple line: individual prediction of serum creatinine model, blue dot: observed data

→ Good fit, no bias

→ Prediction of next creatinine concentrations

CONCLUSION

- High inter- and intra-variability of renal function in ICU patients was partly explained by time-varying creatinine covariate
- A predictive model of serum creatinine evolution has been developed
- We will combine a cefotaxime Pop-PK model with the creatinine biomarker model

Contact

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