

Population pharmacokinetics of imipenem in intensive care unit patients with ventilator-associated pneumonia

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BACKGROUND

- Imipenem (IMP) is often used for empirical treatment of ventilator-associated pneumonia (VAP)
- Large interindividual variations in the pharmacokinetic (PK) parameters of antibiotics have been reported in intensive care unit (ICU) patients [1]

OBJECTIVES

- To estimate population PK parameters of IMP in ICU patients with VAP
- To evaluate the impact of several covariates on PK parameters of IMP

MATERIAL AND METHODS

Study Data

- Prospective study conducted in ICU patients with presumptive diagnosis of gram-negative bacilli VAP
- IMP was given tid as a 0.5h infusion (500 to 1000 mg)
- Blood samples were collected at predose (0 h) and 0.5, 1, 2, 5, and 8 h after the 4th dose
- IMP plasma concentrations were measured by HPLC/UV (LOQ 0.5 mg/L)

Covariates

- Recorded at the 4th dose (except weight and SAPS II at inclusion)
 - Age
 - Gender
 - Weight
 - delta weight
 - SAPS II
 - Shock
 - PEEP
 - PaO₂/FiO₂
 - Creatinin clearance 4h (CrCl_{4H})
 - Serum albumin
 - Edema score (ES)
 - SOFA

PopPK modelling

PK model of IMP concentration: a two-compartment model with 4 PK parameters CL, V₁, V₂ and Q in accordance with published data [2]

Population analysis

- Estimation of population parameters and their variability by the SAEM algorithm using software Monolix 4.12s [3]
- Proportional model for the residual error and exponential model for the between-subject variabilities
- Data below limit of quantification (BLQ) taken into account in SAEM [4]
- Model evaluation via goodness-of-fit plots

Covariate model building

Preliminary screening from individual parameters: using non parametric Spearman correlation or Wilcoxon tests (using software SAS 9.3)

Forward single-parameter selection: For each PK parameter, all significant covariates during screening were integrated step by step in the model. The best model was defined using the Bayesian information criterion (BIC)

Backward multi-parameter selection: A backward selection step was performed, removing covariates one by one, using the Likelihood Ratio Test (LRT) with one degree of freedom. The likelihood was computed by importance sampling. In the final model, p-value of each covariate was obtained by LRT

RESULTS

Patients

- 51 patients (41 males) were included: median age 60 years (range 28-84), weight 77 kg (45-126), serum albumin 18 g/L (10-28) and CrCl_{4H} 86.4 mL/min (9.1-571.4)
- SOFA and SAPS II scores were 6 (2-14) and 40 (19-74), respectively
- Shock was present in 18 (35%) patients with a edema score of 7 (0-18)

Model fitting and goodness-of-fit evaluation

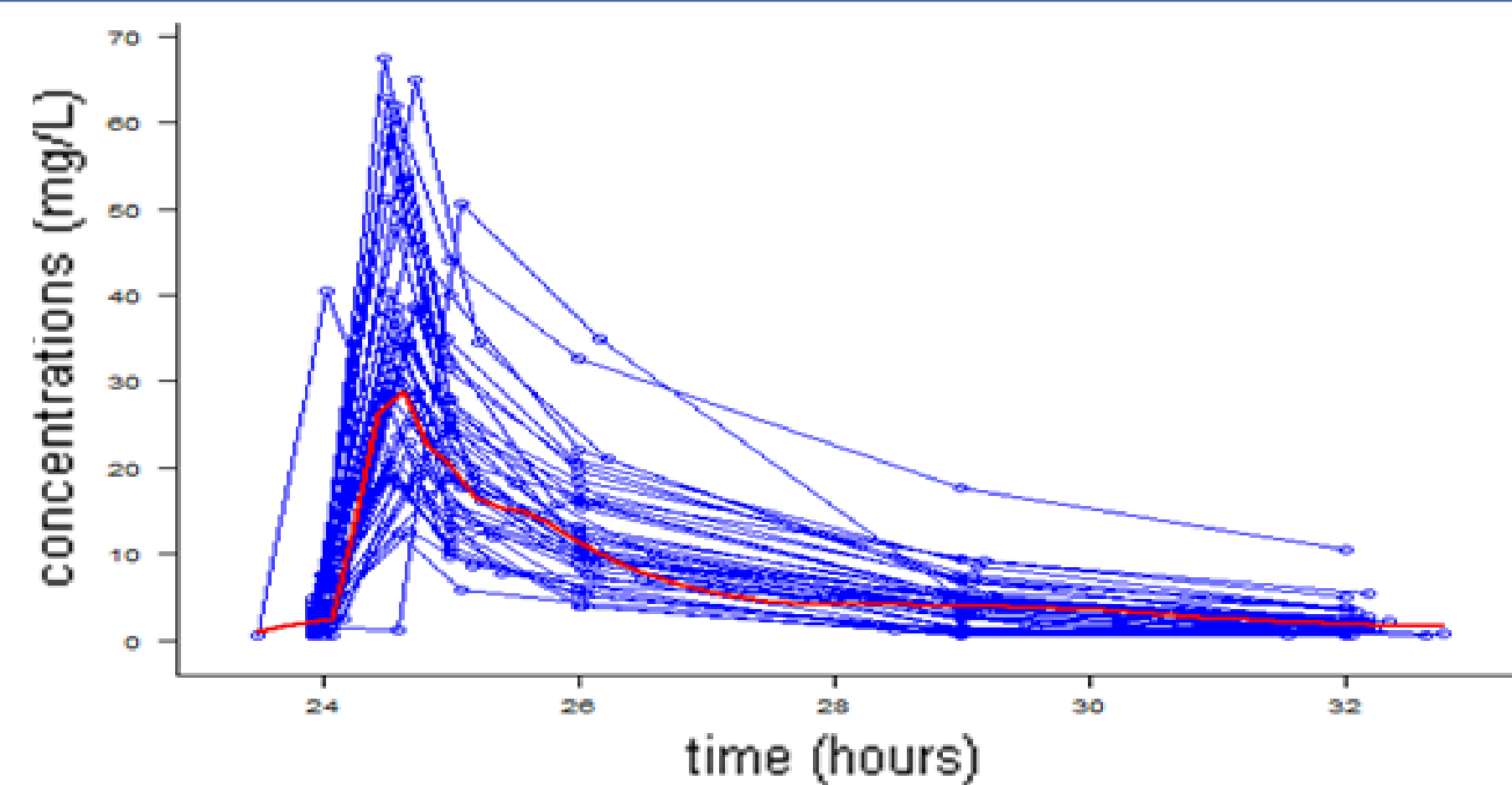


Figure 1: Observed Imipenem concentrations (median=red)

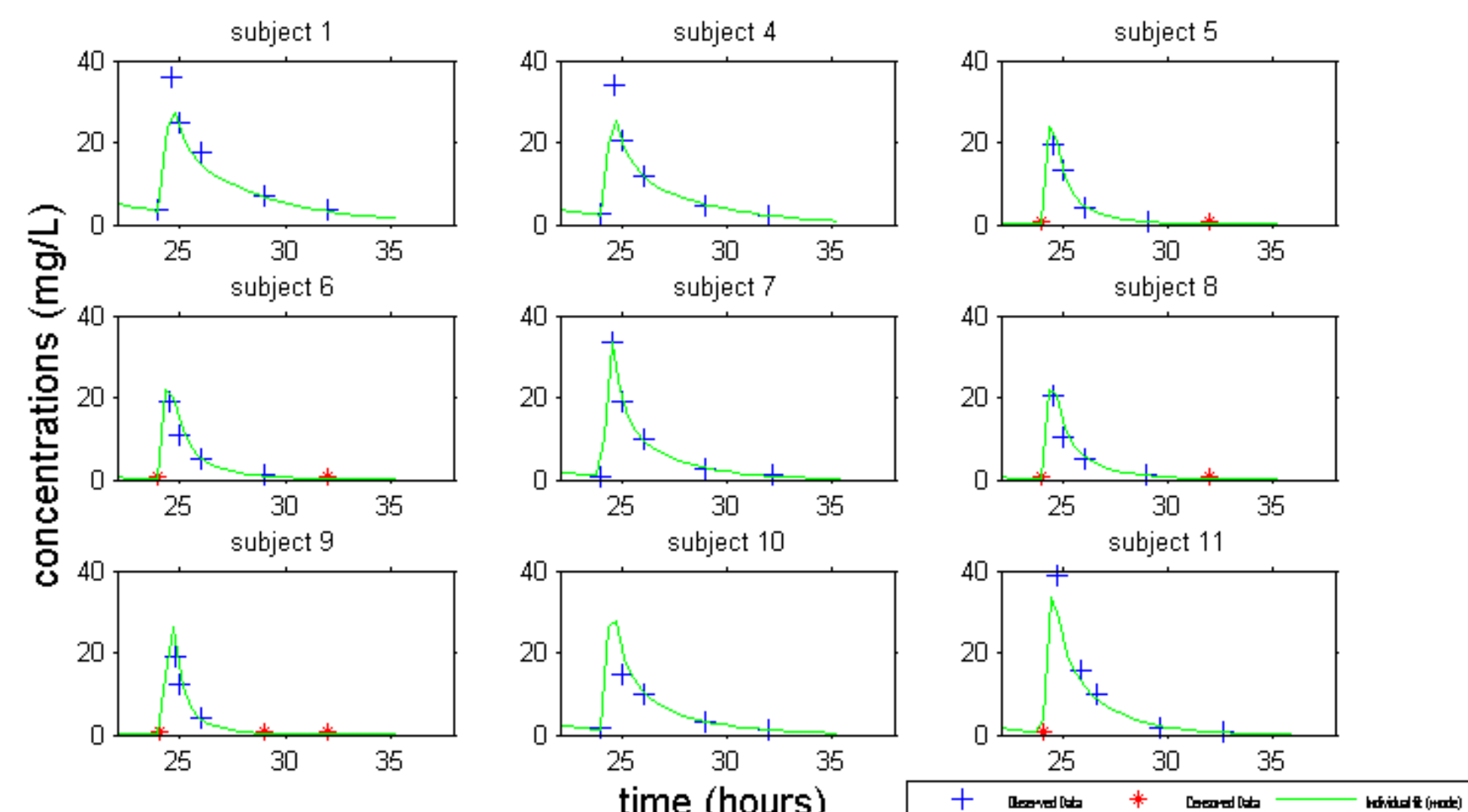


Figure 2: Individual fits with model predicted curves

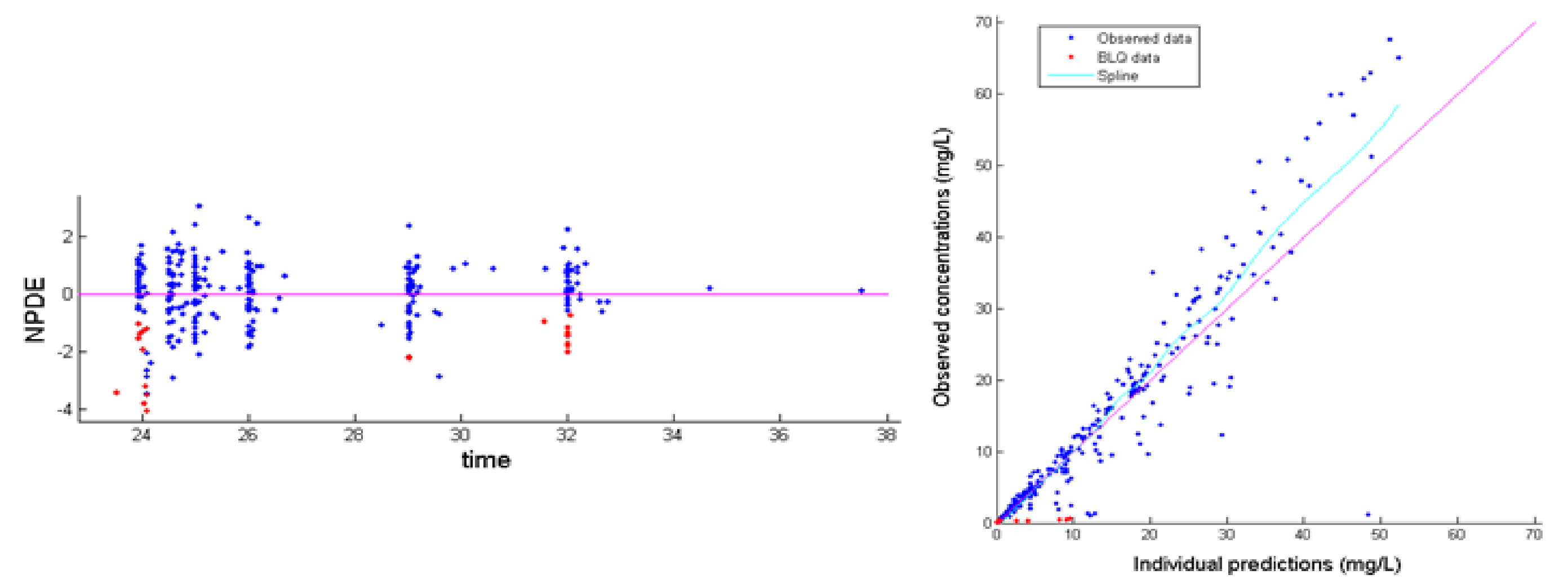


Figure 3: NPDE responses versus time (left) and Observations versus Individual predictions (right)

- Goodness of fit plots were satisfactory

Parameter estimation and relative standard errors (RSE%)

Model	without covariates		with covariates		p-value (LRT)
Parameters	Mean	RSE (%)	Mean	RSE (%)	
<i>Structural model</i>					
CL (L/h)	12.8	6	13.0	5	6.1 10 ⁻⁵
β CrCl _{4H}	.	.	0.22	23	
β age	.	.	- 0.48	34	0.01
V ₁ (L)	17.0	9	17.0	8	0.005
β weight	.	.	0.73	35	
Q (L/h)	19.6	21	20.2	19	0.0007
V ₂ (L)	13.8	11	13.5	10	
β weight	.	.	1.43	25	1.3 10 ⁻⁶
β albumin	.	.	- 1.54	20	
<i>Statistical model</i>					
ω CL	43%	10	33%	11	
ω V ₁	40%	19	24%	23	
ω V ₂	48%	25	22%	54	
σ _{prop}	32%	5	32%	5	
BIC	1595		1555		

Final model with 4 covariates

- Parameters were well estimated with good precision
- Reduction of the between-subject variability was obtained with this model for each individual PK parameter (decrease of 10% for CL, 16% for V₁ and 26% for V₂) and the BIC decreased by 40 points
- The relationship between the most significant covariate and each individual PK parameters in the final model showed on figure 4

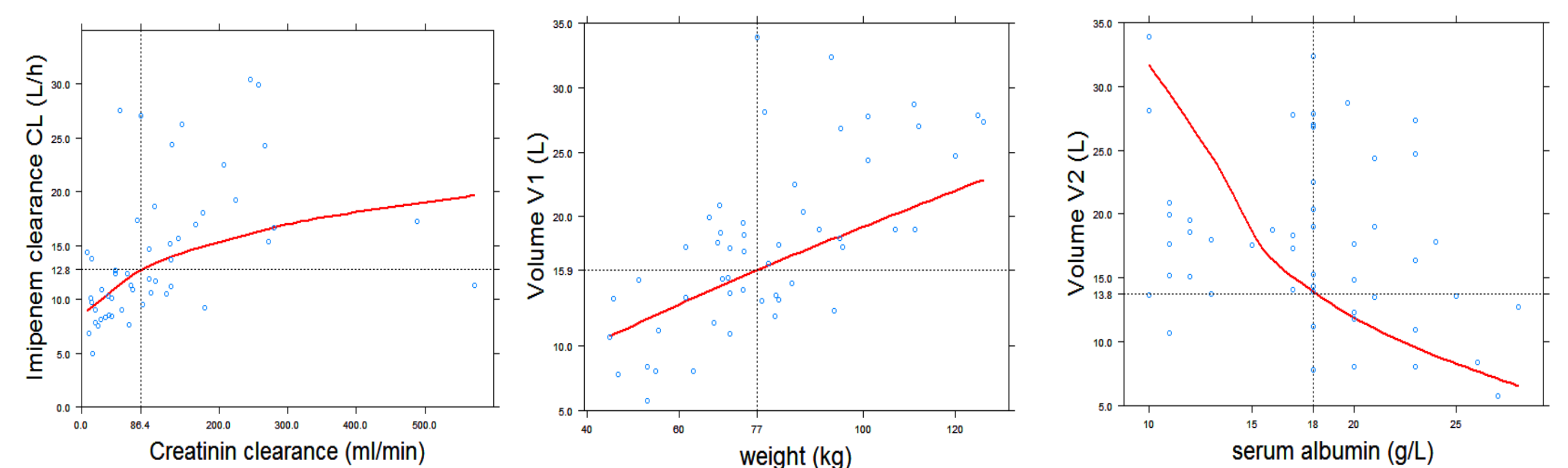


Figure 4: Relationship between individual PK parameters and covariates with model prediction (red)

DISCUSSION

- The large variability of IMP PK parameters in ICU patients with VAP observed in the model without covariates was in accordance with previously published data [2,5,6]
- The IMP PK parameters were best explained by a model with 4 covariates: age, CrCl_{4H}, weight and serum albumin
- Creatinin Clearance is currently widely used to adjust IMP dosage. However, the consideration of these 4 covariates, easily collected in ICU, could refine dose adaptation for critically ill patients.
- Next step: to propose an algorithm for define a dose range of IMP
- This algorithm could help clinicians to achieve pharmacodynamic objective and to limit the emergence of Imipenem resistance

[1] Pea et al. *Clin Pharmacokinet*, 2005; 44:1009-1034.

[2] Sakka S.G and al. *Antimicrobial Agents and Chemotherapy*, 2007; 51:3304-3310.

[3] Kuhn and Lavielle. *Comput Stat Data Anal*, 2005; 49:1020-1038.

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[5] Belzberg et al. *J trauma*, 2004; 56:111-117,

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