

Population pharmacokinetics and dosing regimen optimization of intravenous linezolid in critically ill children

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01. Introduction

Linezolid is a synthetic antibiotic drug from the oxazolidinone class. It is increasingly used in pediatric intensive care units for the treatment of Gram-positive infections that are multi-resistant to other anti-microbial agents. Unpredictable fluctuations in the pharmacokinetic (PK) variables of patients may necessitate adjustment of the drug dose. The objectives of the present study were to establish a population PK model for intravenously administered LZD in critically ill children and to optimize individual's initial dosing regimens.

02. Methodology

Childrens aged 0 to 18 years treated with linezolid administered as a discontinuous infusion were included.

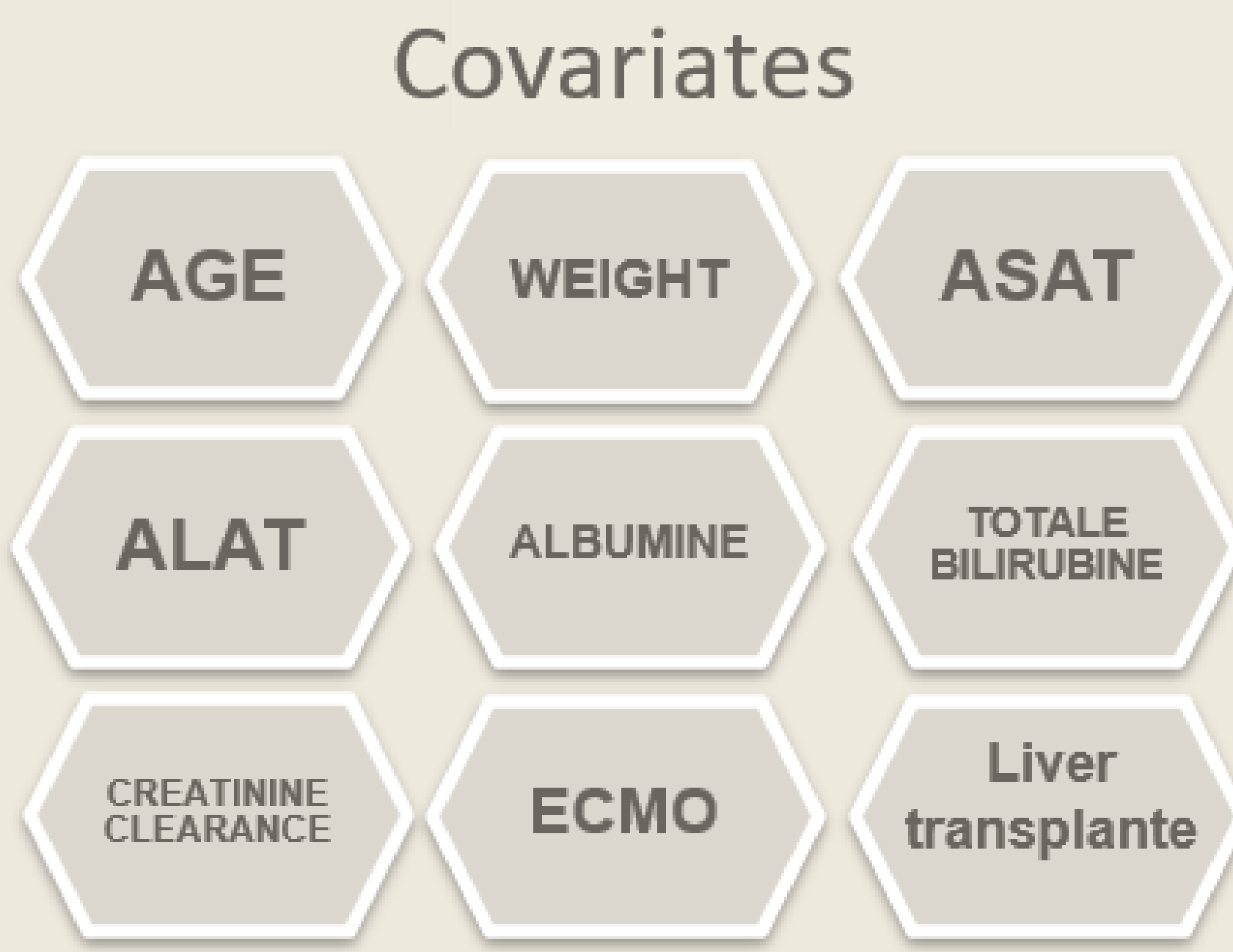
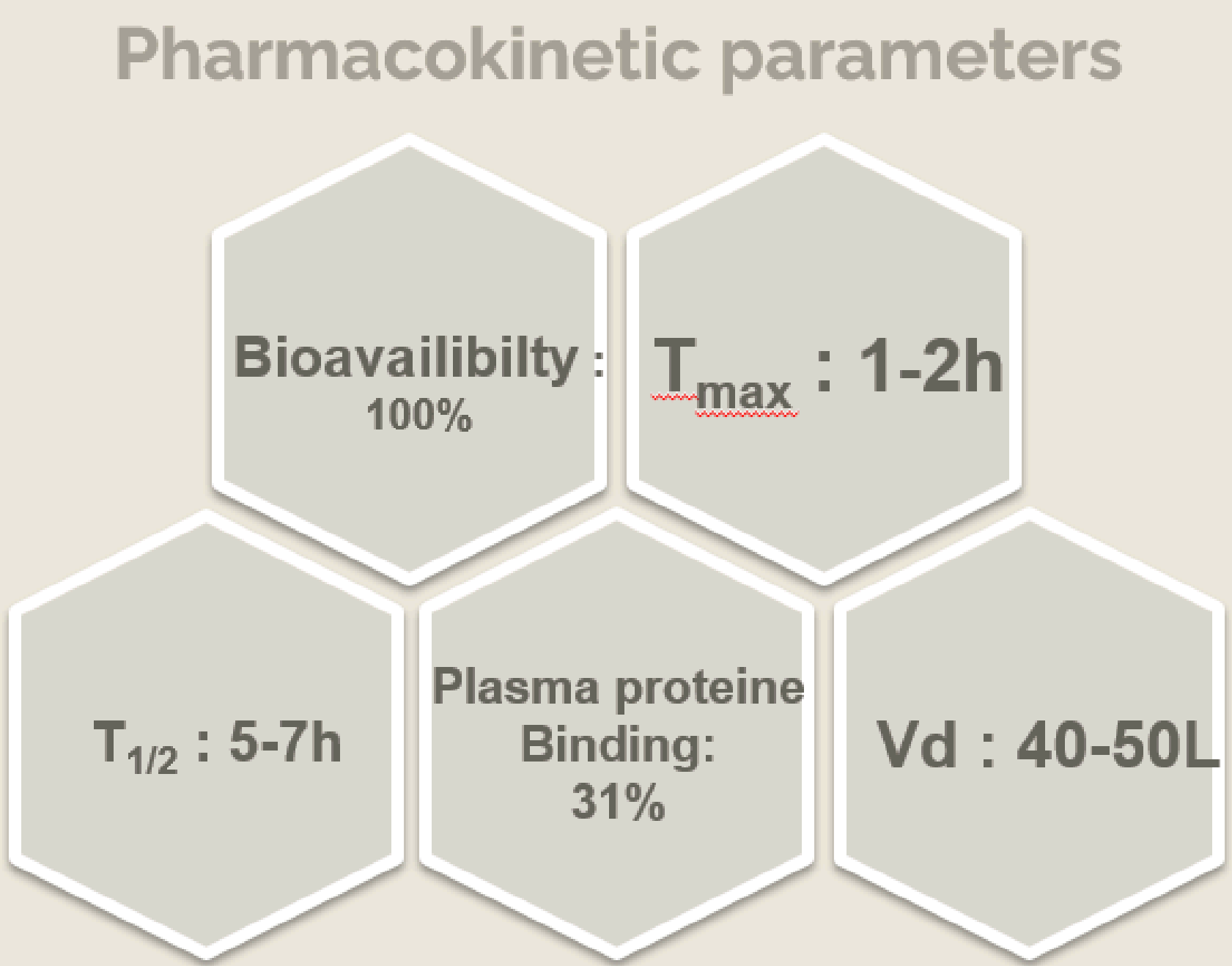
• Dose :
Children > 12 ans : 600mg q12h
pediatric : 10mg/kg q8h

AUC/CMI between 80 and 120
Cmin : 2–7 mg/L

Main adverse effect :
Thrombocytopenia

LZD plasma concentrations were measured using a high-performance liquid chromatography-tandem mass spectrometry method. Data were modeled using nonlinear, mixed-effects modeling software.

"GRAPHICAL DIAGNOSTIC CRITERIA:
1) Observed concentrations (DV) versus predicted concentrations.
2) NPDE
3) PC-VPC



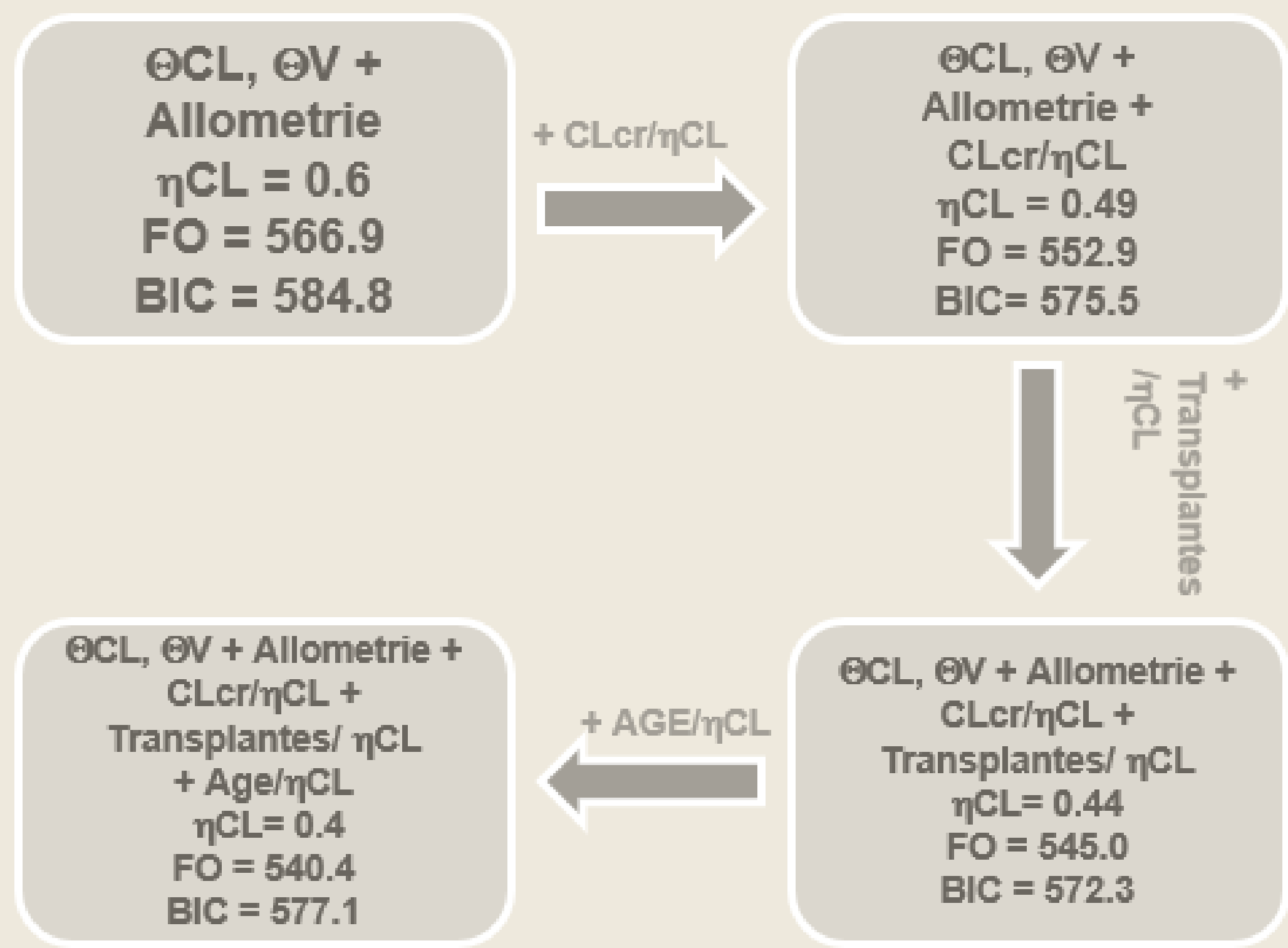
03. RESULTS

Forty-seven patients with a mean age (range) of 0.9 years (0.03 – 15.8 years) and 103 LZD concentration measurements were included. Data were most accurately fit by :

- one-compartment model
- proportional error model
- Retaining only the variability on clearance
- + allometric model

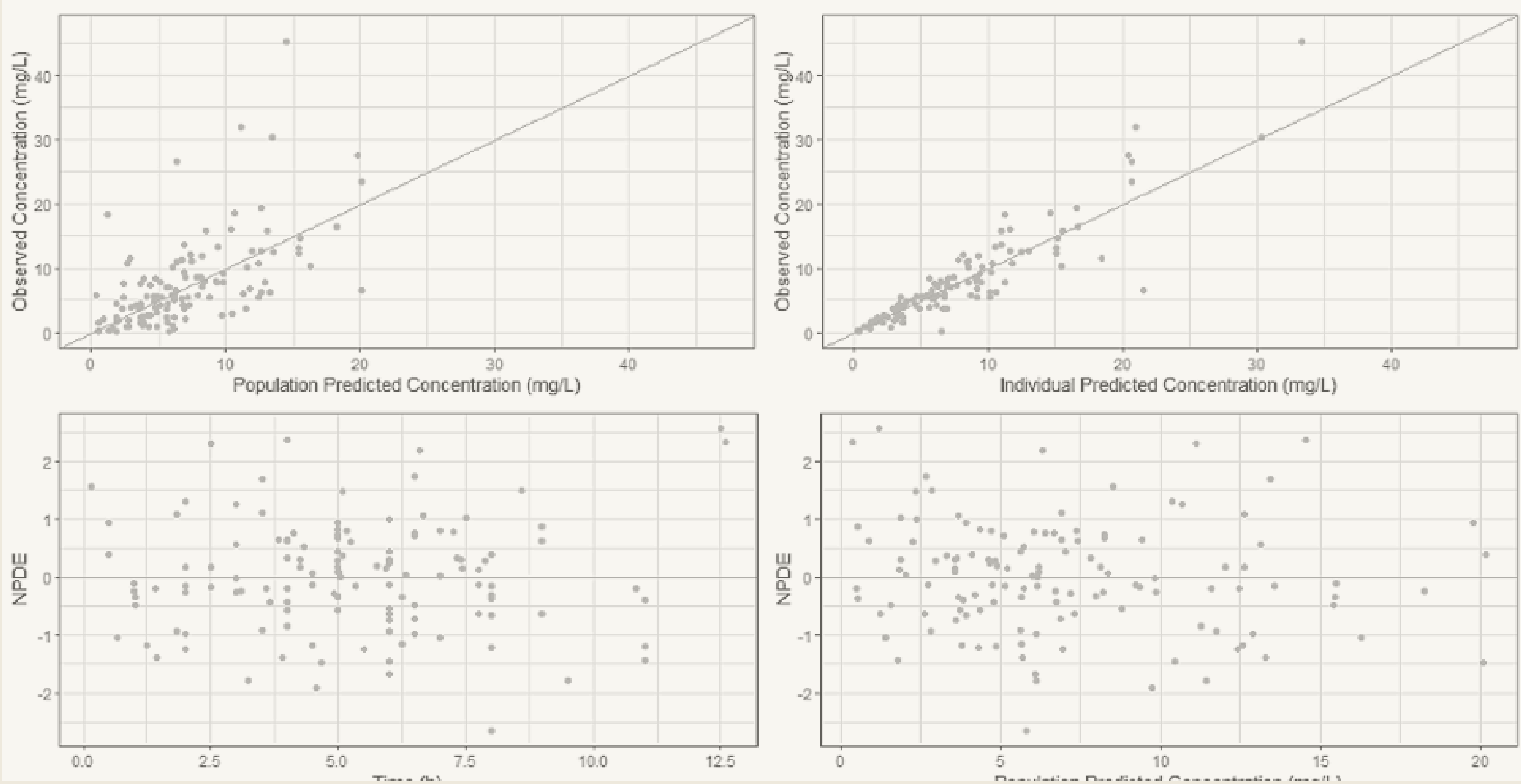
The model incorporating creatinine clearance affecting the inter-individual variability (IIV) of clearance, along with liver transplantation influencing the IIV of clearance, and additionally including the effect of age.

Influence of covariates

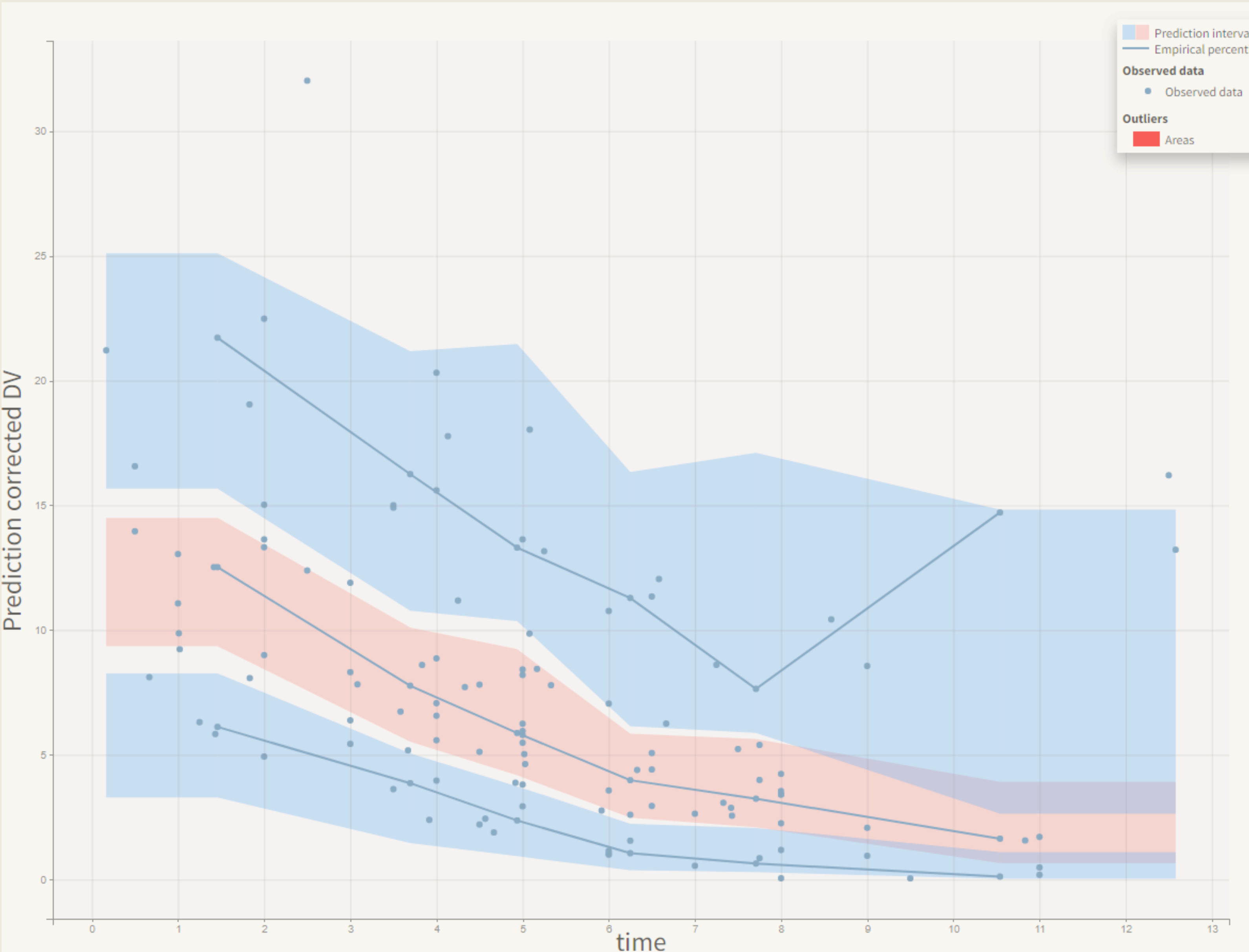


04. Model validation

NPDE



PC-VPC



05. Conclusion

Simulations are currently being performed to propose an optimized dosing regimen for linezolid in this particularly susceptible population.