

# Development of a New Bayesian Estimator for Tacrolimus in Kidney Transplant Patients: A Population Pharmacokinetic approach.

Franç Andreu<sup>1,2</sup>, Helena Colom<sup>2</sup>, Núria Lloberas<sup>1,3</sup>,

<sup>1</sup> Nephrology Department. Hospital Universitari de Bellvitge. <sup>2</sup> Pharmacokinetic Department, Faculty of Pharmacy, UB. <sup>3</sup> Symphony PK sub-study group

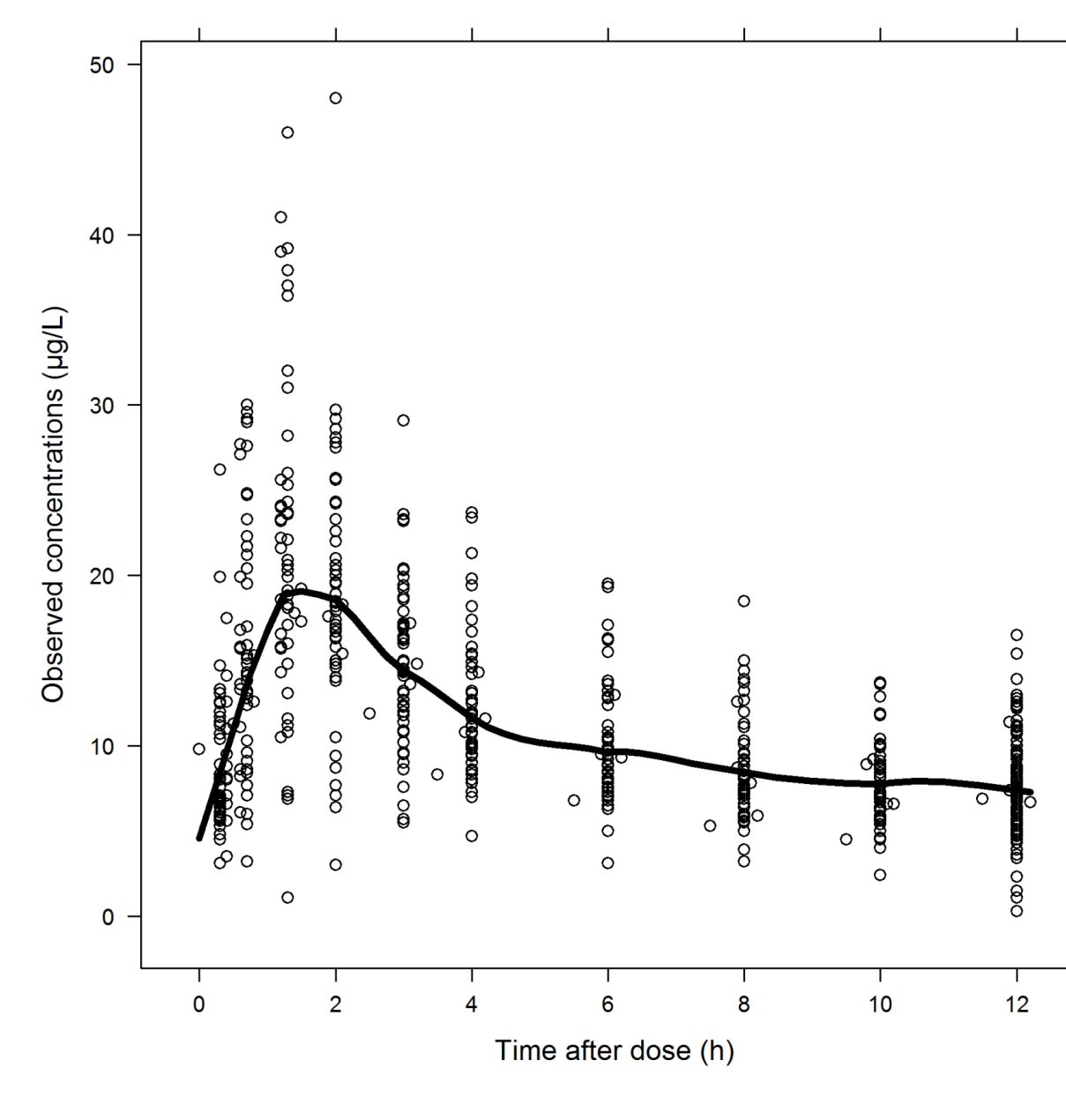


## INTRODUCTION

- Tacrolimus is a calcineurin inhibitor (CNI) well known to prevent the allograft rejection in solid organ and bone marrow transplantations.
- The pharmacokinetics (PK) of tacrolimus is characterized by high variability especially in the absorption process. Several studies have identified body weight, haematocrit, age, liver function and polymorphism, in particular CYP3A5\*3 and ABCB1 as predictive factors of this variability. Moreover time dependent kinetics has been reported.
- The population approach has been a fundamental tool to identify these factors for dose tailoring during the therapeutic drug monitoring thus optimizing efficacy and minimizing side effects such as nephrotoxicity and neurotoxicity

### AIM:

- Identifying characteristics of each patient to generate a model that could explain the variability of Tacrolimus exposure in the target population
- Generate a new acceptable Bayesian Estimator to be easily applied routinely in the Hospital service reducing cost and increasing efficiency.



	mean (min-max)
Number of patients	16
Weight, kg	69 (35-104)
Age, y	52 (31-72)
Gender (male/female)	10/6
CL <sub>CR</sub> *, (mL/min)	58.1 (11.6–122.5)
Plasma Albumin, (g/L)	41.6 (33–47.0)
ALT, (U/L)	35.1 (6.0–318.0)
AST, (U/L)	21.8 (6.6–104.0)
Serum total bilirubin, (mg/dL)	0.54 (0.17–1.22)
Hemoglobin, (g/dL)	12.3 (7.3–16.5)
Haematocrit	0.37 (0.23–0.49)
<b>Concomitant medication</b>	
MMF doses, mg twice daily	1000
MDR1 Polymorphism	
C3435T (CT/TT)	7/3

Figure 1. Tacrolimus Total Blood Concentrations.

Table 1. Demographical Data

## METHODS

- Full pharmacokinetic profiles of tacrolimus profiles from 16 patients at day 7 and months 1, 3, 6 and 12, after the start of the treatment were collected (Fig. 1).
- Demographic, biochemical, concomitant medication, pharmacogenomic data were gathered. (Table 1)
- PPK analysis was performed with PsN-toolkit NONMEM 7.2, using FOCE-I method. Graphical analysis were performed with Xpose4 and R-code. Non compartmental analysis was done with WinNonlin 5.3.
- Model evaluation was performed using goodness-of-fit plots, Bootstrap Analysis (n=200), Prediction Corrected Visual predictive check (pcVPC), posterior predictive check (PPC) and Normalized prediction distribution error (NPDE).
- An external validation was performed with 91 Tacrolimus C<sub>trough</sub>. This performance was evaluated in terms of bias (median prediction error) and precision (Root Median Squarre Error)
- Limited Sampling Strategy (LSS) was performed was chosen on the basis of a combination of a maximum of two or three sampling times in the first 6 hours post-dose. The performance of the Bayesian estimator was estimated by Pearson correlation and, according to Sheiner and Beal, in terms of bias (MPPE) and precision (RMSE).

## RESULTS

- Data set:** 593 Tacrolimus levels from 16 patients were simultaneously analyzed.
- Good correlation between AUC<sub>0-12h</sub> and C<sub>trough</sub> (fig. 2)
- Base Model** (Table 2): PK of Tacrolimus was best described by a two compartment model including 3 absorption transit compartments.
- IIV could be associated to CL, Ka and MT.
- IOV could be associated to CL of Tacrolimus.
- Proportional residual variability
- Covariate inclusion:** ABCB1 and Haematocrite included in CL did not reduce significantly the minimum objective function (MOFV)
- Total bilirubin reduced MOFV but did not result in a decrease of IIV<sub>CL</sub>
- Base model was retained as final model
- Internal validation:** pcVPC (fig. 4), PPC (fig. 5) and npde (fig. 6) showed a good predictability of the model
- External validation:** A good accordance between the observed (DV) and individual predicted (IPRED) concentrations was found. The median values and the 5<sup>th</sup> and 95<sup>th</sup> percentiles of bias and precision were 0.37µg/L (-0.11µg/L – 1.20µg/L) and 0.38µg/L (0.02µg/L – 1.21µg/L) respectively.

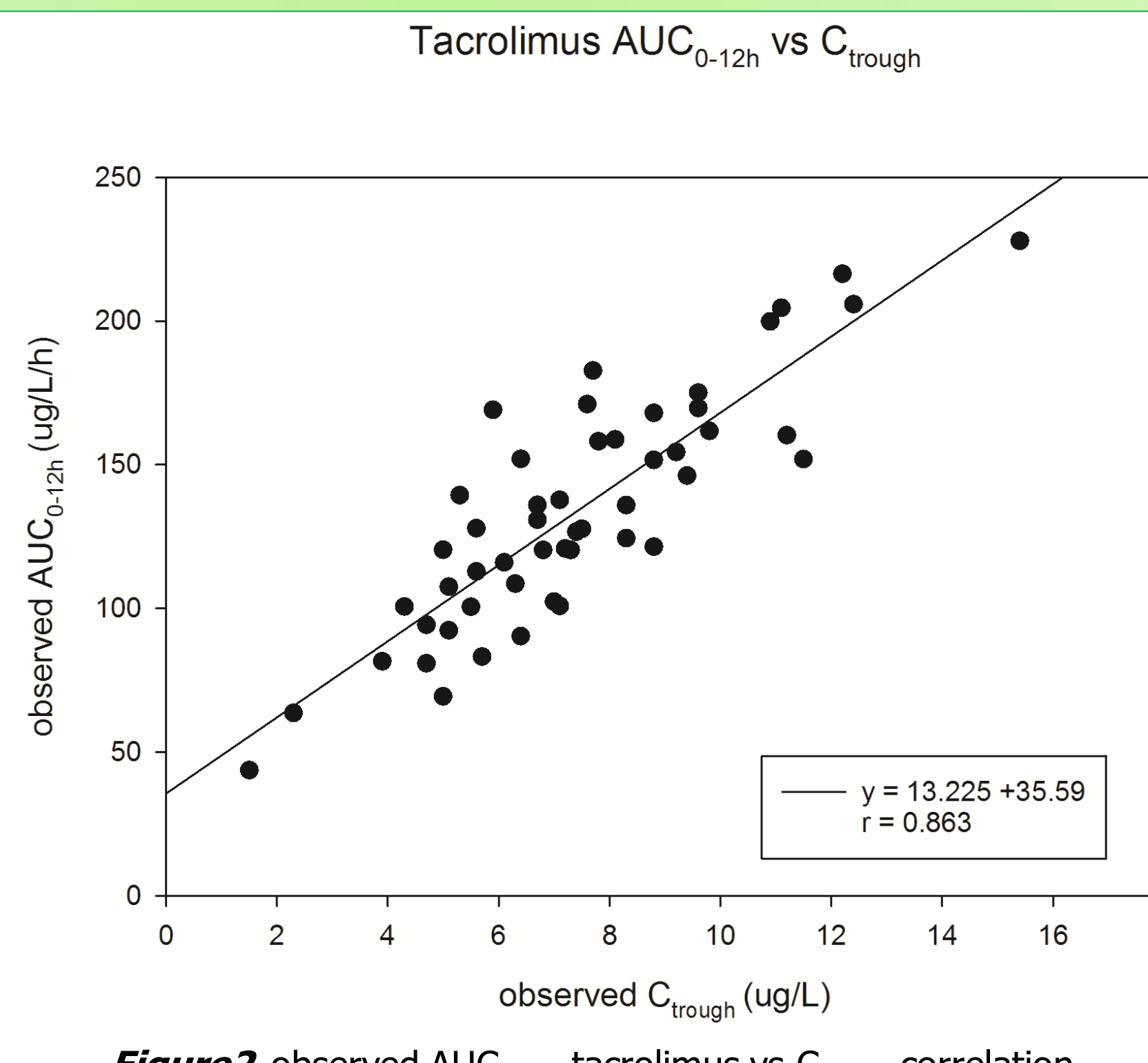


Figure 2. observed AUC<sub>0-12h</sub> tacrolimus vs C<sub>trough</sub> correlation

Parameter	Units	Base model	Bootstrap Analysis
		Estimate (RSE %)	Median (95% CI)
<b>Disposition parameters</b>			
Tacrolimus			
CL	L/h	16.50 (10.9)	16.47 (13.64 – 19.75)
V <sub>c</sub>	L	9.89 (21.9)	10.30 (1.81 – 17.08)
CL <sub>D</sub>	L/h	35.56 (7.8)	35.49 (30.09 – 41.81)
V <sub>p</sub>	L	526.03 (18.0)	541.08 (382.48 – 974.67)
<b>Absorption parameters</b>			
K <sub>a</sub>	h <sup>-1</sup>	0.47 (7.7)	0.471 (0.402 – 0.617)
MT	h	0.83 (10.0)	0.838 (0.604 – 1.105)
K <sub>tr</sub>	h <sup>-1</sup>	3.61 [fixed]	3.61 [fixed]
<b>Interindividual and Interooccasion variabilities</b>			
IOV <sub>CL</sub>	%	29 (24)	28 (22 – 36)
IIV <sub>CL</sub>	%	39 (44)	36 (16 – 54)
IIV <sub>Ka</sub>	%	35 (36)	33 (15 – 46)
IIV <sub>MT</sub>	%	32 (47)	31 (11 – 44)
<b>Residual variability</b>			
Proportional	%	21 (20)	21 (17 – 26)

CL: Clearance, VC: central volume, CL<sub>D</sub>: intercompartmental clearance, V<sub>p</sub>: peripheral volume, Ka: absorption constant, MT: mean transit time

Table 2. Final Parameters Estimates of Tacrolimus model

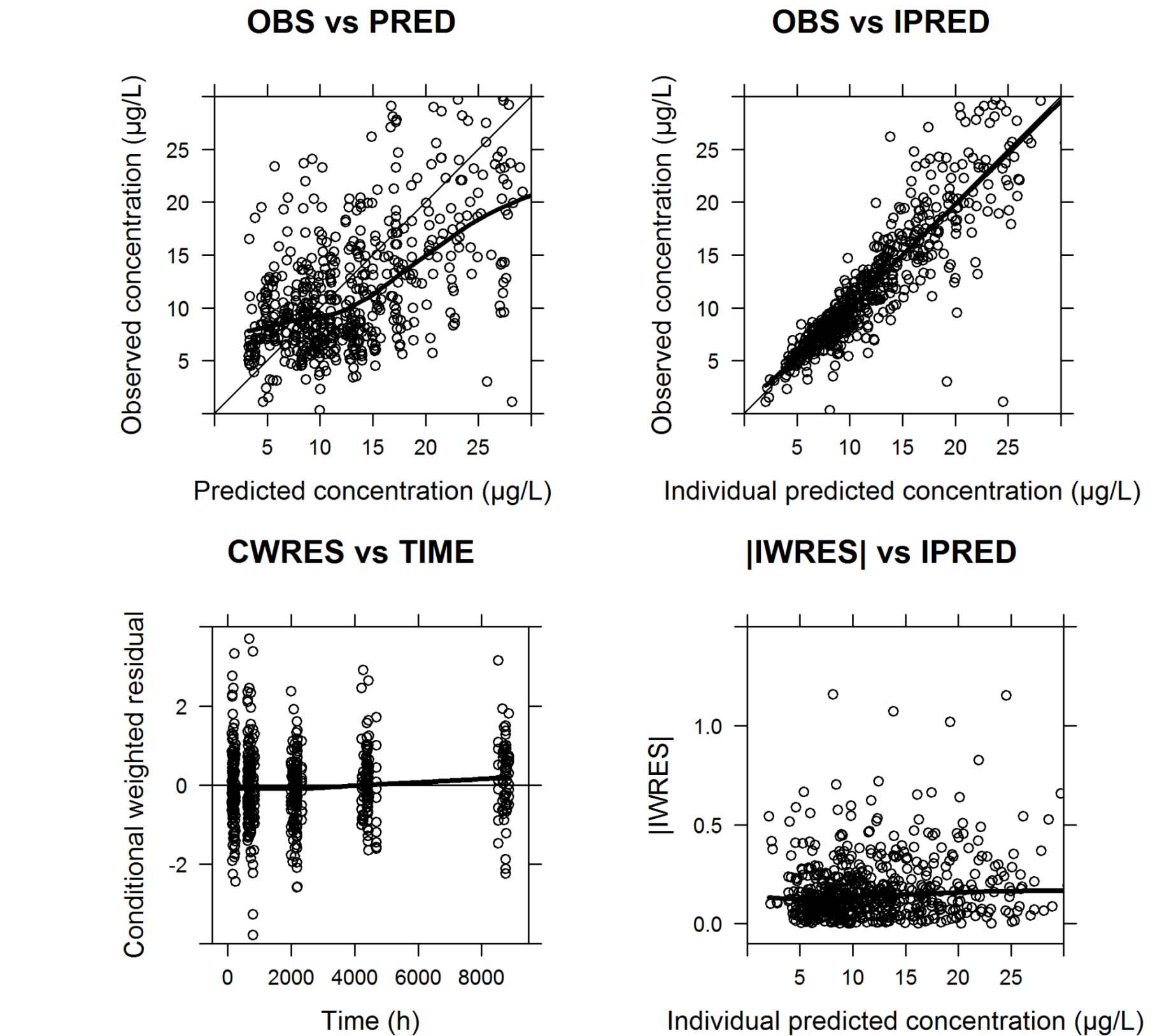


Figure 3. Goodness-of-fit plots for the Tacrolimus population PK model

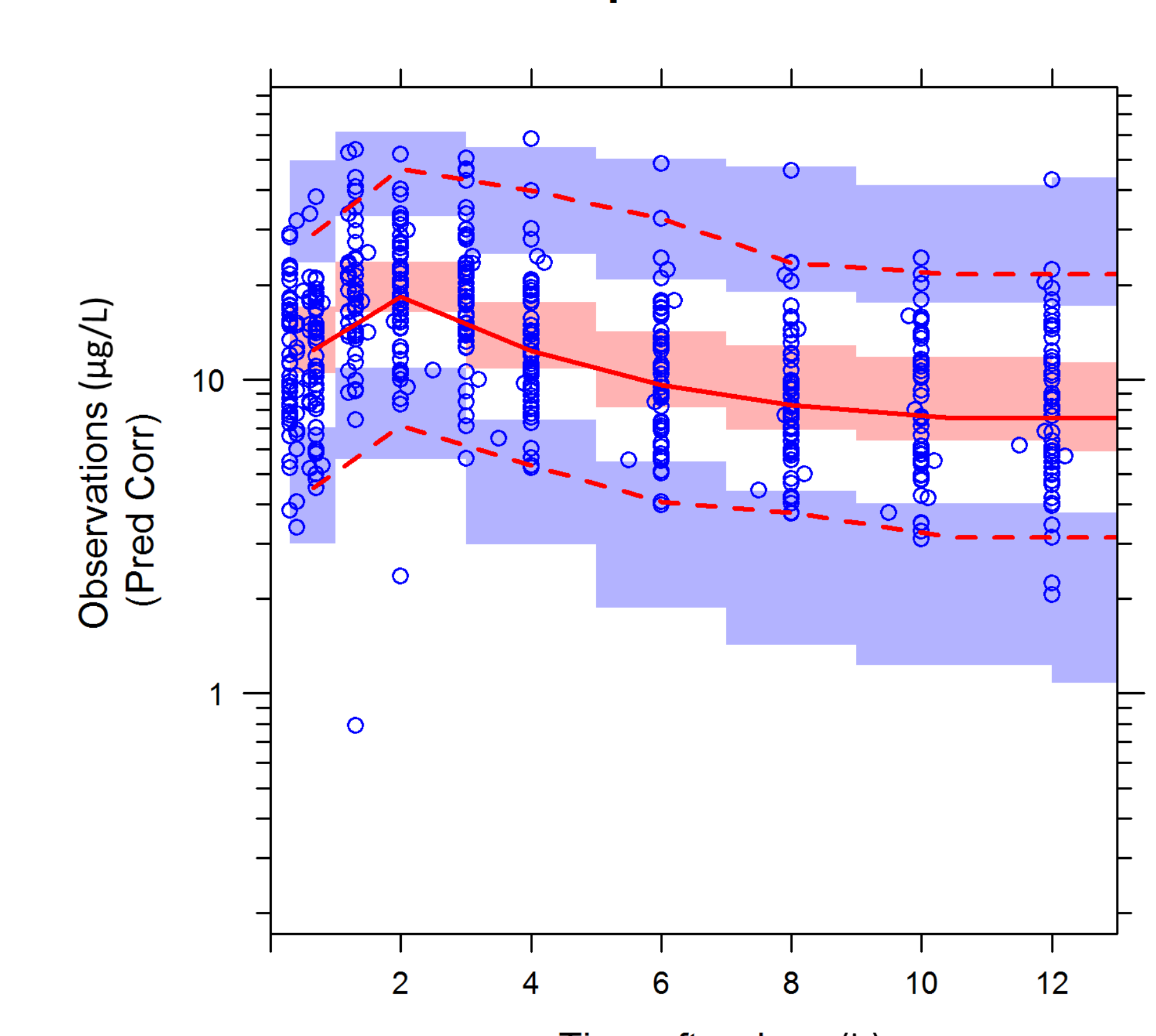


Figure 4. Prediction corrected VPC of Tacrolimus level

- Limited Sampling Strategy:** A two sampling times strategy at 0min pre-dose and 90min post-dose showed good correlation  $r^2=0.86$  and bias of 4.04% (range, -13.30% +16.18%, RMSE=0.81%).
- In order to reduce costs and to achieve the best patient compliance in limited sampling strategy, only one sampling time at pre-dose was considered.
- Differences between predicted concentrations from 0 to 12h by applying a single pre-dose sampling strategy vs observed concentrations of two different patients at different post-transplant times (Fig. 7).
- The LSS at pre-dose showed a performance of  $r^2=0.75$  and bias of 6.78% (range, -16.26% +30.06%, RMSE=1.42%).

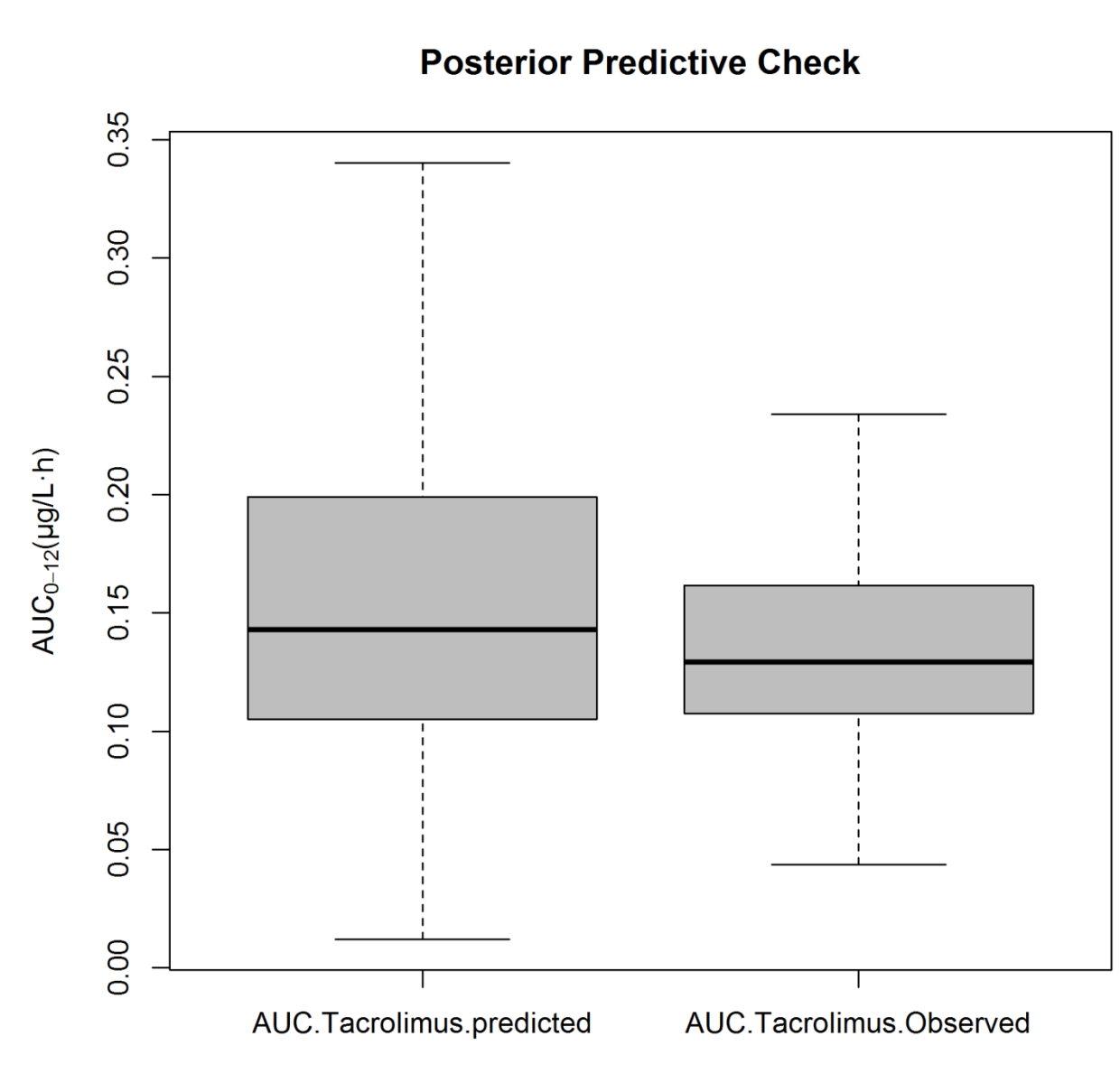


Figure 5. Boxplots of the distributions of predicted and observed AUC<sub>0-12h</sub> (PPC)

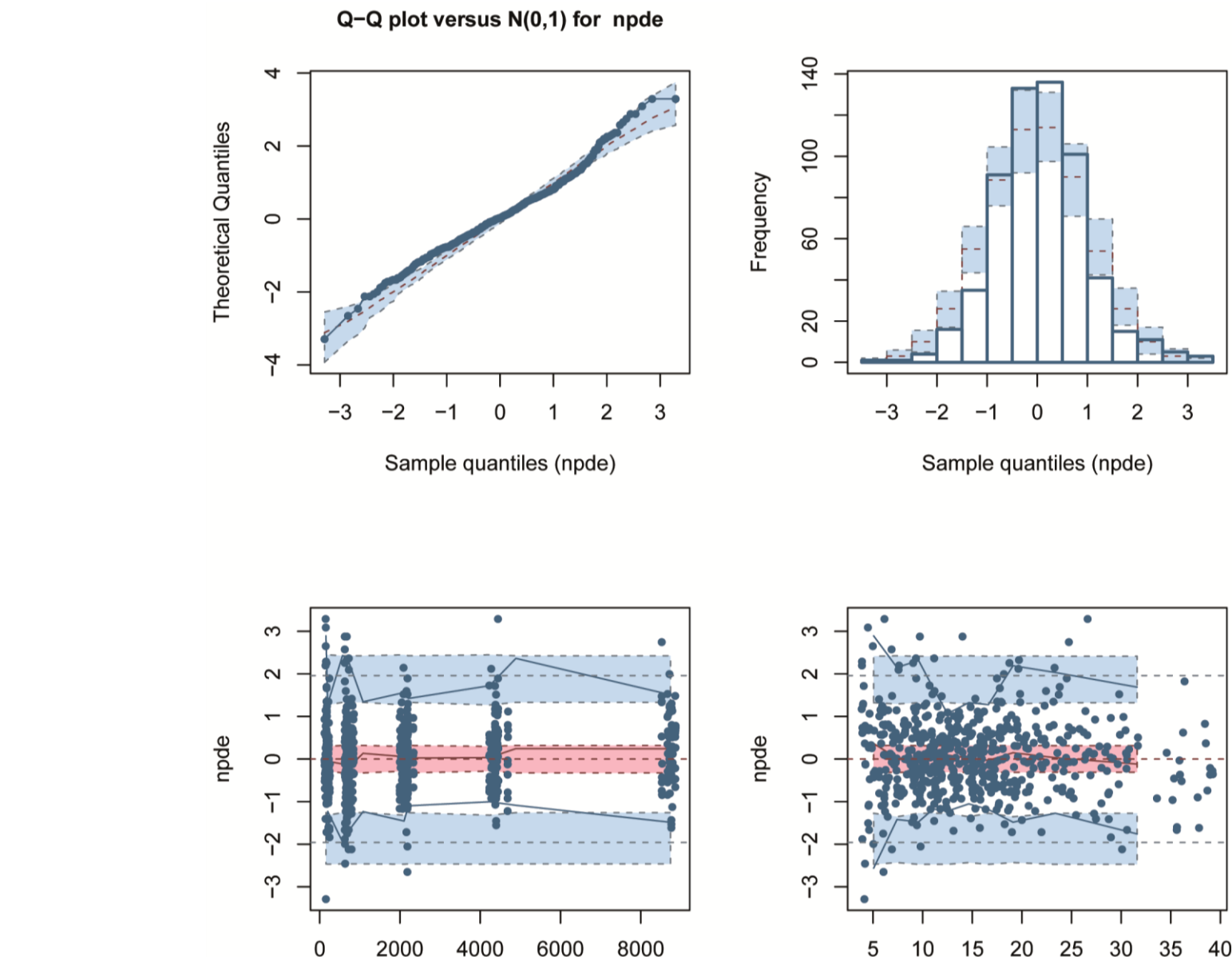


Figure 6. Normalized Prediction Distribution error (NPDE)

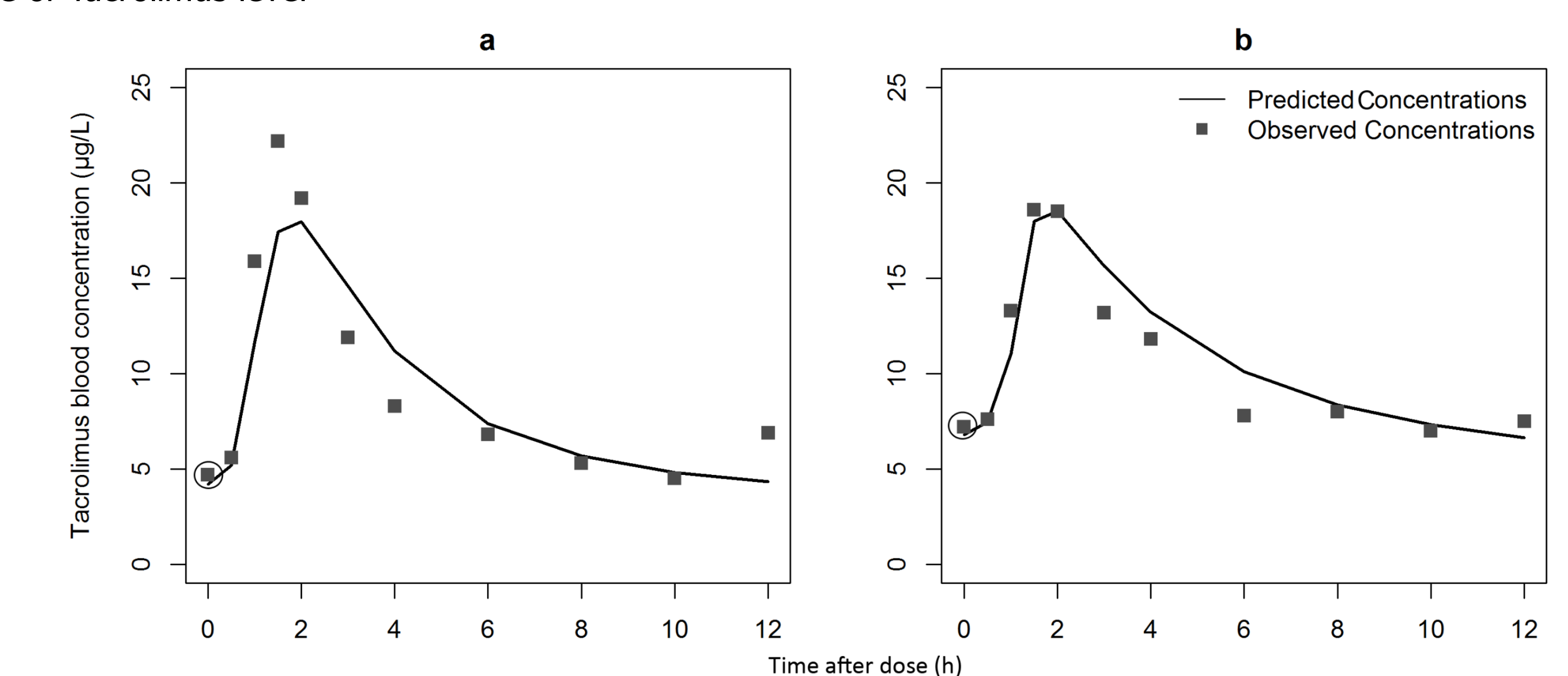


Figure 7. Limited Sampling Strategy: Observed vs predicted concentrations at predose of 2 patients at week 1 (a) and month 3 (b)

## CONCLUSIONS

- A model of tacrolimus in renal transplant patients was built with good accuracy according to an internal and external validation with similar parameter estimates compared to former studies. Haematocrite nor ABCB1 polymorphism reduced the IIV<sub>CL</sub> due to the lack of statistical power.
- A new Bayesian estimator with one single sampling at pre-dose could be applied routinely in clinical practice and reduce economical costs and patient compliance in LSS.