

The expression of *ABCB1* gene influences the PK of rivaroxaban – a PK/PD study in patients with the total hip or knee arthroplasty

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Background

Rivaroxaban is commonly used in patients undergoing hip or knee replacement surgery for prevention of deep vein thrombosis which may lead to pulmonary embolism.¹ Rivaroxaban is a substrate for ABCB1 (P-glycoprotein, P-gp) and BCRP (Breast cancer resistance protein) transporters.²⁻⁴ Currently, it is unclear how the *ABCB1* gene expression influences the PK and PD of rivaroxaban.

Objectives

Our study aims to assess the **population PK and PD of rivaroxaban** in patients undergoing the total hip or knee replacement. We aim to evaluate the **influence of the *ABCB1* gene expression and two single nucleotide polymorphisms (SNP)** on the PK and PD of rivaroxaban.

Methods

- 17 patients**, scheduled for their first total hip or knee replacement;
- polymorphism genotyping and the *ABCB1* gene expression assay;
- rivaroxaban treatment start: 6 h after the surgery, 10 mg /24h;
- total of 82 plasma concentration-time points (cca 5 per patient);
 - 3h, 12h and 24h after the first dose, 3h after the 3rd and 5th dose
- NONMEM 7.3⁵**, Laplacian estimation and M3 for concentrations below the limit of quantification; BIC value was used for model selection;
- Stepwise covariate modelling
 - age, sex, genetic polymorphisms on the gene *ABCB1* – rs10445642 and rs4148738, body mass index, smoking, glomerular filtration, concomitant medication and the *ABCB1* expression
- sequential PK/PD modelling**

Patients

Table 1. Patients' characteristics.

Characteristic	Number / Mean ± SD
Patients	17
Hip/knee arthroplasty	10/7
Female/Male	9/8
Smoking	2
Concomitant therapy with SSRI	2
Age	64.7 ± 10.2
Body mass index	
18.5 - 24.5 kg/m ²	3
25.0 - 29.9 kg/m ²	8
30.0 - 34.5 kg/m ²	5
35.0 - 39.9 kg/m ²	1
Glomerular filtration rate	
≥ 90 mL/min/1.73m ²	5
60-89 mL/min/1.73m ²	11
30-59 mL/min/1.73m ²	1

Results

Pharmacokinetics

Table 2. Estimated values of pharmacokinetic parameters.

Parameter	Population mean (%SE)	IIV, %CV (%SE)
Ka (h ⁻¹)	0.147 (14.3)	204 (8.63)
Cl/F (L/h)	6.12 (15.8)	70.9 (13.6)
V/F (L)	96.8 (13.1)	NA
Covariate on Cl		
- Expression of ABCB1	0.817 (28.8)	NA
Proportional error	0.595 (12.7)	NA

Figure 2. Goodness-of-fit for the final pharmacokinetic model.

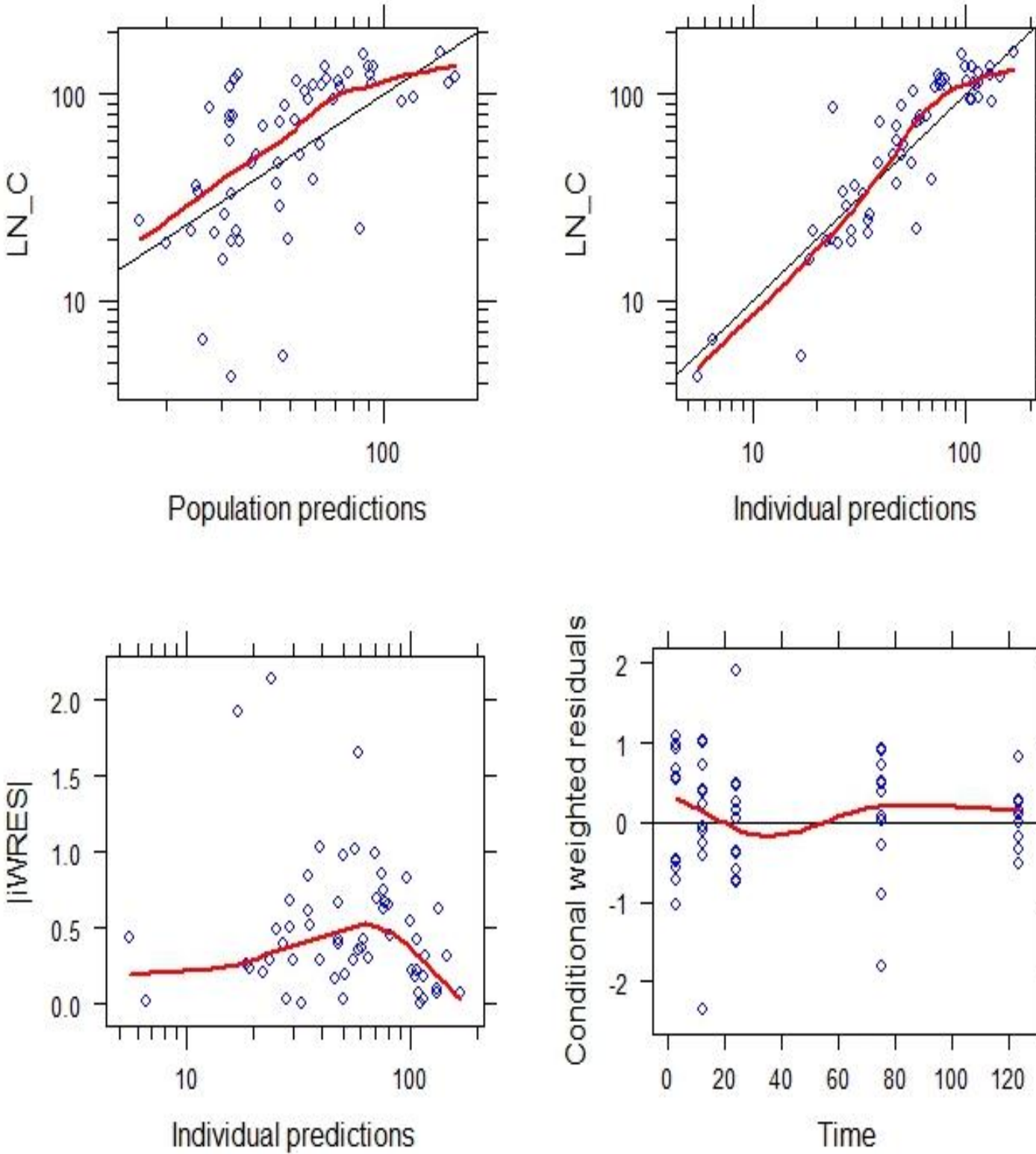


Figure 1. ABCB1 expression in patients before and after surgery. p = 0.000076

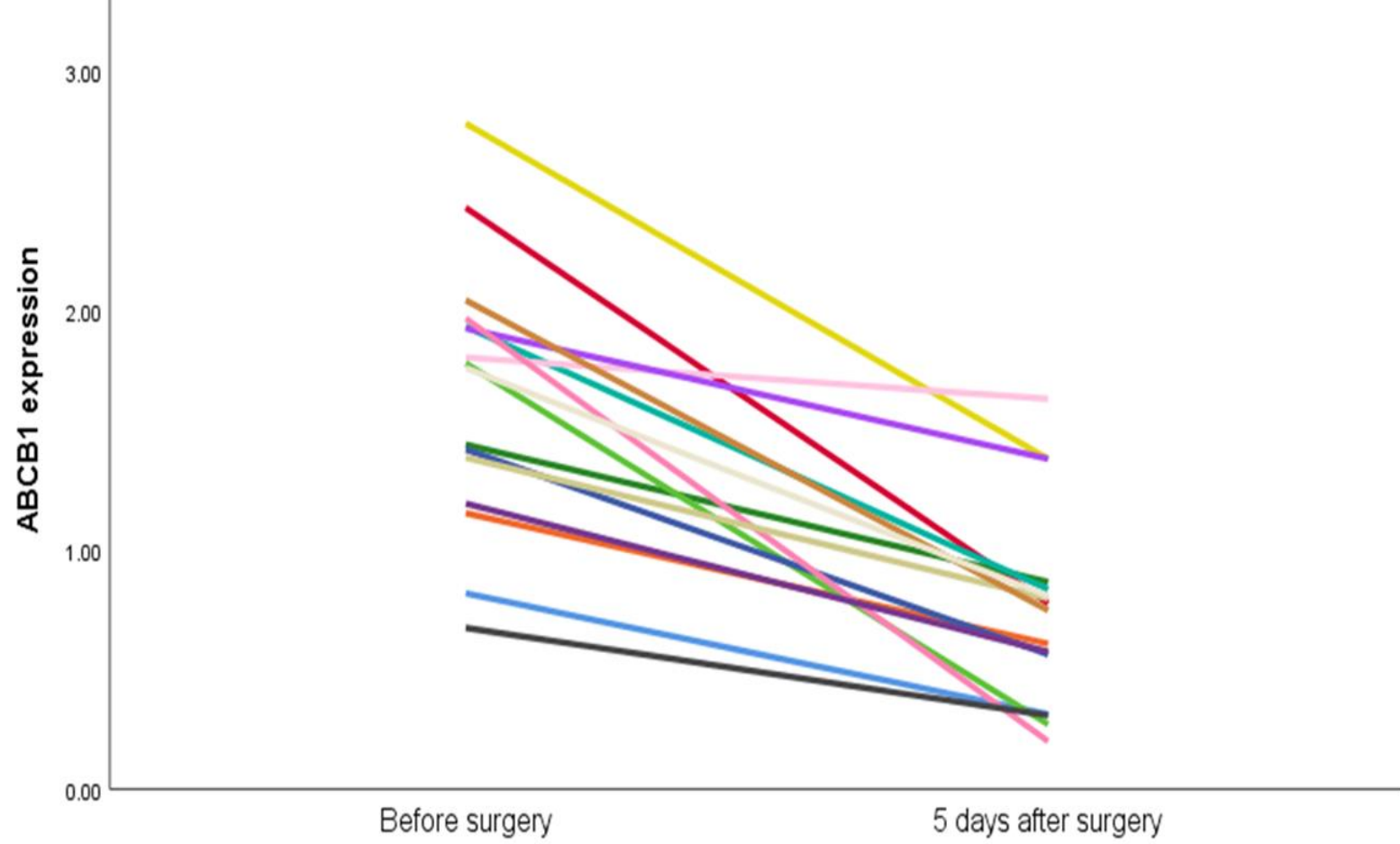
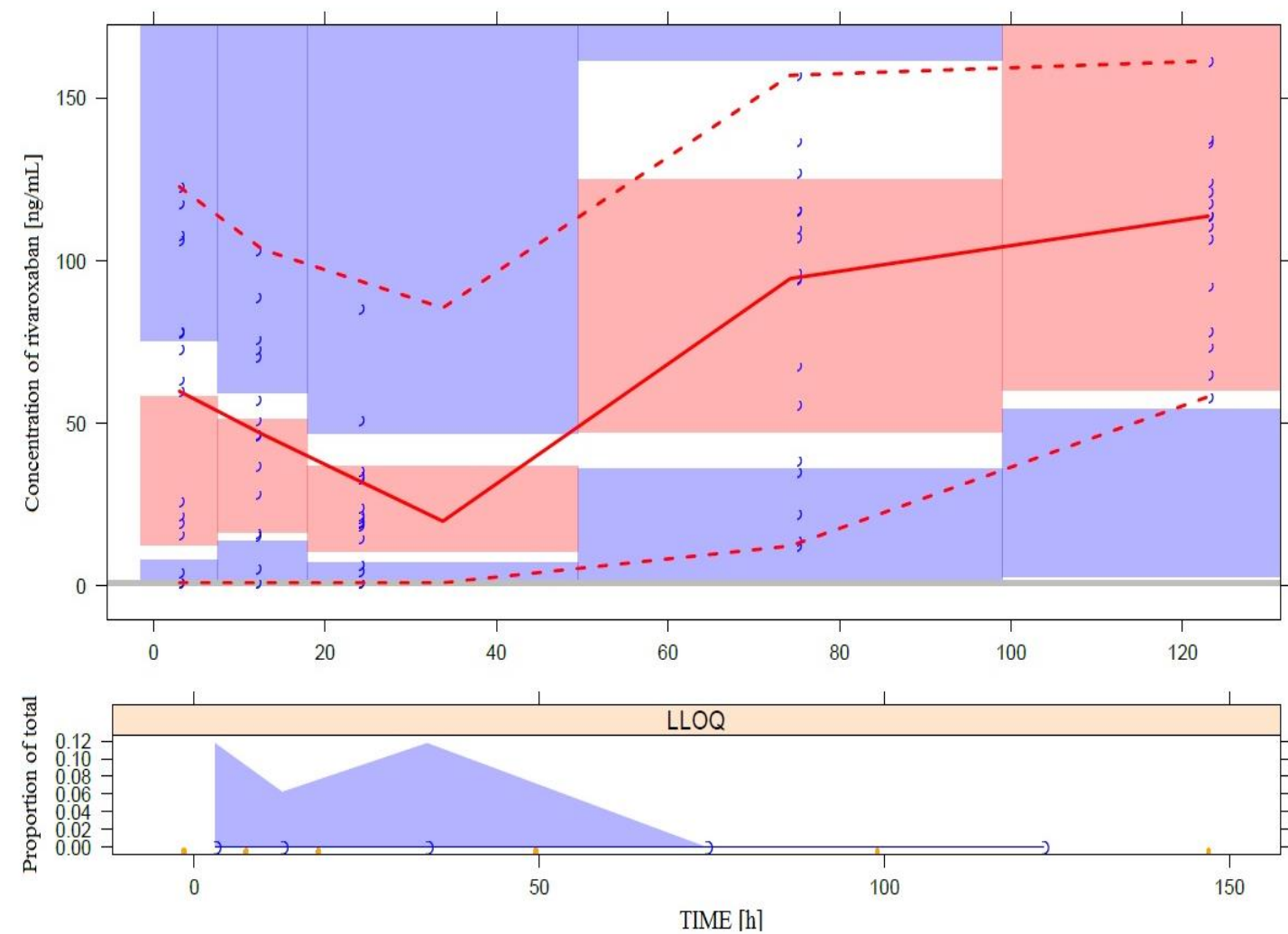


Figure 3. Visual predictive check for the final pharmacokinetic model.



Pharmacodynamics

Prothrombin time (PT)

Table 3. Estimated pharmacodynamic parameters

Parameter	Population mean (%SE)	IIV, %CV (%SE)
PT ₀ [s]	12.8 (4.48)	11.4 (21.1)
Slope [s/ng/mL]	0.215 (58.4)	88.5 (41.9)
Additive error [s]	1.85 (14.1)	NA

Figure 4. Goodness-of-fit

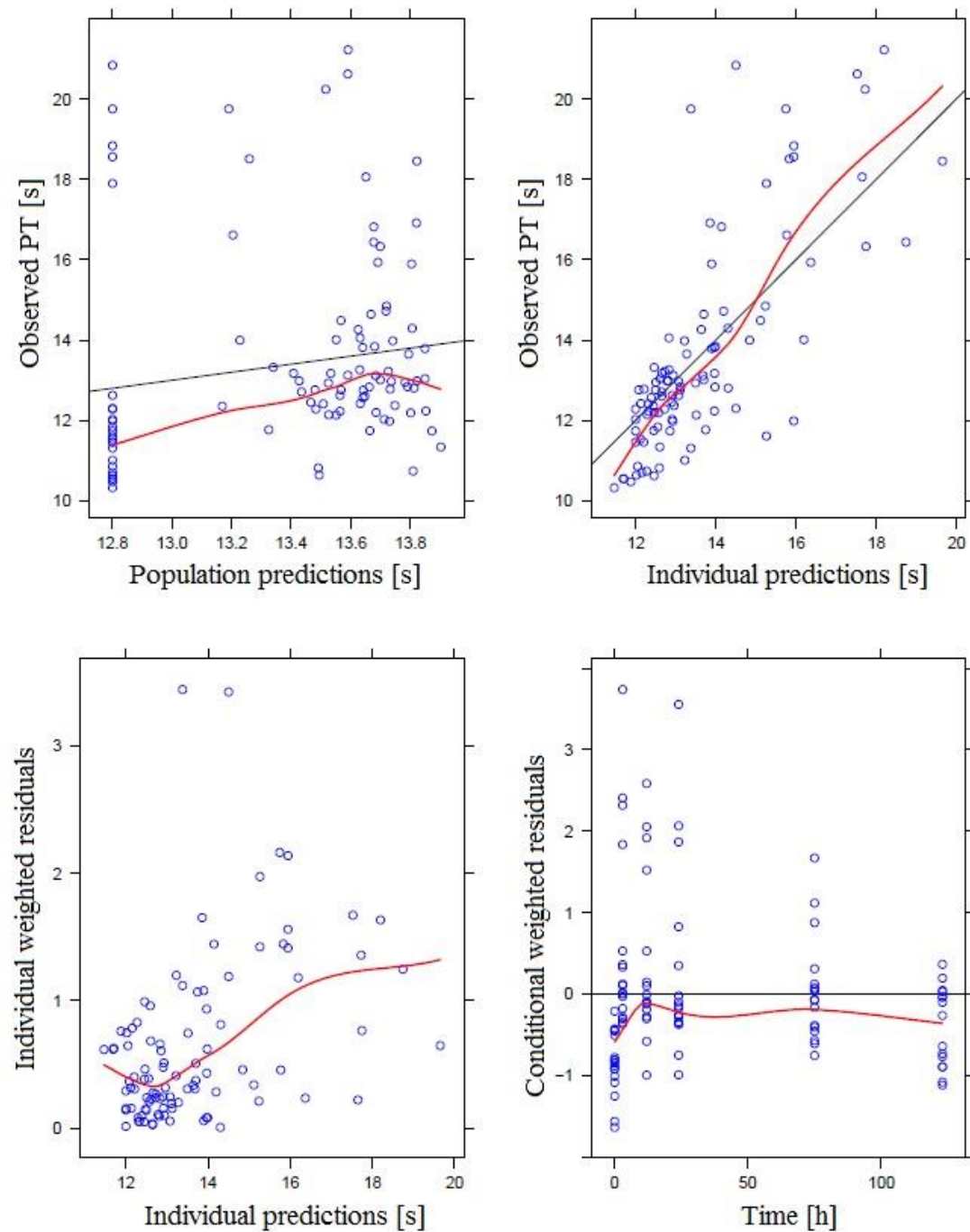
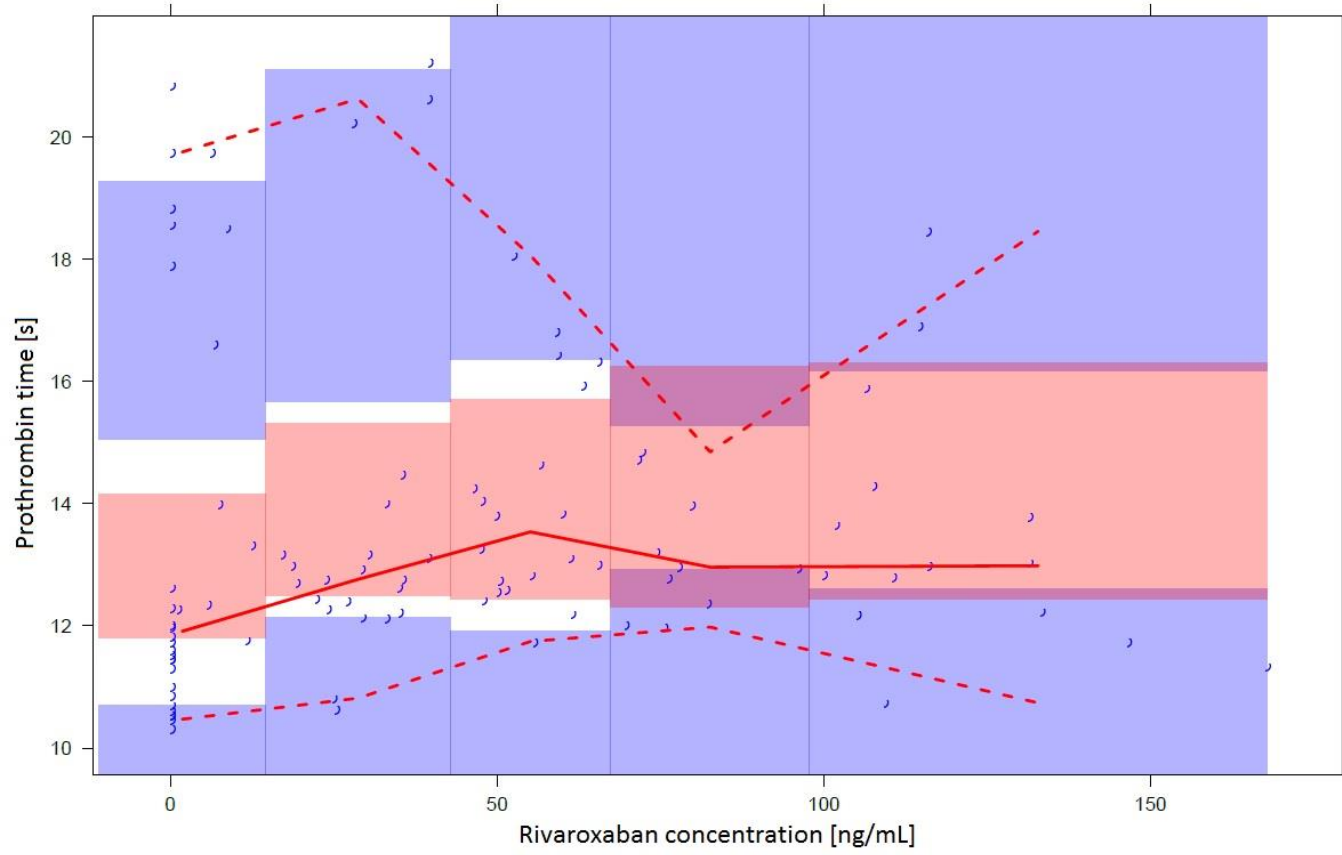


Figure 5. Visual predictive check



Partial thromboplastin time (aPTT)

Table 4. Estimated pharmacodynamic parameters

Parameter	Population mean (%SE)	IIV, %CV (%SE)
aPTT ₀ [s]	32.9 (4.08)	16.5 (12.8)
Slope [s/ng/mL]	1.99 (12.8)	NA
Proportional error	0.130 (9.09)	NA

Figure 6. Goodness-of-fit

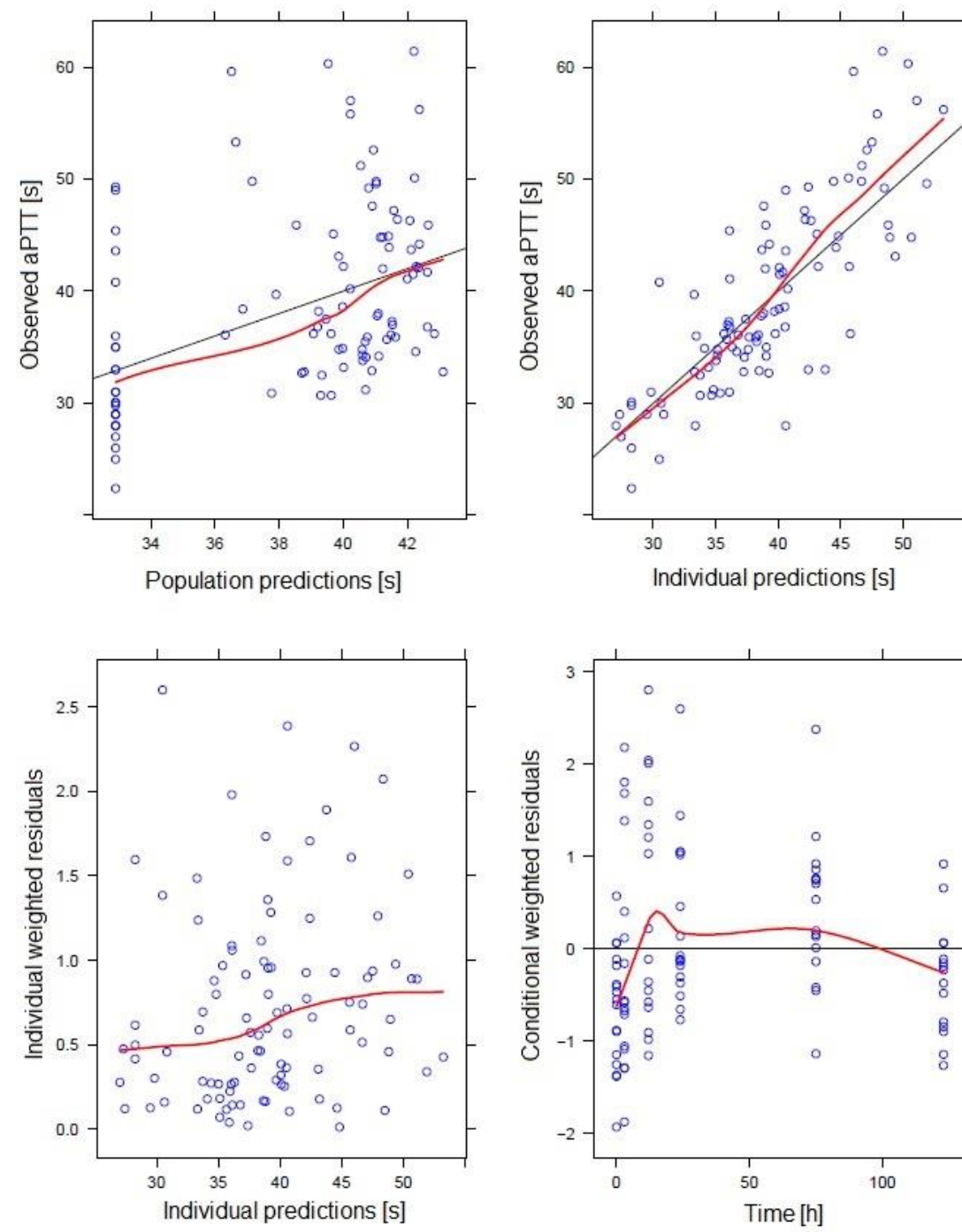
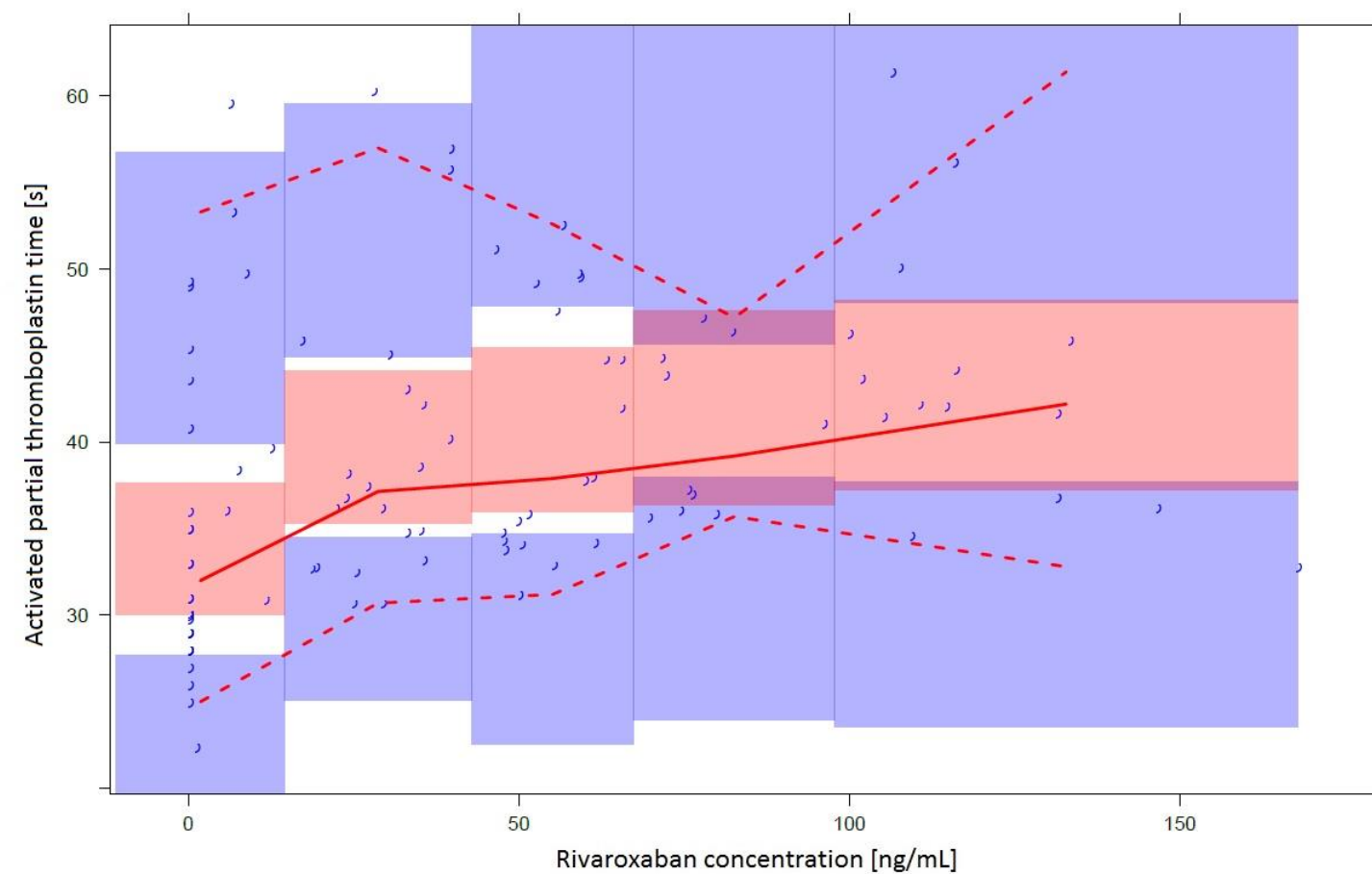


Figure 7. Visual predictive check



Final model

- One-compartment model, first order absorption;**
- PK model – logarithmic transformation of rivaroxaban concentrations;**
- ABCB1 gene expression was associated with the clearance of rivaroxaban (power model);**
- No association with ABCB1 polymorphism was observed;**
- PD models – linear models where the value of the PD markers increased linearly with the natural logarithm of rivaroxaban concentration.**

Eqs 1. Final model equations

$$Cl = 6.12 * (ABCB1/1.25)^{0.817}$$

$$PT = 12.8 + 0.215 * LN(c_{RX})$$

$$aPTT = 32.9 + 1.99 * LN(c_{RX})$$

Conclusions

***ABCB1* gene expression decreased after the orthopedic surgery.**

A one-compartment PK model with the first order absorption is a suitable model to describe the PK of rivaroxaban.

We confirmed the correlation between the *ABCB1* gene expression and the clearance (Cl) of rivaroxaban.

References

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