

Population pharmacokinetics of orally administered letermovir in real world allogeneic hematopoietic cell transplantation recipients

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Introduction

Letermovir (LTV) is approved for cytomegalovirus (CMV) prophylaxis in CMV-seropositive allogeneic hematopoietic stem cell transplant (allo-HSCT) recipients but breakthrough infections and exposure variability persist [1, 2].

Objective: Assessment of factors affecting LTV in **real-world patients** using the population pharmacokinetic (popPK) approach.

Conclusion

The **modified popPK model** revealed substantial differences in C_{min} due to **varying bioavailability** in our real-world data.

Gastrointestinal graft-versus-host disease (GI GvHD) led to a **substantial decrease in relative bioavailability (F_{rel})**. However, small number of events and fixed IIV values from literature warrant careful interpretation.

Results

External validation reveals substantially higher real-world concentrations than predicted

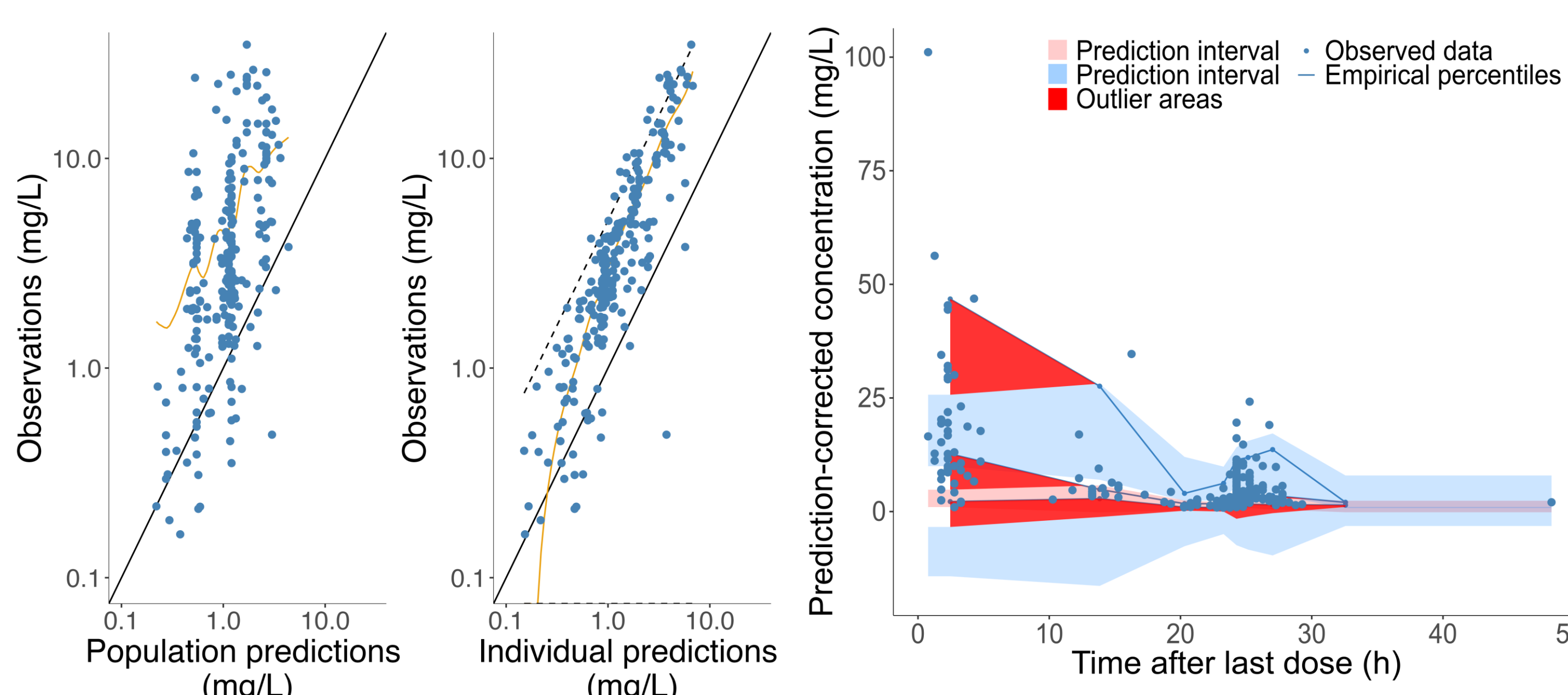


Figure 1 Observed versus predicted LTV concentrations (left) and prediction-corrected visual predictive check (pcVPC) (right) using the published model by Prohn et al. [3]

LTV PK is adequately captured by the modified model

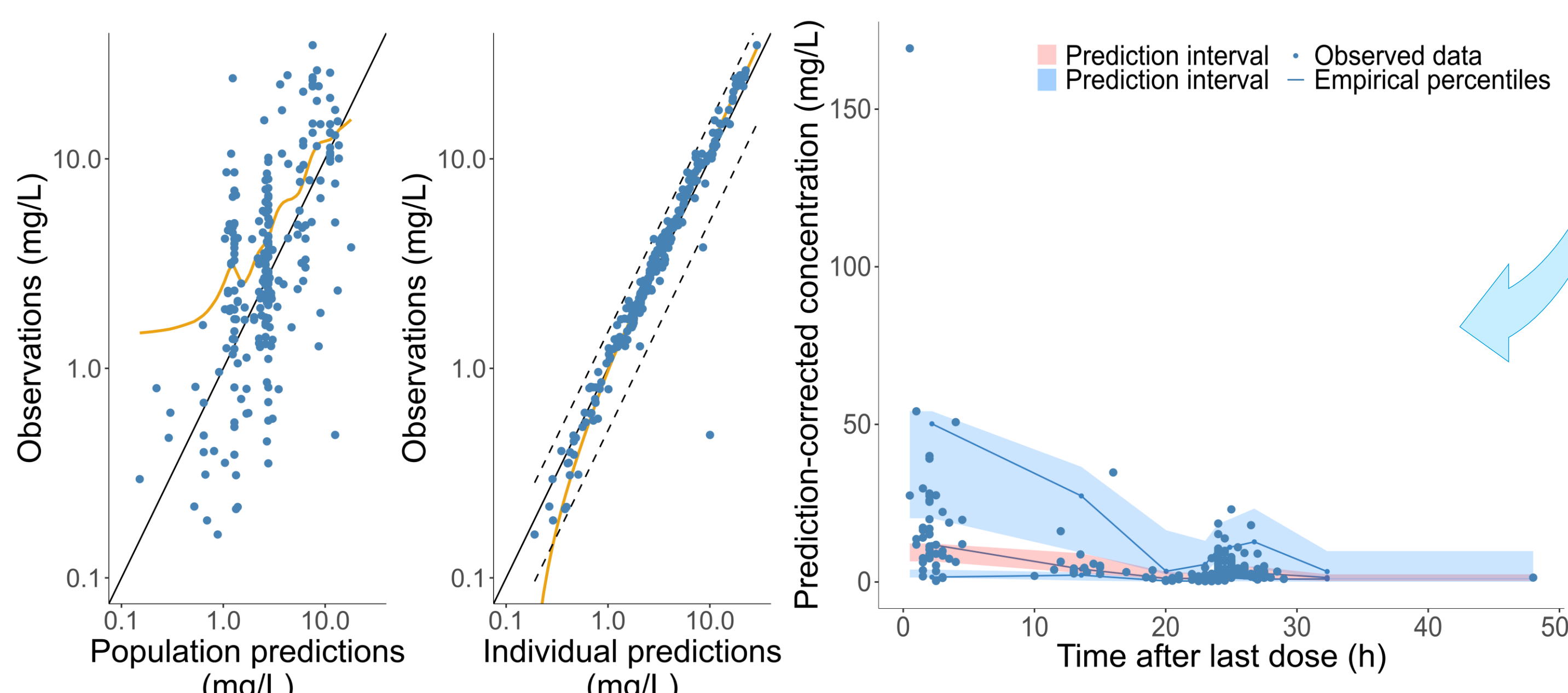


Figure 2 Observed versus predicted LTV concentrations (left) and pcVPC (right) using the modified covariate model.

- F_{rel} fixed to 100 % in patients without ciclosporin A (CsA) comedication.
- Model improvement by estimating CL/F and V_1/F (ΔOFV : -18.2, $\Delta cBIC$: -7.17), while fixation of CL/F to the published value showed only minor changes in model fit (ΔOFV = -3.56; $\Delta cBIC$ = +1.95) → selection as base model (Table 1).

Summary of model development

Table 1 Parameter estimates for key model development steps

Model	Based on Prohn et al. [3]	Base model	Covariate model
-2LL	1426.2	1122.3	1112.6
cBIC	1431.7	1133.3	1129.1
Fixed effects (% RSE)			
T_{lag} (h)	0.674*	0.674*	0.674*
F_{rel}	0.346*	1**	1**
k_a (h ⁻¹)	0.150*	0.150*	0.150*
CL/F (L/h)	4.84*	4.84*	4.84*
V_1/F (L)	19.7*	7.81 (23.0 %)	8.36 (22.0 %)
Q/F (L/h)	1.54*	1.54*	1.54*
V_2/F (L)	25.8*	25.8*	25.8*
$\beta_{CL, CsA}$	-0.302*	-0.302*	-0.302*
$\beta_{F, CsA}$	1.45*	1.45*	1.45*
$\beta_{F, GI\ GvHD}$			-0.765 (7.18 %)
Standard deviation of random effects			
IIV on F_{rel}	0.370*	0.370*	0.370*
IIV on k_a	0.848*	0.848*	0.848*
IIV on CL	0.246*	0.246*	0.246*
IIV on V_2	0.479*	0.479*	0.479*
IOV on F_{rel}	0.444*	0.444*	0.444*
Residual error (% RSE)			
Proportional error	2.47 (11.4 %)	0.339 (9.42 %)	0.301 (8.55 %)

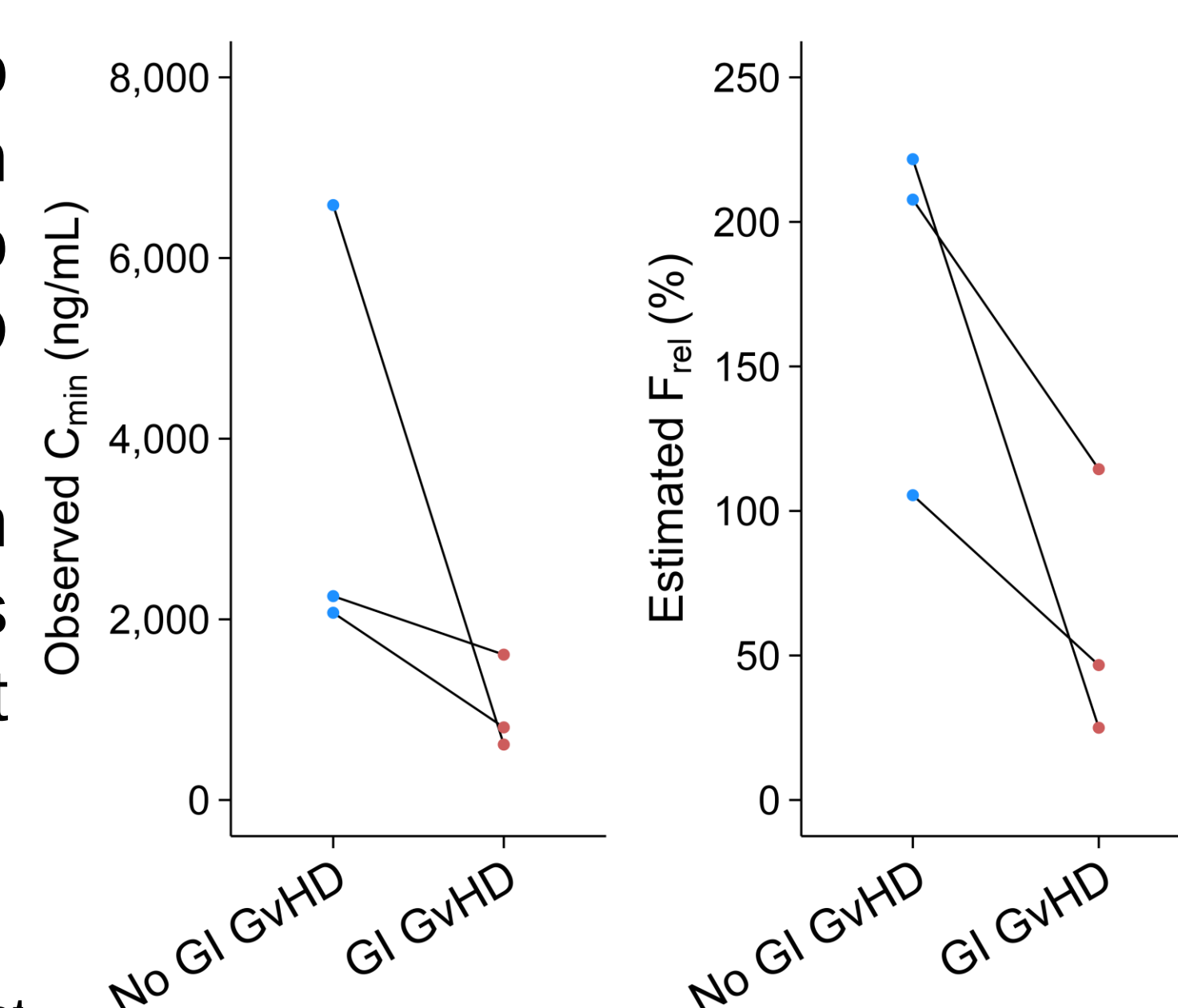
* Fixed to values obtained from Prohn et al. [3] ** Fixed value to describe F_{rel} .

Impact of GI GvHD on LTV exposure

Reduction of F_{rel} by 76.5 % (95 % CI, -87.2 to -65.7 %) in patients with GI GvHD compared to patients without GI GvHD (Wald test: $p < 0.001$).

Notable C_{min} decrease in the individual patients following GI GvHD onset (Figure 3).

Figure 3 Association between onset of GI GvHD and observed C_{min} (left) and estimated F_{rel} (right).



Methods

Based on the published LTV popPK model [3], non-linear mixed effect modeling was conducted using the stochastic approximation expectation maximization algorithm in Monolix 2024R1 [4]:

- 247 LTV samples** from 51 adult allo-HSCT recipients, including four patients who developed GI GvHD during the course of treatment.
- Two-compartment model with linear elimination and differential clearance (CL) and bioavailability (F) depending on CsA co-administration (Eq. 1, 2). Model modifications and exploratory covariate search (demographic factors, occurrence of GI and liver GvHD, comedication)
- Model selection based on log-likelihood and corrected Bayesian Information Criteria (cBIC), parameters' relative standard error (RSE), and goodness-of-fit plots and pcVPC [5].

$$CL = CL_{pop} \times (1 + \beta_{CL, CsA} \times CsA) \quad \text{Eq. 1}$$

$$F = F_{pop} \times (1 + \beta_{F, CsA} \times CsA) \times (1 + \beta_{F, GI\ GvHD} \times GI\ GvHD) \quad \text{Eq. 2}$$

References

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