Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2025, Volume 5, Issue 2, Page No: 88-97

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Population Pharmacokinetic Analysis to Inform Sirolimus Dose Selection in Adult Liver Transplant Patients

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Received: 18 June 2025; **Revised:** 27 Septenber 2025; **Accepted:** 29 September 2025

ABSTRACT

Sirolimus is an immunosuppressive agent frequently prescribed following solid organ transplantation. It exhibits a narrow therapeutic index and substantial interpatient pharmacokinetic variability, making it essential to understand the factors contributing to this variability and to develop individualized dosing strategies. This work sought to establish a population pharmacokinetic model of sirolimus in adults following liver transplantation and to use it as a basis for optimizing dose selection according to individual patient factors. A dataset comprising 216 whole-blood sirolimus concentration measurements from 103 adult liver transplant patients was used for the analysis. Potential covariates affecting sirolimus pharmacokinetics were evaluated using a stepwise modeling approach. In addition, Monte Carlo simulations were performed to explore and propose dosing strategies across different patient subgroups defined by relevant covariate levels. A one-compartment model with first-order elimination best described the sirolimus concentration data. Hematocrit (HCT) was identified as a significant covariate affecting apparent clearance. Monte Carlo simulation results suggested that dosing should be adjusted according to HCT levels. In patients with reduced HCT (28%), suitable regimens included 1.5 mg once daily or alternating doses of 1 mg and 1.5 mg once daily. For patients with normal HCT values, recommended options were 1 mg once daily, 2 mg every other day, or alternating 0.5 mg and 1 mg once daily. By analyzing a comprehensive population pharmacokinetic database of sirolimus in adult liver transplant recipients, we identified hematocrit as a major determinant of dosing requirements. We therefore suggest that sirolimus treatment be tailored to individual HCT levels.

Keywords: Hematocrit, Dosing regimen, Liver transplant, Population pharmacokinetic analysis, Sirolimus

How to Cite This Article: Mansour A, Saeed O. Population Pharmacokinetic Analysis to Inform Sirolimus Dose Selection in Adult Liver Transplant Patients. Ann Pharm Pract Pharmacother. 2025;5(2):88-97. https://doi.org/10.51847/mXLAn8GwTD

Introduction

Sirolimus (rapamycin) is an immunosuppressive agent routinely used after solid organ transplantation to prevent graft rejection. Its mechanism of action involves binding to FK-binding protein-12 (FKBP-12), thereby inhibiting the mammalian target of rapamycin (mTOR) pathway [1]. This blockade prevents cell-cycle progression from the G1 to S phase [2, 3]. Owing to its targeted mechanism, acceptable safety profile, and strong immunosuppressive efficacy, sirolimus has become widely adopted in clinical practice [4].

Following oral administration, sirolimus is absorbed relatively quickly, with peak plasma concentrations generally reached within 0.5–3 hours [5, 6]. It is extensively distributed in tissues and demonstrates a marked affinity for erythrocytes in whole blood [7]. Metabolism occurs primarily via CYP3A4 and CYP3A5 enzymes, as well as the P-glycoprotein efflux transporter, and elimination is mainly biliary and fecal [3, 5, 6].

Sirolimus exposure shows substantial interindividual variability. In renal transplant populations, apparent clearance (CL/F) has been reported to range widely from 90 to 416 mL/h/kg [8], leading to significant differences in systemic concentrations even under identical dosing conditions. In addition, the drug has a narrow therapeutic window (4–8 ng/mL) [9, 10], which necessitates careful dose optimization. As a result, therapeutic drug

monitoring (TDM) based on whole-blood trough concentrations is routinely used to guide clinical dosing adjustments.

However, TDM-based dose adjustment has limitations, as it only becomes applicable after therapy has already been initiated. In contrast, population pharmacokinetic (PK) modeling enables characterization of typical PK behavior, identification of variability sources, and the development of individualized dosing strategies from the start of treatment through follow-up.

Several population PK models of sirolimus have been reported in adult and pediatric transplant recipients [11-15]. Nevertheless, only one study has specifically examined adult liver transplant patients [10], and its relatively small sample size limits the generalizability of its conclusions. Therefore, to address this gap, the present study aimed to investigate covariate effects on sirolimus pharmacokinetics in adult liver transplant recipients and to propose optimized dosing regimens using population PK modeling and simulation approaches.

Materials and Methods

Patient characteristics

For this retrospective analysis, we reviewed records of liver transplant recipients treated with sirolimus at Tongji Hospital (Tongji Medical College, Huazhong University of Science and Technology) from January 2018 to August 2024. Organ donation followed voluntary consent procedures and complied with the Declaration of Istanbul. Ethical approval was obtained from the Tongji Hospital Ethics Committee (TJ-IRB202409087), and informed consent was waived due to the study's retrospective design. The work adhered to the Declaration of Helsinki (2013).

Data retrieved from hospital records included dosing and sampling details (sirolimus regimen, administration and sampling times, TDM concentrations, and daily doses), patient demographics (age, sex, postoperative time, height, weight, BMI), laboratory indices (hemoglobin, hematocrit, liver enzymes and function markers, renal function parameters), and concomitant therapies such as prednisone acetate, mycophenolic acid, esomeprazole, ganciclovir, Wuzhi capsules, and amlodipine.

No identifiable personal data was extracted or analyzed, ensuring full protection of patient confidentiality.

Concentration measurement

Sirolimus whole-blood trough levels (C0) were quantified using an enzyme-multiplied immunoassay method performed on the ARCHITECT i1000 chemiluminescent immunoassay platform (Abbott Diagnostics Inc., Illinois, USA) with the corresponding ARCHITECT Sirolimus assay kit. The assay showed acceptable precision, with both intra-day and inter-day variability below 10%. The validated analytical range of the method was 2–30 ng/mL, and the minimum detectable concentration was 0.3 ng/mL.

Model development

Pharmacokinetic modeling was carried out using NONMEM software (version 7.5; ICON Development Solutions, USA) with the first-order conditional estimation method incorporating interaction (FOCE-I). Model development and evaluation were supported using Perl-speaks-NONMEM (PsN, version 5.2.6). All statistical processing and graphical representations were performed in R software (version 4.2.1).

Base model

A structural one-compartment model incorporating first-order absorption and elimination was applied. Since only trough concentrations (C0) were available, the absorption rate constant (Ka) was set to 0.75 h^{-1} based on literature values. Between-subject variability in the pharmacokinetic parameters was described using exponential functions (Eq. 1).

$$P_i = TV(P) \cdot e^{\#i} \quad (1)$$

In this equation, Pi denotes the estimated PK parameter for the i-th individual, TV(P) represents the typical population estimate for that parameter, and η_i is the interindividual random effect, assumed to follow a normal distribution with mean 0 and variance ω^2.

To characterize the residual unexplained variability (RUV), three error structures were tested: additive (Eq. 2), proportional (Eq. 3), and a combined proportional-additive model (Eq. 4).

$$Y = F + \varepsilon_1 \quad (2)$$
$$Y = F + F \cdot \varepsilon_1 \quad (3)$$
$$Y = F \cdot (1 + \varepsilon_1) + \varepsilon_2 \quad (4)$$

In this expression, Y represents the measured sirolimus level, and F represents the model-predicted value. The term ε denotes residual error, which is assumed to be normally distributed around zero with a variance of σ². Selection of the base model was guided by several criteria: parameter-estimation accuracy, the objective function value (OFV), the Akaike information criterion [16], the Bayesian information criterion [17], and the condition number.

Covariate model

To reduce collinearity, correlations between demographic and laboratory variables were first assessed. In cases of strong interdependence, only a single representative variable was retained for further analysis. Based on this approach, the covariate screening step included continuous variables (age, body weight, postoperative day, daily dose, hematocrit, ALT, and creatinine clearance) and categorical variables (sex and concomitant medications).

All continuous covariates were centered and scaled to their median population values using a power model transformation, as defined in Eq. 5.

$$P_i = TV(P) \cdot \left(\frac{COV_i}{COV_{median}}\right)^{\theta} \quad (5)$$

Here, COVi\mathrm{COV}_iCOVi denotes the value of the continuous covariate for the iii-th individual, while COVmedian\mathrm{COV}_{\text{median}}COVmedian represents the corresponding median value in the study population. The parameter θ\thetaθ describes the magnitude of the covariate effect on the pharmacokinetic parameter.

Categorical variables were incorporated into the model using a proportional (indicator-based) approach, as described in Eq. 6.

$$P_i = TV(P) \cdot (1 + \theta \cdot COV) \quad (6)$$

Here, COV denotes a binary (dummy) covariate coded as 0 in the absence and 1 in the presence of a given characteristic.

Covariate model building was carried out using a stepwise strategy with forward selection followed by backward elimination. Variables were accepted into the model if inclusion produced a reduction in the objective function value (OFV) exceeding 3.84 ($P < 0.05$, df = 1), and they were retained only if exclusion resulted in an OFV increase greater than 6.63 ($P < 0.01$, df = 1).

Model evaluation

The adequacy of the final population pharmacokinetic model was evaluated using several complementary diagnostic approaches. Goodness-of-fit (GOF) plots were first examined to assess agreement between observed concentrations and model-predicted values. Parameter robustness was examined through a nonparametric bootstrap procedure with 1,000 resampled datasets.

Model predictability was further assessed using prediction-corrected visual predictive checks (pc-VPC). In addition, normalized prediction distribution error (NPDE) diagnostics were evaluated to verify whether the model-derived residuals followed a standard normal distribution (mean 0, variance 1). For enhanced visual interpretation, four normalized prediction distribution (NPD) plots were also generated in place of NPDE representations [18].

Dosing regimen recommendation

Monte Carlo simulation was applied to the final population PK model to predict steady-state trough concentrations (C0) under different dosing regimens and covariate conditions. Nine commonly used sirolimus regimens were

evaluated: (1) 0.5 mg once daily, (2) 1 mg once daily, (3) 1.5 mg once daily, (4) 2 mg once daily, (5) 1 mg every other day, (6) 2 mg every other day, (7) alternating 0.5 mg and 1 mg once daily, (8) alternating 1 mg and 1.5 mg once daily, and (9) alternating 1 mg and 2 mg once daily.

Dose recommendations for different covariate subgroups were then derived by comparing simulated steady-state C0 values with the established therapeutic range of 4–8 ng/Ml, ensuring that most predicted exposures remained within this target window [9, 10].

Results and Discussion

Patient characteristics

For the population pharmacokinetic analysis, 216 sirolimus whole-blood trough concentrations were collected from 103 adult liver transplant recipients receiving sirolimus for rejection prophylaxis. The median patient age was 51 years, with a median body weight of 68.0 kg and body mass index of 23.8 kg/m².

Patients received various maintenance dosing regimens, including 0.5 mg once daily, 1 mg once daily, 2 mg once daily, 1 mg every other day, 2 mg every other day, and alternating 0.5 mg and 1 mg once daily, or 1 mg and 2 mg once daily.

A summary of baseline demographic characteristics of the study population is provided in **Table 1.**

Table 1. Baseline characteristics of patients included in the population pharmacokinetic model.

Characteristics	Median [Range]	Mean (SD)
Sex, male/female		99/4
Age (years)	51.0 [28.0–74.0]	50.4 (9.20)
Height (cm)	170 [150–183]	170 (5.40)
Total body weight (kg)	68.0 [39.0–90.0]	68.6 (10.2)
Body mass index (kg/m^2)	23.8 [16.7–30.8]	23.6 (3.11)
Postoperative days (days)	92 [14–699]	145 (140)
Sirolimus daily dose (mg/day)	1.0 [0.5–2.0]	1.02 (0.32)
Sirolimus trough concentration (ng/mL)	5.26 [1.33–12.17]	5.45 (1.96)
Hemoglobin (g/L)	126 [57–168]	125 (23.7)
Haematocrit (%)	38.0 [17.5–49.5]	37.8 (6.60)
Total serum protein (g/L)	74.4 [50.3–105.0]	74.2 (7.82)
Albumin (g/L)	44.2 [27.2–50.9]	43.1 (4.85)
Alanine transaminase (U/L)	21.0 [5.0–187.0]	38.0 (38.5)
Aspartate aminotransferase (U/L)	25.0 [12.0–190.0]	37.1 (32.7)
Alkaline phosphatase (U/L)	104 [8–1040]	145 (131)
γ-Glutamyl transpeptidase (U/L)	58.0 [13.0–1110]	109 (170)
Total bilirubin (μmol/L)	53.55 [2.50–308.0]	22.5 (32.3)
Blood uric nitrogen (mmol/L)	6.07 [2.4–38.7]	7.22 (5.14)
Serum creatinine (μmol/L)	81.0 [49.0–267.0]	94.6 (40.7)
Creatinine clearance (mL/min)[a]	89.4 [27.0–170.0]	88.9 (30.4)
Concomitant medication, with/without		
Ganciclovir		5/98
Prednisone acetate		10/93
Esomeprazole		10/93
Amlodipine		10/93
Mycophenolic acid		24/79
Wuzhi capsule		26/77

Note: [a]: Estimated renal function (creatinine clearance) was computed based on serum creatinine levels via the Cockcroft-Gault formula as follows:

CrCL = [140 − age in years] × weight in kilograms / [0.818 × SCr in μmol/L] × factor, with the factor assigned as 1 for men and 0.85 for women.

Abbreviation: SD, standard deviation.

Model development

A one-compartment, first-order elimination structural model best described the data. Interindividual variability was included for both apparent clearance (CL/F) and volume of distribution (V/F). Residual variability was best characterized by a combined error model, with a covariance term between CL/F and V/F to account for their correlation.

Adding hematocrit (HCT) to the model led to a marked improvement in model fit, evidenced by a 32.9-point reduction in the objective function value (OFV). In the subsequent backward elimination step, none of the tested covariates met the removal criteria (P > 0.01), confirming the stability of the covariate structure. Therefore, HCT was retained in the final model. The resulting population pharmacokinetic model is described in (Eqs. 7–9):

$$K_a\ (h^{-1}) = 0.75 \tag{7}$$

$$CL/F\ (L/h) = 7.09 \times \left(\frac{HCT}{38}\right)^{-0.901} \tag{8}$$

$$V/F\ (L) = 496 \tag{9}$$

The final model estimates are presented in **Table 2.** Parameter precision was acceptable across all fixed and random effects, with relative standard errors consistently under 30%, indicating reliable and stable model estimation.

Table 2. Final population pharmacokinetic parameters and bootstrap assessment results.

Parameters	Bootstrap		Final Model	
	Median	**Estimates**	**RSE (%)**	**2.5%-97.5%**
Fixed effects				
k_a (h^{-1})	/	0.75	Fixed	/
CL/F (L/h)	7.02	7.09	4	6.44–7.59
V/F (L)	515.85	496	15	306.28–687.11
HCT on CL/F	−0.873	−0.901	17	(−1.259)–(−0.551)
Random effects				
$\omega_{CL/F}$(%)	31.9	32.4	9	25.1–37.9
$\omega_{V/F}$ (%)	40.1	42.7	19	17.7–59.2
$\omega COV_{CL/F-V/F}$	0.0695	0.0665	/	0.0062–0.1317
Residual error				
ε_{por}(%)	3.19	3.3	10	2.41–3.81

Abbreviations: CL/F = apparent oral clearance in L/h; RSE = relative standard error; ka = absorption rate constant expressed as h^{-1}; V/F = apparent central compartment volume in L; HCT = hematocrit percentage; ω(V/F) = interindividual variance for apparent central volume; ω(CL/F) = interindividual variance for apparent clearance; ε_prop = proportional component of residual error.

Model evaluation

The goodness-of-fit plots indicated that the final model adequately captured the observed data **(Figure 1).** In both panels a and b of **Figure 1**, the measured concentrations plotted against population-predicted values and individual-predicted values fell symmetrically around the line of unity. Additionally, the majority of conditional weighted residuals clustered near zero and remained within the interval of −2 to +2, as shown in **Figures 1c and 1d.**

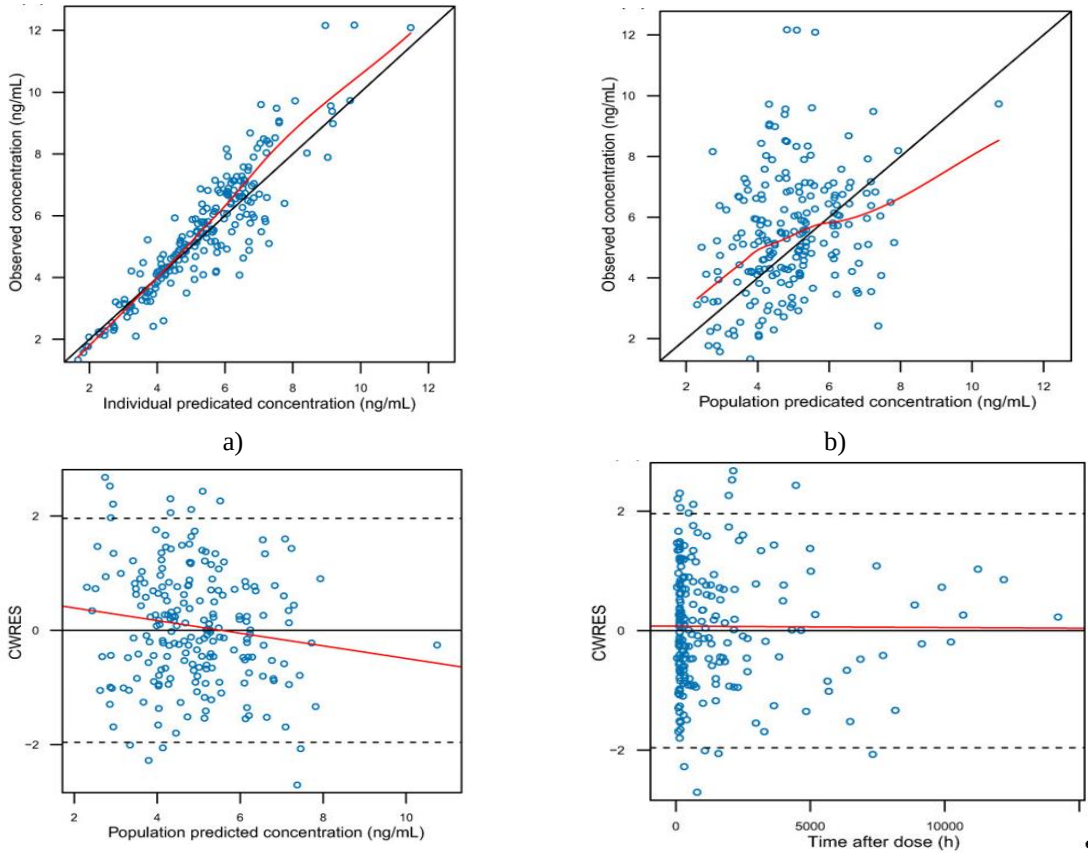

Figure 1. Goodness-of-fit diagnostics for the final pharmacokinetic model: (a) Relationship between observed values and individual predictions; (b) observed values versus population predictions (PRED); (c) conditional weighted residuals (CWRES) plotted against PRED; (d) CWRES versus post-dose time. The diagonal black line marks the line of unity, and the red lines represent loess smoothing.

Out of 1,000 bootstrap iterations, 97.5% converged successfully. Moreover, all final model parameter estimates lay within the 95% bootstrap confidence intervals, indicating strong model reliability **(Table 2).**

The prediction-corrected visual predictive check (pc-VPC) for the final model showed good consistency between predicted and observed concentration data **(Figure 2).** Importantly, the 5th, 50th, and 95th percentiles of the observed concentrations generally remained inside the respective 90% confidence bands.

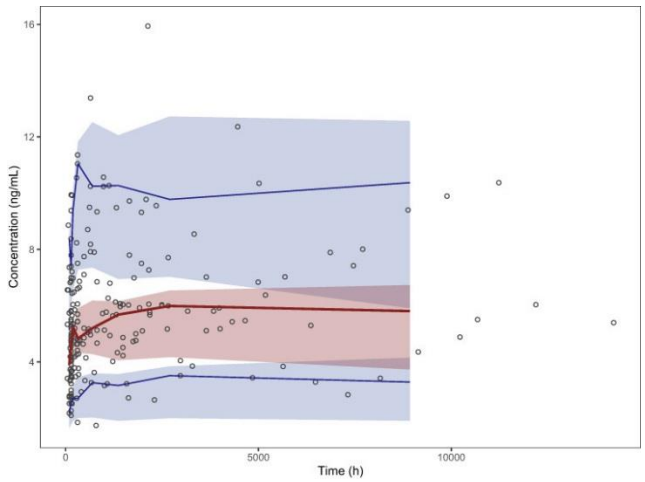

Figure 2. Prediction-corrected visual predictive check for the final population model. Observed data are shown as scatter points. The median observed value is traced by a red solid line, while the 5th and 95th

percentiles are shown as blue solid lines. The surrounding shaded zones indicate 90% confidence intervals around the simulated median (red) and the simulated 5th/95th percentiles (blue).

The normalized prediction distribution (NPD) diagnostic plots **(Figures 3a–3d)** revealed no discernible trends. All four statistical tests—Wilcoxon signed-rank, Fisher's variance, Shapiro–Wilk, and the global test—yielded P-values above 0.5, indicating that the final population PK model adequately captured the observed concentration data.

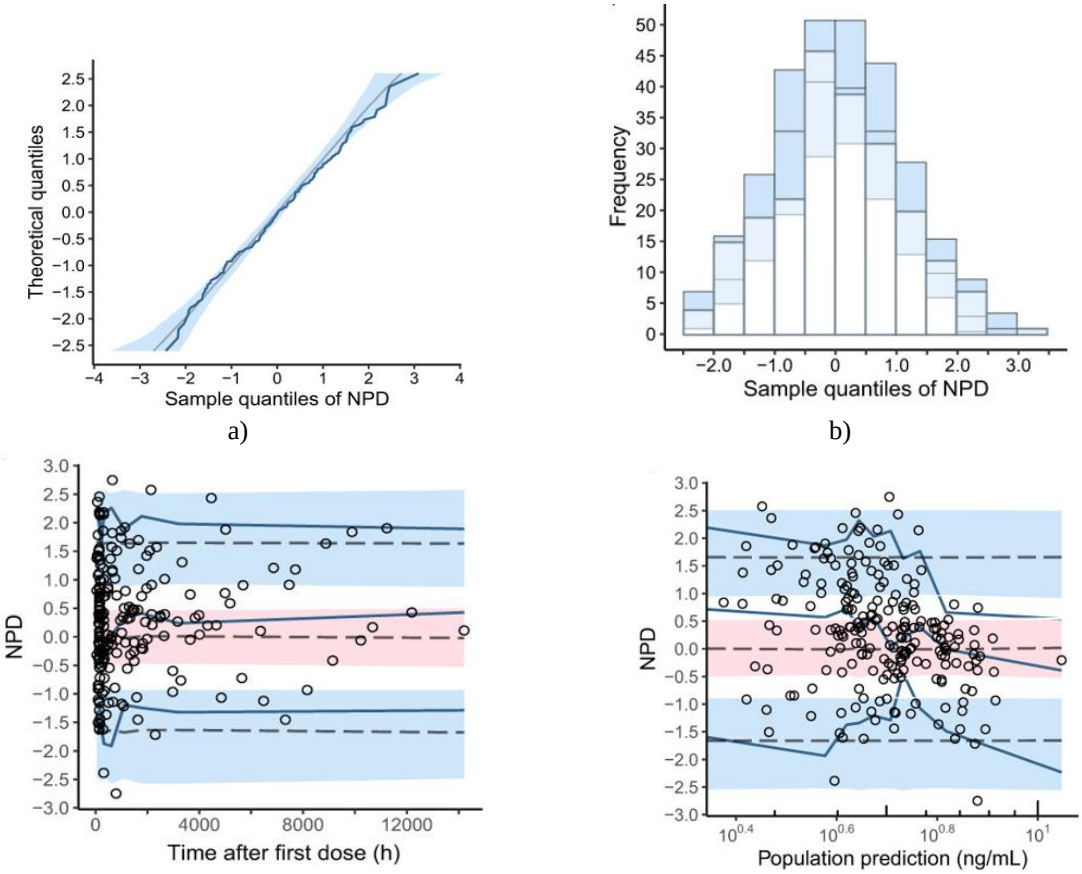

Figure 3. Diagnostic plots based on normalized prediction distribution (NPD) from the final model: (a) Q–Q plot versus the theoretical normal distribution, (b) histogram with superimposed Gaussian density curve, (c) NPD over time after first dose, and (d) NPD versus population-predicted concentrations.

Dosing regimen recommendation

Because hematocrit (HCT) significantly influenced the final model, steady-state trough concentrations (C0) were simulated for nine dosing regimens using HCT values at the 10th, 50th, and 90th percentiles (28%, 38%, and 46%). Results are shown in **Figure 4.**

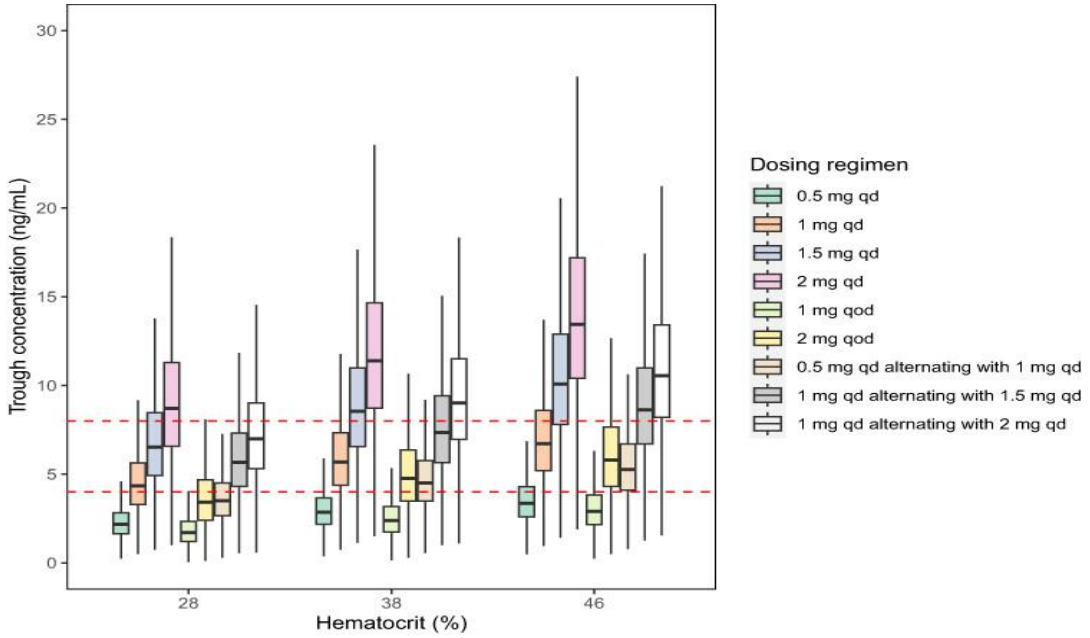

Figure 4. Boxplots of simulated steady-state sirolimus trough concentrations across patients with hematocrit levels of 28%, 38%, and 46%. The dashed lines indicate the therapeutic target range (4–8 ng/mL).

Monte Carlo simulations showed an inverse relationship between hematocrit and required sirolimus dose: higher HCT values were associated with lower doses needed to reach the therapeutic range.

For patients with low HCT (28%), recommended regimens included 1.5 mg once daily or alternating 1 mg and 1.5 mg once daily. For patients with normal HCT (38% and 46%), suitable options were 1 mg once daily, 2 mg every other day, or alternating 0.5 mg and 1 mg once daily.

To the best of our knowledge, this study represents the largest population pharmacokinetic analysis of sirolimus in adult liver transplant recipients conducted to date. A one-compartment model with first-order elimination adequately characterized sirolimus pharmacokinetics in this population. Based on model-informed simulations, practical dosing options were proposed for patients stratified by hematocrit levels.

The pharmacokinetic estimates obtained using sparse sampling were generally consistent with previously published data. Zhang *et al.* [10] reported CL/F (6.97 L/h) and V/F (457.85 L) in adult liver transplant recipients, which closely matched our results (CL/F: 7.09 L/h; V/F: 496 L).

When compared with other transplant populations, including renal [14, 19-21] and cardiac recipients [15], differences in pharmacokinetic parameters were observed. Our estimated clearance was comparable to that reported in heart transplant patients [15], but lower than values reported in renal transplant recipients (8.91–14.4 L/h) [19, 21]. This discrepancy may be explained by differences in hepatic metabolic capacity, as sirolimus is primarily metabolized via hepatic CYP3A enzymes. In liver transplant patients, incomplete recovery of graft function may also contribute to reduced clearance.

The estimated V/F was within the range reported in renal transplant populations (322–727 L [20, 21] but notably lower than that observed in heart transplant recipients (approximately 1350 L) [15]. This difference may be partly attributable to the exclusive use of trough concentrations (C0) in the present study, which limits accurate characterization of the distribution phase.

Among the evaluated covariates, hematocrit was the only significant determinant of CL/F. Higher HCT values were associated with reduced apparent clearance, consistent with findings in oncology populations [22]. Given that approximately 95% of sirolimus is associated with erythrocytes [23], increases in hematocrit likely reduce the fraction of unbound drug, thereby decreasing apparent clearance.

The effects of concomitant medications were also explored. Although mycophenolic acid (MPA) and Wuzhi capsules initially showed potential associations during forward selection, these effects were not retained after backward elimination due to a lack of statistical significance and unstable parameter estimation. Wuzhi capsules are known CYP3A4 inhibitors [24], and sirolimus is extensively metabolized via this pathway; therefore, pharmacokinetic interactions are biologically plausible. In addition, previous work has suggested altered MPA

exposure during co-administration with sirolimus compared with cyclosporine-based regimens [25]. However, further studies with larger datasets are needed to clarify these interactions and optimize combination therapy.

From a clinical perspective, sirolimus therapy in liver transplant recipients requires careful dose adjustment due to its narrow therapeutic index. Simulation results indicated that in patients with normal hematocrit, extended dosing intervals such as alternate-day administration may still maintain trough concentrations within the therapeutic range. This may be explained by the long elimination half-life of sirolimus (~62 h), which supports sustained exposure despite less frequent dosing. Such optimized regimens may help reduce unnecessary dose adjustments and minimize toxicity associated with supratherapeutic levels.

Several limitations should be acknowledged. First, the exclusive use of trough concentrations required fixing the absorption rate constant, which may have affected the precision of distribution parameter estimates. Prospective studies with more robust sampling designs are needed to better characterize the absorption and distribution phases. Second, despite being the largest dataset available for this population, the sample size may still be insufficient to fully evaluate drug–drug interactions involving concomitant medications. Finally, as all data originated from a single center, external validation is necessary to confirm the model's generalizability.

Conclusion

In summary, we established a population pharmacokinetic model of sirolimus in adult liver transplant recipients using the largest dataset reported to date. Hematocrit was identified as a key covariate influencing sirolimus apparent clearance (CL/F). Based on model-informed simulations, we suggest that sirolimus dosing should be individualized according to hematocrit levels across commonly used clinical regimens.

Acknowledgments: The authors gratefully acknowledge Editage (editage.cn) for providing English language editing support.

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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