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Population Pharmacokinetics of Sirolimus in Adult Liver Transplant Recipients: Implications for Individualized Dosing

Bruno Martins[1]*, Lucas Pereira[1], Renata Azevedo[2], Pedro Costa[1]

[1]Department of Drug Design and Pharmaceutical Systems, Faculty of Pharmacy, University of Minho, Braga, Portugal.
[2]Department of Pharmaceutical Sciences and Therapeutics, Faculty of Pharmacy, University of Porto, Porto, Portugal.

***E-mail** ✉ bruno.martins@gmail.com

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ABSTRACT

Sirolimus is an immunosuppressive medication commonly used after solid organ transplantation. Its use is characterized by a narrow therapeutic index and fluctuating pharmacokinetic exposure, making it essential to pinpoint the sources of this variability and to devise individualized treatment strategies. The goal of this work was to conduct a population pharmacokinetic (PK) evaluation of sirolimus in adult liver transplant recipients and to generate dosage recommendations tailored to patient-specific factors. For the analysis, a collection of 216 sirolimus concentration readings from whole blood was gathered from 103 adult subjects. A stepwise method was used to identify covariates affecting the PK profile of sirolimus. To propose dosing protocols for individuals presenting with varying covariate magnitudes, Monte Carlo simulations were undertaken. A one-compartment model with first-order elimination best represented the dataset. The apparent clearance of sirolimus was notably impacted by hematocrit (HCT). Based on Monte Carlo simulations, for subjects with a reduced HCT of 28%, protocols involving 1.5 mg once daily or a rotation between 1 mg once daily and 1.5 mg once daily were advisable. For subjects with a standard HCT level, the suggested protocols were 1 mg once daily, 2 mg every other day, or a rotation between 0.5 mg once daily and 1 mg once daily. Drawing on our population PK model of sirolimus in adult liver transplant recipients, which constitutes the most extensive sample to date, we propose that dosing protocols be customized to accommodate distinct HCT levels in these patients.

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

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Introduction

Sirolimus, also known as rapamycin, is an immunosuppressive agent administered after solid organ transplantation to prevent allograft rejection. Its mechanism involves binding to FK-binding protein-12 (FKBP-12), thereby inhibiting mammalian target of rapamycin (mTOR) signaling [1]. This hindrance blocks the transition from the G1 to the S phase of the cell cycle [2, 3]. Based on this singular mode of action, coupled with its pronounced efficacy and tolerable safety profile, sirolimus has broad clinical application [4].

Upon oral ingestion, sirolimus undergoes swift absorption, with maximal plasma concentrations generally reached between 0.5 and 3 hours [5, 6]. The compound is widely distributed throughout tissues and organs, with a strong affinity for sequestration in erythrocytes in whole blood [7]. Sirolimus acts as a substrate for cytochrome P450 (CYP) 3A4, CYP3A5, and the efflux transporter P-glycoprotein, undergoing elimination principally through biliary and fecal routes [3, 5, 6].

Significant between-subject variability (BSV) characterizes the metabolic processing of sirolimus. Earlier investigations involving renal transplant patients indicated that apparent clearance (CL/F) ranged from 90 to 416 mL/h/kg [8], resulting in marked differences in drug levels after an equivalent sirolimus dose. Alongside this,

sirolimus exhibits a tight therapeutic span of 4–8 ng/mL [9, 10]. In light of these obstacles, therapeutic drug monitoring (TDM) of sirolimus whole-blood trough levels (C0) has been widely adopted to customize dosing in clinical settings.

Nonetheless, dose adaptation rooted in the TDM framework has inherent shortcomings, particularly because it can only be operationalized after treatment has commenced. As an alternative, population pharmacokinetic (PK) analysis is an effective tool that provides standard PK measures for the intended group, identifies sources of variability, and supports the formulation of personalized pharmacotherapies, applicable at therapy initiation and throughout its course.

Presently, several population PK studies of sirolimus involving both adult and pediatric cohorts are available [11-15]. To the extent of our awareness, though, merely one such population PK inquiry has addressed sirolimus in adult liver transplant recipients [10]; however, the work's modest participant count curtailed the reach and transferability of its outcomes. Consequently, mindful of this information gap, our investigation set out to assess the impact of diverse covariates on sirolimus PK in adult liver transplant recipients and to formulate dosing recommendations using a modeling and simulation approach.

Materials and Methods

Patient characteristics

For this study, we retrospectively collected data on patients who received sirolimus tablets after liver transplantation at Tongji Hospital (Tongji Medical College, Huazhong University of Science and Technology) from January 2018 through August 2024. Every organ donation was voluntary and accompanied by documented informed consent, and all such donations conformed to the Declaration of Istanbul. Owing to its retrospective character, the study was sanctioned by the Tongji Hospital Ethics Committee (number: TJ-IRB202409087) with a waiver of written informed consent. In addition, the investigation was conducted in accordance with the Declaration of Helsinki (2013).

The clinical information listed below was obtained from patient files: (1) dosing and sampling particulars, covering sirolimus dosing schedules, dates and times for every administration and blood draw, drug levels measured through TDM, and sirolimus daily dose; (2) demographic particulars, covering postoperative day, age, sex, height, weight, and body mass index; (3) physiological indices, covering hemoglobin, hematocrit (HCT), alanine aminotransferase, aspartate aminotransferase, total protein, albumin, total bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, blood urea nitrogen, serum creatinine, and creatinine clearance; (4) co-prescribed agents, covering prednisone acetate, mycophenolic acid (MPA), esomeprazole, ganciclovir, Wuzhi capsules (a traditional Chinese herbal product, customarily given to address drug-induced hepatic dysfunction), and amlodipine. Every author confirmed that the dataset contained no personally identifiable information, thereby preserving the confidentiality and privacy of patient records.

Concentration measurement

The C0 of sirolimus was determined via an enzyme multiplied immunoassay technique on an Architect i1000 Automatic Chemiluminescence Immunoassay Analyzer (Abbott Diagnostics Inc., IL, USA) paired with an ARCHITECT Sirolimus Reagent Kit. The within-day and between-day coefficients of variation fell under 10%. The analytical measuring interval extended from 2 to 30 ng/mL, with a lower detection limit of 0.3 ng/mL.

Model development

Data computations relied on a nonlinear mixed-effects modeling platform (NONMEM, v7.5, Icon Inc., PA, USA) using the first-order conditional estimation method with η-ε interaction (FOCE-I). Perl-speaks-NONMEM (PsN, v5.2.6) was applied to build and validate the population PK model. All statistical analyses and figure generation were performed in R v4.2.1.

Base model

The structural foundation consisted of a one-compartment model with first-order absorption and elimination. Since solely C0 observations were gathered, the absorption rate constant (Ka) was set to 0.75 h^{-1}, in keeping with earlier published work [10]. The BSV across PK parameters was depicted through exponential formulations (Eq. 1).

$$P_i = TV(P).e^{\eta i} \quad (1)$$

Where Pi represents the PK parameter estimate for the ith individual, TV(P) is the typical population estimate of the PK parameter, and ηi reflects the across-subject variation, which is assumed to follow a normal distribution with mean 0 and variance ω².

To capture the residual unexplained variability (RUV), additive (Eq. 2), proportional (Eq. 3), and combined (proportional along with additive) structures (Eq. 4) were tested.

$$Y = F + \varepsilon_1 \quad (2)$$

$$Y = F + F \cdot \varepsilon_1 \quad (3)$$

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

Where Y indicates the measured sirolimus level and F the model-determined level; at the same time, ε captures the residual discrepancy, which is assumed to follow a normal distribution with mean 0 and variance σ².

Choosing the base model required weighing multiple factors: the precision of parameter estimates, the objective function value (OFV), the Akaike information criterion [16], the Bayesian information criterion [17], and the condition number.

Covariate model

To address collinearity issues, the interrelationships among demographic factors and physiological indicators were first examined. When a strong correlation existed between two variables, only a single representative was included in the model. Consequently, the following were investigated: (1) continuous covariates, which included age, daily dose, postoperative day, weight, HCT, alanine aminotransferase, and creatinine clearance; and (2) categorical covariates, which included sex and concurrently administered drugs.

A power function was applied to normalize continuous covariates to the population median, as outlined in Eq. 5.

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

Where COV_i is the continuous covariate value specific to the ith individual; COV_{median} is the median for that continuous covariate across the population, and θ is the coefficient describing the magnitude and direction of the covariate's impact on the PK parameters.

Categorical covariates were handled using a proportional model structure, as in Eq. 6.

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

Where COV stands for the categorical covariate, assigned a value of either 0 or 1.

A stepwise method of forward inclusion and backward elimination was used to screen potential covariates. A covariate was judged statistically meaningful and retained in the model when its introduction resulted in an OFV drop exceeding 3.84 ($P < 0.05$; df = 1), and its subsequent removal led to an OFV increase exceeding 6.63 ($P < 0.01$; df = 1).

Model evaluation

The performance of the final population PK model was verified by inspecting goodness-of-fit (GOF) plots, which illustrated the degree of agreement between the empirical data and the model's projections. A nonparametric bootstrap procedure with 1000 iterations was employed to assess the stability of the final parameter estimates. The model's forecasting ability was further assessed through a prediction-corrected visual predictive check (pc-VPC). Moreover, the distributional properties of the model were checked by examining normalized prediction distribution error (NPDE) plots, which verified conformity to a standard normal distribution (mean of 0, variance of 1). To achieve a higher level of visual detail in this assessment, a set of four normalized prediction distribution (NPD) plots was generated in place of standard NPDE diagnostics [18].

Dosing regimen recommendation

Based on the final population PK model, Monte Carlo simulations were run to predict the steady-state C0 concentrations achievable with nine typical sirolimus dosing schedules across differing covariate levels. The nine schedules evaluated were: (1) 0.5 mg qd (administered once daily); (2) 1 mg qd; (3) 1.5 mg qd; (4) 2 mg qd; (5) 1 mg qod (administered every other day); (6) 2 mg qod; (7) a regimen alternating 0.5 mg qd with 1 mg qd; (8) a regimen alternating 1 mg qd with 1.5 mg qd; and (9) a regimen alternating 1 mg qd with 2 mg qd. The final dosing recommendations for patients with different covariate values were derived from simulated steady-state C0 ranges, with the criterion that a substantial majority of the resulting concentrations fall within the established therapeutic window of 4–8 ng/mL [9, 10].

Results and Discussion

Patient characteristics

The population PK analysis was based on 216 whole-blood sirolimus measurements from 103 adult individuals. All were recipients of a liver transplant and were given sirolimus to avert rejection. The cohort's median age was 51 years, median weight was 68.0 kg, and median body mass index was 23.8 kg/m². The sirolimus regimens employed within this group consisted of 0.5 mg once daily, 1 mg once daily, 2 mg once daily, 1 mg every other day, 2 mg every other day, an alternating pattern of 0.5 mg once daily and 1 mg once daily, and an alternating pattern of 1 mg once daily and 2 mg once daily. A summary of the participants' baseline demographic characteristics is given in **Table 1**.

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

Variable (Characteristics)	Median [Range]	Average (SD)
Gender (male/female)	—	99/4
Age (years)	51.0 [28.0–74.0]	50.4 (9.20)
Stature (cm)	170 [150–183]	170 (5.40)
Body weight (kg)	68.0 [39.0–90.0]	68.6 (10.2)
Body mass index (kg/m²)	23.8 [16.7–30.8]	23.6 (3.11)
Days after surgery (day)	92 [14–699]	145 (140)
Daily sirolimus dose (mg/day)	1.0 [0.5–2.0]	1.02 (0.32)
Sirolimus trough level (ng/mL)	5.26 [1.33–12.17]	5.45 (1.96)
Hemoglobin (g/L)	126 [57–168]	125 (23.7)
Hematocrit (%)	38.0 [17.5–49.5]	37.8 (6.60)
Serum total protein (g/L)	74.4 [50.3–105.0]	74.2 (7.82)
Serum albumin (g/L)	44.2 [27.2–50.9]	43.1 (4.85)
ALT (U/L)	21.0 [5.0–187.0]	38.0 (38.5)
AST (U/L)	25.0 [12.0–190.0]	37.1 (32.7)
ALP (U/L)	104 [8–1040]	145 (131)
GGT (U/L)	58.0 [13.0–1110]	109 (170)
Total bilirubin (μmol/L)	53.55 [2.50–308.0]	22.5 (32.3)
Blood urea nitrogen (mmol/L)	6.07 [2.4–38.7]	7.22 (5.14)
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)

Note: [a]Computed from serum creatinine (SCR) using the Cockcroft–Gault equation: creatinine clearance = [140 – age (years)] × weight (kg) / [0.818 × SCR (μmol/L)] × k, where k takes the value of 1 for males and 0.85 for females.
Abbreviation: SD = standard deviation.

Model development

A one-compartment disposition model with first-order elimination provided the best fit to the dataset. BSV was assigned to both CL/F and the apparent volume of distribution (V/F). RUV was captured through a combined (additive plus proportional) error structure. The correlation linking CL/F and V/F was determined.

The inclusion of HCT led to a statistically significant decline in OFV of 32.9. In the backward deletion phase, no covariates were discarded ($P > 0.01$). Hence, upon completion of the stepwise screening, HCT remained as the sole covariate in the conclusive model. The definitive population PK model took the form expressed in Eqs. 7–9:

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

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

$$V/F\ (L) = 496 \quad (9)$$

Table 2 lists the parameter estimates belonging to the final model. All parameters had relative standard errors below 30%, confirming robust precision in the estimation.

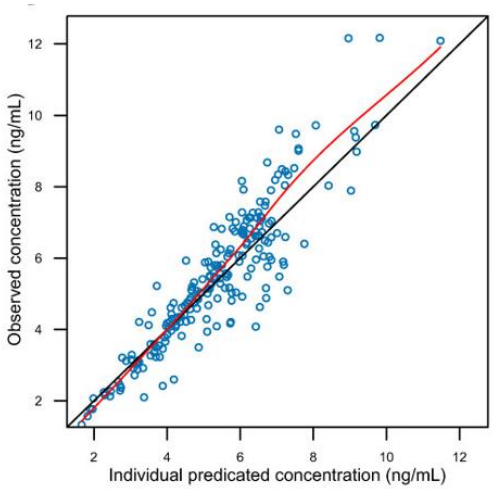
Table 2. Population pharmacokinetic parameter estimates and bootstrap results of the final model.

Parameter	RSE (%)	Final model estimate	Bootstrap 2.5%–97.5%	Bootstrap median
Fixed-effect parameters				
Absorption rate constant, ka (h^{-1})	Fixed	0.75	/	/
Apparent clearance, CL/F (L/h)	4	7.09	6.44–7.59	7.02
Apparent volume of distribution, V/F (L)	15	496	306.28–687.11	515.85
Effect of HCT on CL/F	17	−0.901	(−1.259)–(−0.551)	−0.873
Inter-individual variability (random effects)				
Variability in CL/F, ω(CL/F) (%)	9	32.4	25.1–37.9	31.9
Variability in V/F, ω(V/F) (%)	19	42.7	17.7–59.2	40.1
Covariance between CL/F and V/F, ωCOV(CL/F–V/F)	/	0.0665	0.0062–0.1317	0.0695
Residual unexplained variability				
Proportional error, ε_{por} (%)	10	3.3	2.41–3.81	3.19

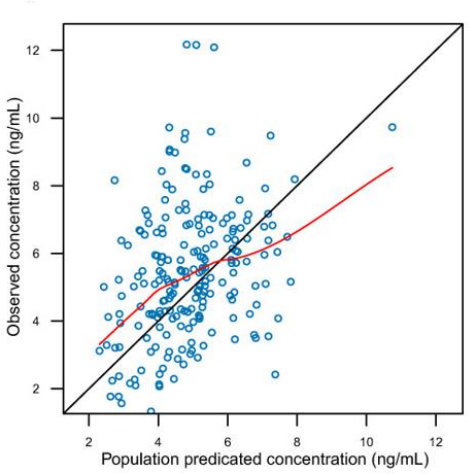
Abbreviations: CL/F = apparent clearance (L/h); HCT = hematocrit (%); ka = absorption rate constant (h−1); V/F = apparent central volume of distribution (L); RSE = relative standard error; ω_(CL/F) = between-subject variability for the apparent clearance; ω_(V/F) = between-subject variability for the apparent central volume of distribution; ε_por = proportional residual variability.

Model evaluation

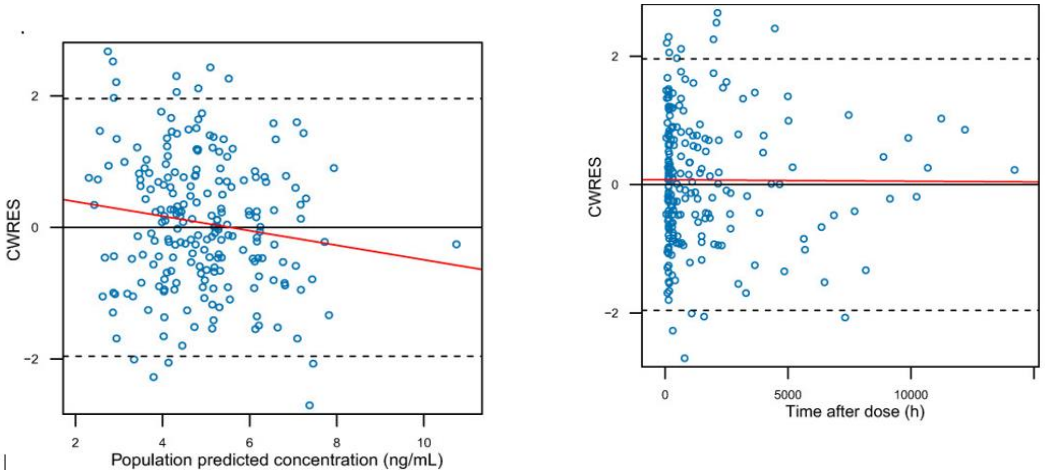
Inspection of the GOF plots confirmed that the final model effectively described the empirical measurements **(Figure 1).** Plots of observed concentrations against individual and population predictions showed substantial scatter, straddling the identity line **(Figures 1a and 1b)**. The great majority of the conditional weighted residuals were concentrated tightly around the zero ordinate and stayed within a band of ± 2 **(Figures 1c and 1d).**



a)



b)



c) d)

Figure 1. Goodness-of-fit plots of the final model: (a) Observed versus individual predicted concentration; (b) observed versus population predicted concentration (PRED); (c) conditional weighted residuals (CWRES) versus PRED; (d) CWRES versus time after dose. The black solid lines represent the lines of identity, whereas the red solid lines trace the loess smooth lines.

The bootstrap run completed successfully for 97.5% of the 1000 replicate samples. The final model's parameter estimates were enclosed within the 95% confidence intervals (CIs) derived from the bootstrap results, lending support to the model's stability **(Table 2).**

The PC-VPC outcomes for the final model indicated satisfactory alignment between simulated and observed concentrations **(Figure 2)**. In particular, the 5th, 50th, and 95th percentiles of the measured data were almost entirely within the corresponding 90% CIs derived from simulation.

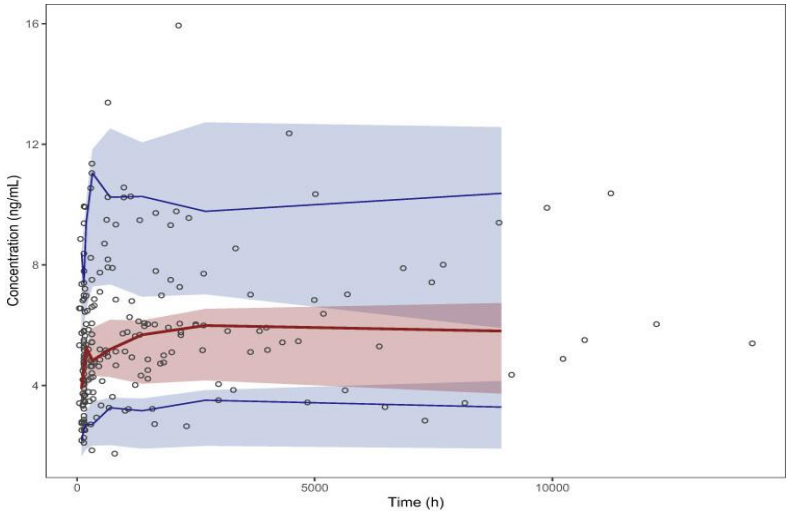


Figure 2. Prediction-corrected visual predictive check of the final model. Individual dots mark the measured concentrations; the continuous lines trace the median (red) and the 5th and 95th percentiles (blue) of the measured values. The shaded bands correspond to the 90% confidence intervals constructed for the median (red) and for the 5th and 95th percentiles (blue) of the simulated replicates.

The NPD diagnostic graphs exhibited no apparent structural trends **(Figures 3a–3d).** All P values stemming from the Wilcoxon signed-rank, Fisher's variance, Shapiro–Wilk, and global tests lay above 0.5, suggesting that the final population PK model was well suited to reproduce the characteristics of the gathered data.

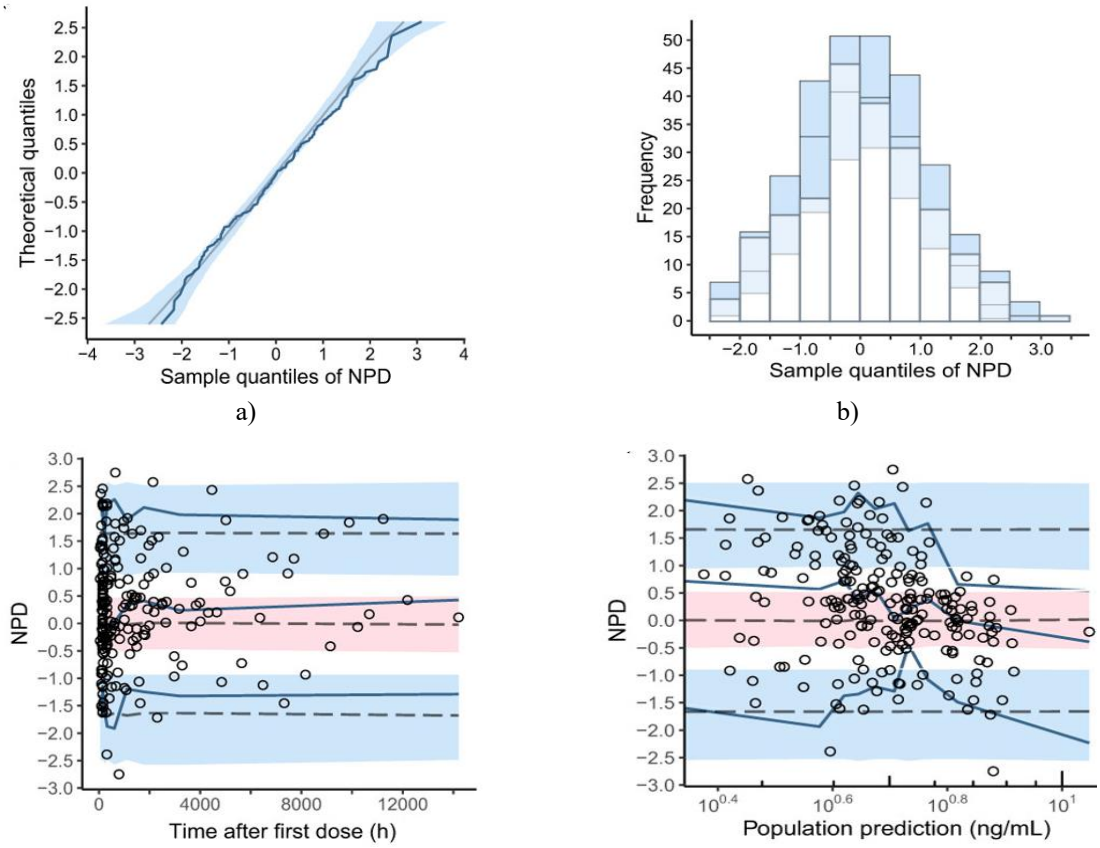


Figure 3. Normalized prediction distribution (NPD) plots of the final model: (a) Quantile-quantile plot comparing the NPD distribution against the theoretical normal distribution; (b) histogram of the NPD distribution with the standard normal density curve superimposed; (c) NPD plotted against time elapsed after the first dose; (d) NPD plotted against population prediction.

Dosing regimen recommendation

Because HCT formed part of the final population PK model, Monte Carlo simulations were carried out to project steady-state C0 concentrations across the nine commonly encountered sirolimus regimens, each evaluated at three distinct HCT thresholds representing the 10th, 50th, and 90th percentiles of the study cohort's HCT span: namely 28%, 38%, and 46%. The simulated distributions are displayed in **Figure 4**.

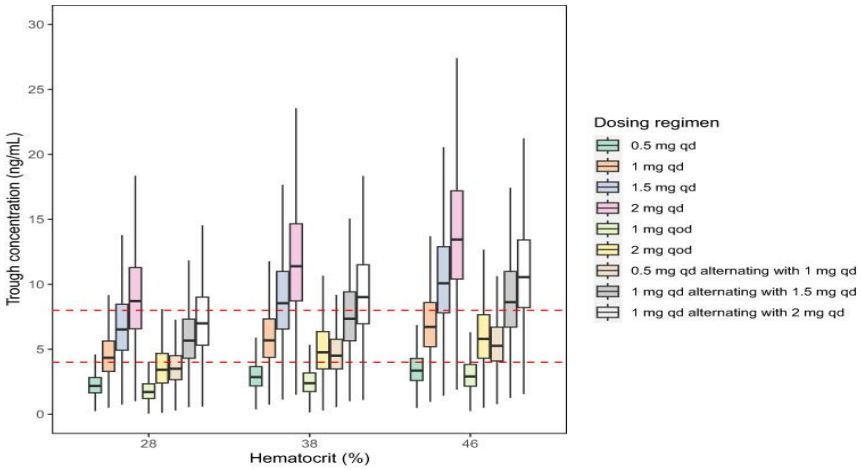


Figure 4. Boxplot illustrating the distributions of simulated steady-state sirolimus whole-blood trough concentrations for patients possessing hematocrit levels of 28%, 38%, and 46%. The two dashed horizontal lines denote the sirolimus therapeutic window (4–8 ng/mL).

The Monte Carlo experiments indicated that, as HCT increases, the daily dose required to achieve levels within the therapeutic window—when the frequency of administration remains unchanged—decreases progressively. For patients with a low HCT of 28%, the recommended approaches are 1.5 mg once daily and a rotation of 1 mg once daily with 1.5 mg once daily. For patients with normal HCT of 38% or 46%, the recommended approaches are 1 mg once daily, 2 mg every other day, or a rotation of 0.5 mg once daily with 1 mg once daily.

To the best of our knowledge, the present work constructs a population PK framework for sirolimus in liver transplant patients that draws upon the most extensive sample assembled to date. A one-compartment model with first-order elimination well characterized the drug's pharmacokinetics. Based on the model-based evaluation, a series of clinically actionable dosing alternatives was proposed for individuals stratified by HCT.

The PK estimates obtained here from sparsely timed specimens were consistent with previously published figures. Zhang *et al*. [10] reported a CL/F of 6.97 L/h and a V/F of 457.85 L for adult liver graft recipients, values that closely accord with our own determinations (CL/F: 7.09 L/h, V/F: 496 L).

In addition, distinct population PK analyses of sirolimus have been carried out in other transplant settings, including renal [14, 19-21] and cardiac allograft populations [15]. Our CL/F estimate coincided with that reported for cardiac transplant recipients [15] and lay slightly below the range documented for renal transplant recipients (8.91–14.4 L/h) [19, 21]. This observation may stem from the liver's prominent role in CYP3A-mediated sirolimus metabolism; if the newly transplanted hepatic tissue has not yet fully restored function, a depressed CL/F could ensue.

Turning to V/F, our figure fell within the range observed for renal transplant patients (322–727 L) [20, 21], yet was substantially smaller than the 1350 L value reported for cardiac allograft patients [15]. This discrepancy may arise because only trough concentrations were available, making accurate estimation of V/F inherently difficult.

HCT was the sole covariate found to influence CL/F in the final population PK construct significantly. Greater HCT values were associated with reduced CL/F, a pattern that corroborates earlier work in subjects with advanced malignancies [22]. Since an estimated 95% of sirolimus is sequestered within red blood cells [23], higher HCT levels are likely to shrink the pool of unbound, free drug, thereby depressing CL/F.

The role of concurrent pharmacotherapy in shaping sirolimus pharmacokinetics was also examined. During forward selection, the co-presence of MPA or Wuzhi capsules was tentatively introduced into the model as binary covariates; however, in the subsequent backward deletion phase, both were discarded because they failed to reach statistical significance and had poorly estimated covariate effect coefficients.

Wuzhi capsules act as potent inhibitors of CYP3A4 [24]. Because CYP3A4 is the primary enzyme responsible for sirolimus biotransformation, the concurrent administration of its inhibitors can perturb the drug's metabolic profile. Moreover, a potential interactive effect linking MPA and sirolimus exists. Dösch *et al*. [25] observed that dose-normalized MPA trough concentrations in the sirolimus/MPA cohort were lower than those in the cyclosporin A/MPA cohort. Hence, subsequent studies featuring richer co-medication data are required to refine sirolimus dosing recommendations.

In everyday practice, adult liver transplant recipients tend to follow an intricate sirolimus regimen dictated by its limited therapeutic margin. The simulation findings revealed that, under normal HCT conditions, the recommended dosing approaches also accommodate an extended dosing interval—specifically, every other day. This observation is likely explained by the prolonged elimination half-life of sirolimus, which reaches 62 hours, allowing trough levels to remain comfortably within the therapeutic window in these patients. A well-optimized dosing strategy can thus help clinicians sidestep repetitive dosage modifications and lower the frequency of supratherapeutic concentration-related adverse events.

Several constraints bound the present work. First, the database included only trough-level measurements, which necessitated holding the Ka constant and weakened the trustworthiness of the calculated V/F. Dedicated prospective trials are consequently warranted to probe the absorption and distribution kinetics of sirolimus. Second, although this investigation incorporates the largest sirolimus concentration dataset in adult liver transplant recipients to date, the available information still falls short of a complete assessment of how concomitant drugs affect sirolimus pharmacokinetics. Third, owing to the single-center origin of all data, the transferability and extrapolative capacity of this model must be examined further.

Conclusion

In sum, this analysis provides a population PK characterization of sirolimus in adult liver transplant recipients, using the largest sample reported to date. HCT emerged as a significant modifier of sirolimus CL/F. We advocate individualizing dosing regimens across the nine commonly used schedules based on distinct HCT levels.

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