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Pharmacokinetic Model Based on Stochastic Simulation and Estimation for Therapeutic Drug Monitoring of Tacrolimus in Korean Adult Transplant Recipients

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Background: Tacrolimus shows high variability in inter- and intraindividual pharmacokinetics (PK); therefore, it is important to develop an appropriate model for accurate therapeutic drug monitoring (TDM) procedures. This study aimed to develop a pharmacokinetic model for tacrolimus that can be used for TDM procedures in Korean adult transplant recipients by integrating published models with acquired real-world TDM data and evaluating clinically meaningful covariates.

Methods: Clinical data of 1829 trough blood samples from 269 subjects were merged with simulated data sets from published models and analyzed using a nonlinear mixed-effect model. The stochastic simulation and estimation (SSE) method was used to obtain the final parameter estimates.

Results: The final estimated values for apparent clearance, the volume of distribution, and absorption rate were 21.2 L/h, 510 L, and 3.1/h, respectively. The number of postoperative days, age, body weight, and type of transplant organs were the major clinical factors affecting tacrolimus PK.

Conclusions: A tacrolimus PK model that can incorporate published PK models and newly collected data from the Korean population was developed using the SSE method. Despite the limitations in model development owing to the nature of TDM data, the SSE method was useful in retrieving complete information from the TDM data by integrating published PK models while maintaining the variability of the model.

Key Words: therapeutic drug monitoring, Korean population, tacrolimus, pharmacokinetics, nonlinear mixed-effect modeling

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INTRODUCTION

Tacrolimus is a calcineurin inhibitor widely used as an immunosuppressant; it is also used as the first line of treatment after kidney and liver transplantation in Korea. Tacrolimus is primarily metabolized in the liver before elimination and is rarely excreted through the urine. Although its half-life is reportedly approximately 12 hours, it is highly variable from 3.5 to 40.5 hours depending on patient demographics and conditions.[1] The absorption rate is also variable, reaching peak blood concentrations in 0.5–6 hours with approximately 25% bioavailability.[1] Tacrolimus has a narrow therapeutic index,[1] and the correlation between blood concentrations and doses is poor, indicating highly variable inter- and intraindividual pharmacokinetics (PK).[2–4] Various factors, including ethnicity, sex, age, transplant organ, disease, steroid usage, and time after treatment initiation, contribute to the variability in tacrolimus PK.[5] Therefore, therapeutic drug monitoring (TDM) is a general clinical practice in patients with a transplant to maintain effective therapeutic levels and to avoid toxicity.[3]

In standard TDM procedures, the selection of tacrolimus dosage based on "a priori model-based individual dosing" and optimizing individual PK parameters using the Bayesian estimation method are critical for improving targeted exposure in patients. The population PK model plays the most important role.[6] This technique focuses on estimating individual PK parameters that maximize the likelihood of an observed concentration considering both fixed and random effects. Thus, for desirable TDM results, the PK model should include clinically relevant covariates and the proper magnitude of random effect parameters for the population subjected to TDM. However, for Korean adult transplant recipients, there are only a few full-PK studies that can be used to build a population PK model.[7,8] These were based on the data from a single hospital, which could not be considered a representative population. Moreover, the models require covariates that are not routinely captured in Korean clinical practice

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(eg, genotype and hematocrit in some centers during later periods after transplant). These factors limited the utilization of TDM in many transplantation centers.

Therefore, in this study, we aimed to establish a population PK model with enhanced clinical utility regarding covariate application and individual PK parameter distributions. A tacrolimus population PK model was built from a combined multicenter data set containing simulated data from the existing literature and data collected from several institutions. Because most of the actual data in the TDM procedure were trough concentrations and did not provide sufficient information to build a structural model, the simulated data sets were used as the backbone for model development. Furthermore, instead of using a single simulated data set, the stochastic simulation and estimation (SSE) method was used to obtain a more generalized outcome with the precision of the estimated PK parameter values.

MATERIALS AND METHODS

Strategy for Model Development

The overall strategy of this analysis is shown in Figure 1. This study comprised 2 steps. In the first step, we integrated an observed data set with a simulated data set from previously published models.[7,8] We developed the final model from an integrated data set using a previously built structural model[7] and performed covariate analysis. In the second step, the identical integration and parameter estimation procedure was repeated 1000 times using the final model built in sep 1. The final parameter was acquired by summarizing 1000 sets of estimated parameters. Finally, the tacrolimus PK model was developed using the final structural model built in step 1 and the summarized final parameters estimated in step 2. The ratio of individual numbers in the observed and simulated data sets was 9:1.

Observed Data set

Tacrolimus concentration data of Korean patients older than 18 years, who underwent kidney or liver transplantation at the Inje University Busan Paik Hospital (IUBPH) and Chonnam National University Hospital (CNUH) between 2005 and 2019, were collected. The data acquisition was approved by the institutional review board of each hospital (approval number: 12-194 for IUBPH and CNUH-2018-099 for CNUH). Blood samples were collected before the administration of the morning dose. The dosage was changed, if needed, based on the tacrolimus trough concentration and the patient's target therapeutic range. Generally, the target therapeutic range was 8–12 ng/mL throughout the first postoperative month, 8–10 ng/mL for up to 3 months, 6–8 ng/mL until 6 months, and 4–6 ng/mL thereafter. However, the target therapeutic range could differ depending on the type of transplant organ, patient status, institution, combination drug regimen, and clinician's decision. Sample analysis was performed using affinity column-mediated immunoassay on the Dimension EXL 200 system (Siemens, Berlin, Germany) and chemiluminescence microparticle immunoassay using the ARCHITECT i2000 system (Abbott Laboratories, Abbott Park, IL) at IUBPH and CNUH, respectively. The range of quantification was 2–30 ng/mL. Because the concentration results from these methods are generally accepted and used for clinical decision making, the data from the 2 hospitals were considered compatible despite possible quality differences for accuracy and precision. Age, sex, weight, height, drug name, transplant organ, and the number of postoperative days (PODs) were considered potential covariates, and

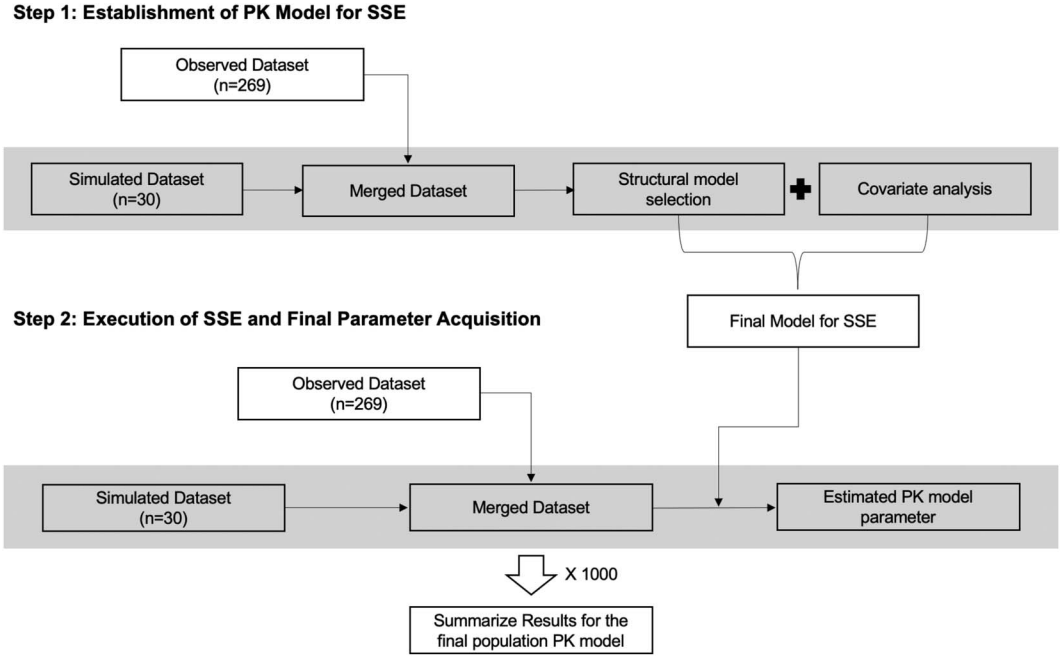

FIGURE 1. Overall strategy of the analysis.

missing values were imputed using the missForest package (ver1.4)[9] in R (ver4.0.3).

Simulated Data set

Two published PK models were used in the simulation.[7,8] These studies were performed using data from patients in Korea who had undergone kidney transplantation and received an immunosuppressive regimen, including tacrolimus (Prograf, Astellas Pharma Korea, Seoul, Korea). One model was based on prospectively collected trough concentrations from 122 patients during the first month after transplantation and densely sampled concentrations from 55 patients (predose, 0.5, 1, 2, 4, 6, 8, and 12 hours after administration) 10–15 days after transplantation[7] (PK model for an early posttransplant period). The second model was based on retrospectively collected trough concentrations from 80 patients during the follow-up period of 400 days after transplantation (PK model for the late posttransplant period).[8] Simulations were performed to reproduce the data by reflecting their sampling points (9 points for the early period and 5 points for the late period in each virtual individual). Concentrations outside the quantification limit for the observed concentrations were omitted. Covariate values included in the models were randomly sampled based on the distribution of corresponding variables in the previous reports. In each simulated data set, 30 individuals were included for both early and late posttransplant periods with 420 simulated concentrations (270 from the early period and 150 for the late period). This number of simulated subjects was considered the minimum number to maintain the general trend of the observed data and to secure the condition for estimating the magnitude of between-subject variability (ω^2), which is assumed to be normally distributed (according to the central limit theorem).

Base Model Development

The base model was developed using the combined data of an observed and a simulated data set using population PK analysis. Population PK analysis was performed using the first-order conditional estimation method with an interaction (FOCE + I) in nonlinear mixed-effect modeling (NONMEM, version 7.5, ICON Development Solution, Ellicott City, MD). R, Rstudio (ver1.4.1), and Xpose4 package (ver4.7.1)[10] were used for graphical analyses and model diagnostics.[11]

Based on the population PK models from original articles, which were used as the backbone in this study, one-compartment PK models with first-order and lag time were selected as the structural model.[7,8] The interindividual variability of each PK parameter was assumed to follow the log-normal distribution and described using an exponential model as follows:

$$P_i = P_{TV} \times \exp(\eta_i), \quad (1)$$

where P_i denotes the individual parameter (eg, *CL/F* or *V/F*) for the i-th individual, P_{TV} is the typical value of the model parameter for the population, and η_i is the interindividual random effect following a normal distribution with a mean of zero and variance of ω^2, accounting for the deviation of the i-th individual from the typical value *of* P_{TV}. The OMEGA BLOCK option was used to evaluate the covariance between the random effects. Residual variability for each institution was evaluated using proportional, additive, and combined models. The models were assessed based on objective function value and goodness-of-fit plots.

Covariate Analysis

Covariate analysis was performed on variables (sex, age, body weight, transplant organ type, POD, and drug name) that could be acquired in the clinical TDM practice and expected to explain the interindividual and interoccasion variabilities. The effect of the data source (literature, IUBPH, or CNUH) was also considered. A generalized additive model (GAM) and graphical analysis were used for covariate screening, and a forward selection-backward elimination method with the NONMEM minimization process was used for covariate selection (forward selection P value $<$ 0.05, backward elimination P value $<$ 0.01).

Evaluation of the PK Model Performance for SSE

The final base model was assessed by bootstrapping and visual predictive check validation. The medians and fifth–95th percentiles of the results from 1000 random samplings were compared with the original parameters in bootstrapping. The observed concentrations and 90% prediction intervals of the simulated concentrations versus time were plotted, and any bias or trend was evaluated. Bootstrapping and visual predictive check (VPC) validation processes were performed using R, NONMEM, and Wings for NONMEM (WFN, ver750, http://wfn.sourceforge.net/).

Stochastic Simulation and Estimation

As shown in step 2 (Fig. 1), 1000 data sets consisting of 30 subjects for each model were simulated using published PK models with sampled covariates from their raw data. Subsequently, the simulated data were combined with the observed data set. Finally, the population PK parameters were estimated based on the final PK model for each of the 1000 combined data sets using the FOCE-I method in NONMEM. Thus, 1000 sets of population PK parameters were estimated, and the median of the successfully estimated values of each parameter was selected as the final parameter.

All statistical analyses were performed using the R software (ver4.0.3). The results of the SSE analysis are presented as mean ± 90% confidence interval and relative standard error (RSE) to assess the robustness of the estimated parameters.

Final Model and Parameter Evaluation

Visual predictive check validation (VPC) was performed to evaluate the accuracy and robustness of the final model and estimated parameters from the SSE analysis. Because each patient included in the data set had a different dosage regimen, sampling time, and covariate values, a prediction-corrected VPC (pcVPC) suggested by Bergstrand et al[12] was conducted instead of a traditional VPC. Traditional VPC is known for deceiving the analysis of TDM data because its dose adjustments and the observed dependent variable are inherently

correlated.[12] The pcVPC method is useful, as it helps avoid misleading diagnoses because the variability caused by independent variables (time, dosage, and other covariate values) within a bin can be corrected by normalizing the dependent variable based on the population prediction.[12] Population prediction correction was performed on log-transformed dependent variables, as shown in Equation (2):[12]

$$\ln\left(\mathrm{pcY}_{ij}\right) = \ln\left(\mathrm{Y}_{ij}\right) + \left(\ln(\mathrm{PRED}_{bin}) - \ln\left(\mathrm{PRED}_{ij}\right)\right), \quad (2)$$

where pvY_{ij} is the prediction-corrected observation of the prediction for the ith individual at the jth time point, Y_{ij} is the observation or prediction for the ith individual and jth time point, $PRED_{bin}$ is the median of typical population predictions for the specific bin of independent variables, and $PRED_{ij}$ represents the typical population predictions for the ith individual at the jth time point. In total, 1000 simulated replicates of the original design were used to determine a 90% prediction interval. Perl-speaks-NONMEM (PsN, ver4.8.1, http://uupharmacometrics.github.io/PsN/install.html)[13] and Rstudio with R were used for the simulation and pcVPC.

RESULTS

Population PK Modeling for the Final Structural Model

For the analysis, 1829 tacrolimus observations (1535 from IUBPH and 294 from CNUH) from 269 patients (122 from IUBPH and 147 from CNUH) who underwent tacrolimus TDM were included as an observed data set and were combined with the simulated data set. In this process, observations that were not within the quantification limit were excluded (4 observations). Patient demographic information from the institutions is presented in Table 1. The characteristics of the patients at each institution were comparable. As the original articles suggested, tacrolimus PK data were well-described by a one-compartment, first-order elimination model with lag time. The final parameter values from the structural model were within a reasonable range; POD, age, and organ transplantation were selected as significant covariates. The goodness-of-fit plots and VPC of the PK model with all covariates suggest that the final model adequately describes the observed data. The final estimated PK parameters are presented in Table 2.

TABLE 1. Patient Demographics

Characteristics	Number of Patients
IUBPH	
No. of patients	122
Male/female	64/58
Age (yr)	46.6 ± 12.3
Body weight (kg)	63.2 ± 17.0
Height (cm)	165 ± 8.90
Type of drug	
Tacrobell	56 (48.7%)
Prograf	59 (51.3%)
Type of transplantation	
Kidney	114 (93.4%)
Liver	4 (3.28%)
CNUH	
Number of patients	147
Male/female	89/58
Age (yr)	49.2 ± 11.2
Body weight (kg)	67.1 ± 14.1
Height (cm)	164 ± 8.23
Type of drug	
Tacrobell	0 (0.00%)
Prograf	147 (100%)
Type of transplantation	
Kidney	125 (85.0%)
Liver	22 (15.0%)

POD, age, and transplantation organ (liver and kidney) were selected as statistically significant covariates of apparent clearance (CL/F), and weight was included as a significant covariate of the apparent volume of distribution (V/F). POD had a significant effect on CL/F in both kidney and liver transplant patients, but the effect differed with the transplant organs. In kidney transplant patients, after an immediate decrease post transplantation, CL/F increased as POD increased by 40% within 4 weeks after transplantation. However, the CL/F started to decrease gradually after 1 month until it reached a plateau. In liver transplant patients, baseline CL was lower than that of kidney transplant patients and recovered to a similar value in the late period. The changes in CL/F by POD in both kidney and liver transplant patients are shown in Figure 2. The age and body weight of the patients affected the CL/F and V/F, respectively. As age increased, CL/F decreased, and as body weight increased, V/F increased in both kidney and liver transplant patients.

SSE Analysis and Final Parameters

The results of the SSE analysis of 1000 simulation sets are presented in Table 3. The success rate of parameter estimation, including rounding errors with significant digits ≥2, was 72.4% (724 of 1000 simulation sets). Thus, the confidence intervals of the mean values and RSEs were calculated from 724 sets of successfully estimated parameters. The RSEs of the PK parameters ranged from 0.75% to 27.0%, and the sizes of interindividual variability of PK parameters ranged from 0.223 to 0.826. Among the major PK parameters, the apparent central volume (V/F) had the largest RSE value, and the absorption rate constant (k_a) had the largest interindividual variability. Based on the 90% confidence intervals of the means and RSEs, the final parameter estimated from the SSE analysis was dependable and robust. The final estimated values of CL/F and V/F were close to those reported in other studies (21.2 L/h and 510 L, respectively).[7,8] However, considering the distribution patterns of PK parameters (skewed distributions), medians were found to be more appropriate than means as representative values, and therefore, they were selected as the final parameters of the PK model.

TABLE 2. Parameter Estimates of Final PK Model

Parameter	Description	Estimate	%RSE	Bootstrap Median (95% CI)
Structural model				
$CL/F = \theta_1 \cdot \left(\frac{Age}{49}\right)^{\theta_2} \cdot (POD^{\theta_3}\ in\ early\ phase) \cdot (POD^{\theta_4}\ in\ late\ phase)$				
$\theta_{1,\ preop}$	Oral clearance (*CL/F*) before surgery (L/h) in kidney transplant patients	21.9	12.2	22.3 (12.5,28.8)
$\theta_{1,\ postop,\ kidney}$	Baseline *CL/F* after surgery in kidney transplant patients (L/h)	20.5	5.9	20.3 (18.1,22.9)
$\theta_{1,\ postop,\ liver}$	Baseline *CL/F* after surgery in liver transplant patients (L/h)	12.9	17.9	12.7 (7.74,20.2)
θ_2	Age effect	−0.397	27.7	−0.443 (−0.767, −0.191)
$\theta_{3,kidney}$	POD effect in early period in kidney transplant patient	0.112	13.3	0.107 (0.0748, 0.138)
$\theta_{3,\ liver}$	POD effect in liver transplant patient	0.0557	63.2	0.0589 (0.00161, 0.195)
$\theta_{4,\ kidney}$	POD effect in late period in kidney transplant patient	−0.023	13.3	−0.0237 (−0.0506, −0.00148)
$V/F = \theta_5 \cdot \left(\frac{WT}{62.4}\right)^{\theta_6}$				
θ_5	Apparent volume (L)	499	12.2	482 (355, 647)
θ_5	Body weight effect	1.30	34.6	1.26 (0.0756, 2.29)
k_a	Absorption rate constant	2.59	14.3	2.60 (1.96, 3.47)
$ALAG_1$	Lag time of first-order absorption	0.25 (fix)		
Interindividual variability (CV%)				
$\omega_{CL/F}$	Interindividual variability of *CL/F*	43.4	6.4	50.8 (39.7, 67.5)
$\omega_{V/F}$	Interindividual variability of *V/F*	84.2	11.9	89.6 (30.0, 118)
Correlation coefficients				
$\rho_{CL/F\text{-}V/F}$	Correlation coefficients between *CL/F* and *V/F*	0.221	40.5	0.198 (0.0186, 0.281)
Residual error				
$\sigma_{add,\ 1*}$	Additive error	0.0001 (fix)		
$\sigma_{prop,\ 1*}$	Proportional error	0.244	3.6	0.244 (0.227, 0.262)
$\sigma_{add,\ 2*}$	Additive error	−2.77	13.7	−2.91 (−3.5, −2.1)
$\sigma_{add,\ 3*}$	Additive error	2.78	10.3	2.71 (2.34, 3.03)

*Number refers to the hospital where data were collected (1: Seoul National University Hospital, 2: Inje University Busan Paik Hospital, 3: Chonnam National University Hospital).

PK, pharmacokinetics; POD, postoperative days; CI, confidential interval; CL, clearance; F, bioavailability; V, volume of distribution; WT, body weight.

Final Model Assessment

To assess the appropriateness of the final parameters estimated from the SSE analysis, pcVPC was performed with 13 bins for each institution per period. Because the sampling points were not spread evenly throughout the sampling period, the time interval of each bin was set according to the number of observations in each bin instead of the automated binning process provided by the PsN. The results of pcVPC of institutions based on PODs are presented in Figure 3. Based on the pcVPC results, the central trend and variability in the observed data could be reproduced appropriately by simulating the final PK model, indicating that the predictive performance of the final PK model was acceptable.

DISCUSSION

In this study, we developed a population PK model of tacrolimus that can play the role of a backbone for practical TDM procedures in Korean populations by reflecting the clinically relevant covariates and suggesting the feasible magnitude of PK parameters in the target population. The final estimated values of *CL/F* and *V/F* (21.2 L/h and 510 L, respectively) were close to those reported in other studies.[7,8] Considering previous reports,[4,7,8,14–16] the population values and variabilities of the parameters were not overestimated, and the residual error was within the known intrapatient variability of tacrolimus and conventional precision range of analysis. The final model appropriately described the observed data with an acceptable prediction interval.

We managed to overcome the limitations owing to the nature of TDM data in PK model development and demonstrated the possibility of using the SSE method as a valuable tool to integrate the published models with acquired data, especially when the raw data of published models could not be obtained. SSE can reduce the potential bias of a single simulated data set produced by the errors of generated random number. After summarizing the outcome from repeated estimation results, the variability of those errors can be referred as the precision of the parameters while the central tendency remains.[17] Multiple studies have shown that stochastic modeling can reduce the errors and provide a better estimate than the deterministic method because this rigorous statistical approach can decompose the error into variability and system errors.[17–21]

As the present model was developed using real-world data, several clinically meaningful covariates were identified

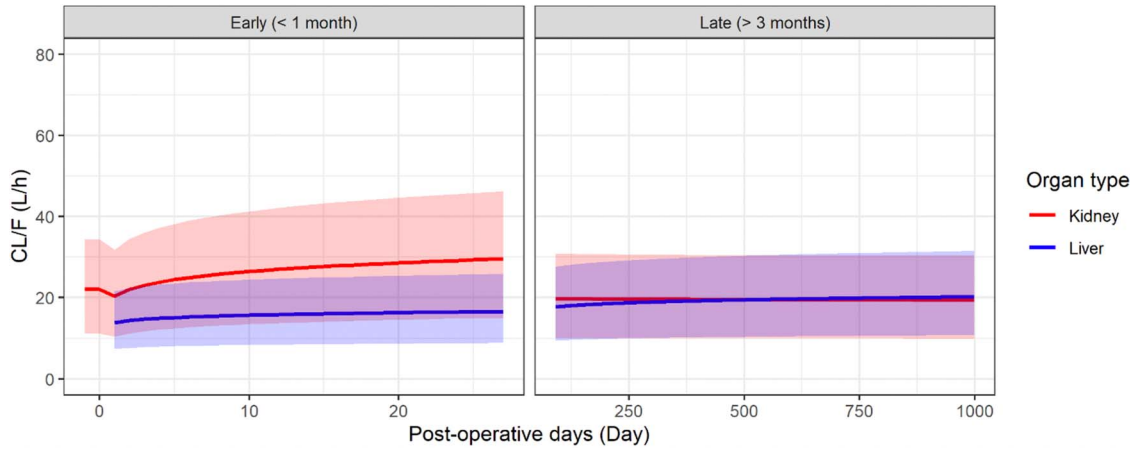

FIGURE 2. Clearance (*CL/F*) profile of 1000 simulated patients for the 1000-day posttransplantation by transplant organ type. *Red line* represents the mean *CL/F* in liver transplant patients. *Blue line* represents the mean *CL/F* in kidney transplant patients *Semitransplant red field* represents prediction interval (PI) between 10% and 90% in kidney transplant patients. *Semitransplant blue field* represents PI between 10% and 90% in liver transplant patients.

during the process. POD, age, and transplant organ (liver and kidney) were found to have a significant effect on *CL/F*, whereas only weight was associated with *V/F*. During the early period, *CL/F* gradually increased with time after immediate reduction owing to transplantation surgery, regardless of the transplant organ type. This finding is consistent with that

TABLE 3. Final Parameter Estimates Using SSE Method (n = 1000)

Parameter	Description	Median	Mean (±95% CI)	%RSE
Structural model				
$CL/F = \theta_1 \cdot \left(\frac{Age}{49}\right)^{\theta_2} \cdot (POD^{\theta_3}\ in\ early\ phase)$				
$\theta_{1,\,preop} \cdot (POD^{\theta_4}\ in\ late\ phase)$	Oral clearance (*CL/F*) before surgery (L/h) in kidney transplant patient	21.2	21.1 ± 0.0322	1.55
$\theta_{1,\,postop,\,kidney}$	Baseline *CL/F* after surgery in kidney transplant patients (L/h)	18.8	18.8 ± 0.0224	1.22
$\theta_{1,\ postop,liver}$	Baseline *CL/F* after surgery in liver transplant patients (L/h)	11.4	11.1 ± 0.0159	1.31
θ_2	Age effect	−0.382	−0.379 ± 0.00418	11.2
$\theta_{3,kidney}$	POD effect in early period in kidney transplant patient	0.118	0.118 ± 0.000191	1.65
$\theta_{3,liver}$	POD effect in liver transplant patient	0.0582	0.0585 ± 0.000184	3.03
$\theta_{4,kidney}$	POD effect in late period in kidney transplant patient	−0.0100	−0.0101 ± 0.000139	14.0
$V/F = \theta_5 \cdot \left(\frac{WT}{62.4}\right)^{\theta_6}$				
θ_5	Apparent volume (L)	510	503 ± 1.95	4.38
θ_6	Body weight effect	1.30	1.37 ± 0.0363	27.0
k_a	Absorption rate constant	3.10	3.21 ± 0.0427	16.4
$ALAG_1$	Lag time of first-order absorption	0.25 (fix)	0.25 (fix)	
Interindividual variability				
$\omega_{CL/F}$	Interindividual variability of *CL/F*	0.223	0.223 ± 0.00155	7.06
$\omega_{V/F}$	Interindividual variability of *V/F*	0.826	0.829 ± 0.00699	8.57
Correlation coefficients				
$\rho_{CL/F\text{-}V/F}$	Correlation coefficients between *CL/F* and *V/F*	0.191	0.190 ± 0.00349	18.7
Residual error				
$\sigma_{add,\ 1*}$	Additive error	0.0001 (fix)	0.0001 (fix)	
$\sigma_{prop,\ 1*}$	Proportional error	0.0653	0.0657 ± 0.000754	11.7
$\sigma_{add,\ 2*}$	Additive error	−2.48	−2.44 ± 0.0418	17.4
$\sigma_{add,\ 3*}$	Additive error	2.86	2.85 ± 0.0021	0.75

*Number refers to the hospital where data were collected (1: Seoul National University Hospital, 2: Inje University Busan Paik Hospital, 3: Chonnam National University Hospital).

CI, confidential interval; CL, clearance; F, bioavailability; V, volume of distribution; WT, body weight.

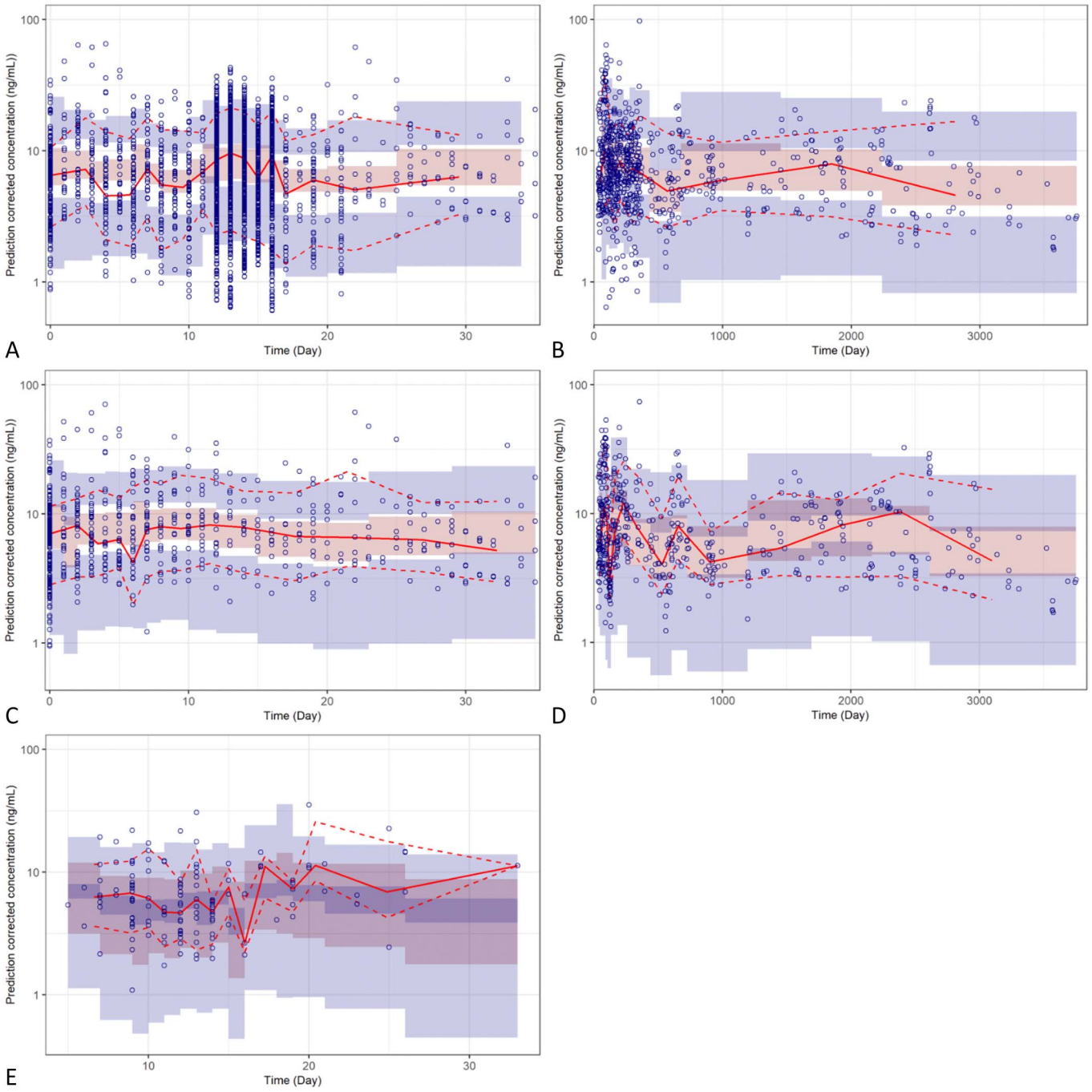

FIGURE 3. Prediction-corrected VPC (pcVPC) plot based on institution data and postoperative days (A: All data in early period, B: All data in late period, C: IUBPH data in early period, D: IUBPH in late period, E: CNUH data). *Solid red line* represents the median of prediction-corrected blood concentration (ng/mL), and *semitransparent red field* represents a simulation-based 95% confidence interval (CI) for the median. The observed 10% and 90% percentiles are presented with *dashed red lines*, and the 95% CIs for the corresponding simulation-based percentiles are presented as *semitransparent blue fields*. The prediction-corrected observed blood concentrations are presented as *blue circles*.

of previous reports.[7,22,23] The immediate decrease in *CL*/*F* after transplantation may be due to the decreased CYP3A activity from hyperacute postsurgical changes, such as acute inflammation and perfusion injury,[24–26] and also by increased bioavailability because of low gastrointestinal motility and decreased gut metabolism.[7,27] An increase in *CL*/*F* during the early period could be explained by several factors, including the recovery of gastrointestinal motility and CYP3A activity, coadministration of corticosteroids, and postoperative hypermetabolism.[25] Corticosteroids are known to induce

both CYP3A and P-glycoprotein, responsible for the metabolism and absorption of tacrolimus, respectively[27]; therefore, they can increase *CL* and decrease *F* of tacrolimus.[28–31] However, the *CL*/*F* of liver transplant patients was mostly lower than that of kidney transplant patients during the early period, probably because it takes up to 6 months for the liver, which is responsible for the elimination of tacrolimus from the body, to recover to its normal functions after transplantation.[23,32]

After the early period, *CL*/*F* decreased with time and reached a plateau after 1 year in kidney transplant patients. This was related to a reduction in corticosteroid administration and multiple other factors including a reduction in postoperative hypermetabolism, ischemia–reperfusion injury, and increased hematocrit levels as the kidney function recovered.[8,29,33] When tacrolimus binds to hematocrit extensively, whole-blood clearance decreases with increasing hematocrit levels.[34–36] However, unlike in kidney transplant patients, a decrease in *CL*/*F* was not observed in liver transplant patients during the late period. Instead, it plateaued after a gradual increase, possibly due to the recovery and stabilization of liver function. The plateau level values of CL/F in both kidney and liver transplant patients were similar.

Patient's age was also identified as a major factor affecting *CL*/*F*. A possible explanation for the decrease in *CL*/*F* owing to aging may include age-related differences in P-glycoprotein and CYP3A enzyme activities as organ functions deteriorate in old age.[37,38] Furthermore, in the case of *V*/*F*, the body weight of the patient was another significant covariate, and this finding was also consistent with that of previous reports.[8]

CONCLUSION

A tacrolimus PK model that can describe published PK models and newly collected data from the Korean population was developed using the SSE method. Although there are limitations in the model development owing to the nature of TDM data, the SSE method was found useful for obtaining the complete information from TDM data by integrating published PK models while maintaining the variability of the model.

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