

Pharmacogenomic Analysis of CYP3A5*3 and Tacrolimus Trough Concentrations in Vietnamese Renal Transplant Outcomes

Thi Van Anh Nguyen^{1,*}, Ba Hai Le^{2,*}, Minh Thanh Nguyen^{2,*}, Viet Thang Le^{3,*}, Viet Tien Tran^{4,*}, Dinh Tuan Le^{5,*}, Duong Anh Minh Vu^{2,*}, Quy Kien Truong^{3,*}, Trong Hieu Le^{2,*}, Huong Thi Lien Nguyen^{2,*}

¹Department of Pharmacy, 103 Military Hospital, Hanoi, Vietnam; ²Department of Clinical Pharmacy, Hanoi University of Pharmacy, Hanoi, Vietnam; ³Department of Nephrology and Dialysis, 103 Military Hospital, Hanoi, Vietnam; ⁴Department of Infectious Diseases, 103 Military Hospital, Hanoi, Vietnam; ⁵Department of Rheumatology and Endocrinology, 103 Military Hospital, Hanoi, Vietnam

*These authors contributed equally to this work

Correspondence: Huong Thi Lien Nguyen, Department of Clinical Pharmacy, Hanoi University of Pharmacy, 13-15 Le Thanh Tong, Hoan Kiem, Hanoi, Vietnam, Tel +84904308406, Email huongntl@hup.edu.vn

Purpose: CYP3A5 polymorphisms have been associated with variations in the pharmacokinetics of tacrolimus (Tac) in kidney transplant patients. Our study aims to quantify how the CYP3A5 genotype influences tacrolimus trough concentrations (C_0) in a Vietnamese outpatient population by selecting an appropriate population pharmacokinetic model of Tac for our patients.

Patients and Methods: The external dataset was obtained prospectively from 54 data of adult kidney transplant recipients treated at the 103 Military Hospital. All published Tac population pharmacokinetic models were systematically screened from PubMed and Scopus databases and were selected based on our patient's available characteristics. Mean absolute prediction error (MAPE), mean prediction error, and goodness-of-fit plots were used to identify the appropriate model for finding the formula that identifies the influence of CYP3A5 genotype on the pharmacokinetic data of Vietnamese patients.

Results: The model of Zhu et al had a good predictive ability with MAPE of 19.29%. The influence of CYP3A5 genotype on tacrolimus clearance was expressed by the following formulas: $CL/F = 27,2 \times [(WT/70)^{0,75}] \times [(HCT/0,35) - 0,501] \times [(POD/180)^{0,0306}] \times CYP3A5(L/h)$. The simulation result showed that Tac C_0 was significantly higher in patients not expressing CYP3A5 ($p < 0.001$).

Conclusion: The incorporation of the CYP3A5 phenotype into Zhu's structural model has significantly enhanced our ability to predict Tacrolimus trough levels in the Vietnamese population. This study's results underscore the valuable role of CYP3A5 phenotype in optimizing the forecast of Tac concentrations, offering a promising avenue to assist health-care practitioners in their clinical decision-making and ultimately advance patient care outcomes.

Keywords: tacrolimus, population pharmacokinetic, CYP3A5, Vietnam

Introduction

Tacrolimus (Tac) is the most used immunosuppressive medication to prevent acute rejection following renal transplantation. It has a narrow therapeutic index and its pharmacokinetics (PK) exhibits high inter- and intra-individual variability. Therefore, therapeutic drug monitoring (TDM) of Tac has been implemented regularly to maintain efficacy and minimize side effects. In Vietnam, the initial dose of Tac is adjusted exclusively based on the patient's weight. Subsequently, therapeutic drug monitoring for tacrolimus involves monitoring the trough concentration (C_0), relying solely on the physician's experience due to the absence of any tools or software incorporating patient information. In our most recently published study, it was observed that utilizing this approach was associated with a significant occurrence of acute rejection following kidney transplantation, particularly in cases with lower C_0 levels.¹

The significant occurrence of acute rejection in our population can be attributed to the prevalence of various CYP3A5 gene polymorphisms, particularly the highly prevalent *3 allele, which has been consistently shown in previous pharmacogenetic studies to influence individual dosage requirements and the variability of tacrolimus levels.²⁻⁴ Some studies conducted in Vietnam have also examined the high prevalence of the *3 allele of the CYP3A5 gene and its impact on Tacrolimus trough concentration.^{5,6} However, a precise formula to accurately quantify the influence of CYP3A5 genotype on the pharmacokinetic data of Vietnamese patients for determining the Tacrolimus dose has not yet been identified.

Pharmacist-led activities for individualized dosing have gained recognition worldwide as a valuable approach to optimizing medication therapy. For tacrolimus, by utilizing a model-informed precise dosing (MIPD) tool that incorporates covariates such as CYP3A5 genotype into a population pharmacokinetic (PopPK) model, pharmacists are able to provide the most effective approach for determining appropriate individual doses and facilitating TDM in routine practice.⁷ However, it is important to note that PopPK models used in these tools have not been specifically tested on Vietnamese kidney transplantation patients.

Therefore, the objectives of the present study were as follows: (1) to identify the optimal population pharmacokinetic model of tacrolimus integrating the CYP3A5 phenotype specifically tailored for Vietnamese Renal Transplant Outpatients and (2) to analyze the impact of the CYP3A5 phenotype on tacrolimus trough concentrations through the simulation of Tac C0 utilizing the selected pharmacokinetic model. The results of this study will provide robust evidence of the influence of the CYP3A5 genotype, enabling the development and implementation of MIPD software tools, which will assist in determining the optimal individual starting dose and facilitating TDM in Vietnamese kidney transplant patients.

Materials and Methods

Patients and External Data Collection

The external dataset was obtained prospectively from data of 54 outpatient renal transplant recipients treated at 103 Military Hospital, Vietnam. Patients between the ages of 18 and 75 years who received a single organ renal transplant from either a living donor or a deceased donor were eligible, and the patients received Tac as a primary immunosuppressant treatment. The exclusion criteria were retransplanted patients and non-Vietnamese renal transplant recipients.

Tac C0 was collected before the morning dose when the patient who was on the outpatient drug monitoring schedule went back to the clinic. The administering time and the sampling time of patients were accurately recorded. Demographic and clinical information data were also collected.

Immunosuppression Regimen

The immunosuppressive protocol at our institution consists of a triple-drug therapy consisting of tacrolimus, mycophenolate mofetil (MMF), and steroids. Induction therapy included basiliximab 20 mg (Simulect[®], Novartis) at day 0 and day 4 after transplantation, 500 mg intravenous (IV) methylprednisolone (Solu Medrol[®]; Pfizer) pre and 12 h post-operation. Oral tacrolimus (Prograf[®], Astellas Pharma) was started at night 1 day before transplantation with a dose of 0.1 mg/kg/day administered in two divided doses. Subsequent doses were adjusted based on clinical evaluation and Tac levels. Mycophenolate mofetil (Cellcept[®], Roche) was started with tacrolimus at a dose of 1 g twice a day and adjusted to lower doses in the presence of diarrhea or prolonged fever. The next IV dose of steroid decreased by half in consecutive days to 40 mg/day within one to two weeks post-transplant. Oral prednisolone (15 mg/day) was initiated right after and was tapered every week to a stable period of 5 mg/day.

Bioassay

Tac C0 was quantified by chemiluminescence immunoassay (CMIA, analyzed on the Architect system, Abbott Diagnostics, IL, USA). The detection limit was 1.5 ng/mL. The correlation coefficient of >0.90 for specimens between 2.0 and 30 ng/mL. The Precision of ≤10% total coefficient variation (CV).

Pharmacogenetic analysis: The determination of CYP3A5 genotype was performed on blood samples from each patient. Two single nucleotide polymorphisms of CYP3A5, CYP3A5*1 and CYP3A5*3 were determined by direct sanger sequencing (ABI3500 Biosystem, Thermo Fisher Scientific, Waltham, MA, USA).⁸

Reviews of the Published Tacrolimus Population Pharmacokinetic Models

Published tacrolimus PopPK models were systematically searched from PubMed and Scopus databases from the date of their inception to May 2022. Additional studies were also screened from the reference lists of the identified articles. Search terms included (“kidney” OR “renal”) AND “transplant” AND “Tacrolimus” AND (“population pharmacokinetic”). Studies published in English, twice-daily oral tacrolimus, and conducted in patients >18 years were included. Exclusion criteria for study selection were external validation studies. Based on screened Tac PopPK models in adult renal transplantation, we continued to choose models in which the covariates resemble ours such as PopPK models containing CYP3A5 alleles and studies that had model data.

External Predictability Evaluation

The external evaluation was conducted by using MONOLIX software (version 2020 R1 Lixoft, France). Published models were re-modeled and the parameters were set to the published values in Monolix. The output was analyzed using the R package (version 3.1.1, <http://www.r-project.org>). The predictive performances of the model in the external dataset were assessed using two approaches: a priori and a posteriori (Bayesian approach).⁹ By using an a priori approach, the prediction value was estimated based on only typical parameters of the selected PopPK model and covariates such as hematocrit (HCT), weight, and genotypes. Meanwhile, the predictions that followed the Bayesian approach were estimated by integrating the observed concentrations in patients.

The predictive performances of the model were evaluated through by Goodness of fit plot and two parameters that describe the accuracy and precision of model prediction (MPE and MAPE).

- MPE (mean prediction error):

$$\text{MPE} = \frac{\sum_{j=1}^n (\text{pred}_j - \text{obs}_j)}{n} \quad (1)$$

- MAPE (mean absolute prediction error):

$$\text{MAPE} = \frac{\sum_{j=1}^n \left(\frac{|\text{pred}_j - \text{obs}_j|}{\text{obs}_j} \right) \times 100}{n} \quad (2)$$

where n is the number of concentration points; pred_j and obs_j are population predicted and observed tacrolimus concentrations, respectively.

Model performance based on the MAPE values was classified as acceptable prediction (MAPE < 50%), good prediction (10% < MAPE < 20%), and excellent prediction (MAPE < 10%).¹⁰

Impact of the CYP3A5 Phenotype on Tacrolimus Target Concentrations

Using the appropriate model, simulations (N=1000) were conducted to examine the impact of the CYP3A5 phenotype on achieving target concentrations of tacrolimus. The simulation was performed using Simulix 2023R1 (Lixoft SAS, a Simulations Plus company, France).

Simulated patient Tac C0 data were divided into two groups based on their allelic status for CYP3A5 – CYP3A5*3 (non-expressors) and CYP3A5*1 (expressors). The statistical significance of differences between the two groups was examined using the independent *t*-test. Statistical analyses were performed using RStudio; a p-value less than 0.05 was considered statistically significant.

Results

Patients and External Validation Data

A total of 54 kidney transplant patients with 167 Tac C₀ samples were collected for external evaluation. The characteristics of these patients are summarized in Table 1.

On average, the postoperative day of our patients was approximately 4 years. Approximately 60% of the patients expressed a genotype with a CYP3A5*3 variant. The mean tacrolimus concentration was 5.6 ± 1.5 ng/mL. Figure 1 illustrates the tacrolimus concentrations of patients over time.

Reviews of the Published Tacrolimus Population Pharmacokinetic Models

Following systematic research, a total of 256 articles were selected from PubMed and Scopus databases. After removing some duplications, 160 full texts were chosen when reviewing the titles and abstracts. Of 160 studies, 38 were chosen based on the inclusion and exclusion criteria. We then added articles from reference lists, and 44 Tac PopPK models in adult renal transplantation were collected. Finally, based on the available characteristics of our external cohort, five models were chosen for evaluating prediction. A PRISMA flow diagram of study selection is presented in Figure 2.

Table 2 describes the characteristics of the patient population used to build PopPK models. Most studies (4/5) were undertaken in the Asian population. Although the study period varied greatly, from immediate up to a few years following transplantation, 3/5 studies were performed within the first year and two studies within 3 years. The median (range) number of patients was 102.5 (32–234). The mean age of subjects used for model building was between 38 and 55 years old. More than half of patients carried CYP3A5*3/*3 allele.

Only one study was developed using intensive sampling data, while the remainder used Tac C₀. 4/5 studies used immunoassays to measure Tac concentrations.

The PopPK of Tac was described using a one-compartment model with first-order elimination in four studies (Table 3). One model utilized the Erlang (transit) model to describe the absorption phase. Inter-patient variability was described using exponential error models in 4/5 studies. Additive, proportional, and combined (ie, additive, and proportional) error models were tested to describe the residual variability. Four covariates were identified as having a significant influence on Tac whole-blood CL/F: postoperative days, hematocrit (HCT), patient weight, and CYP3A5 phenotype. The influence of the CYP3A5 genotype on tacrolimus clearance was expressed by the following formulas.

Table 1 Characteristics of Our External Dataset

Characteristics	Results (N=54)
Sex, n (%)	
Male	42 (77.8%)
Female	12 (22.2%)
Age ^a	36.0 ± 8.2
Weight (kg) ^b	58 (53.0–63.0)
Hematocrit (%) ^a	43.5 ± 3.8
Postoperative period (days) ^a	1426.6 ± 74.2
Total daily tacrolimus dose (mg) ^b	6.0 (4.0–7.0)
Tacrolimus trough concentration (ng/mL) ^a	5.6 ± 1.5
CYP3A5 genotype, n (%)	
*1/*1/*1*3	23 (42.6%)
*3*3	31 (57.4%)

Notes: ^aMean ± SD, ^bMedian (quartile).

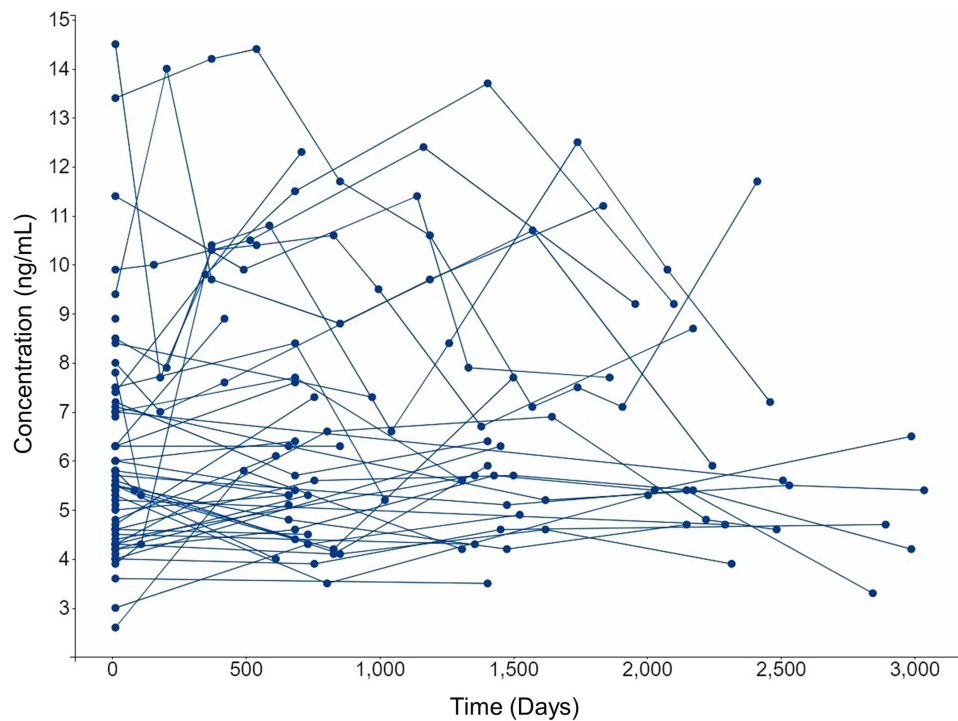


Figure 1 Tacrolimus concentration over time of the observed patients.

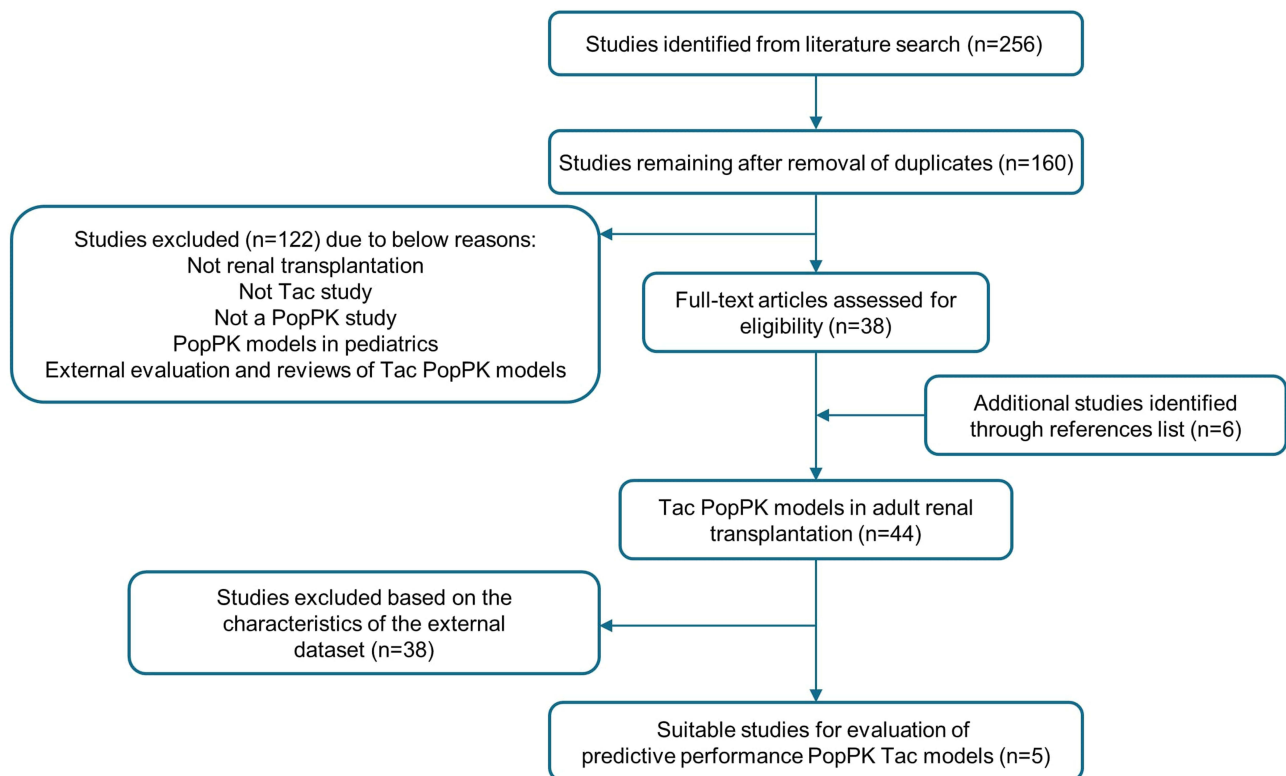


Figure 2 PRISMA diagram of screening Tacrolimus PopPK studies.

Table 2 Summary of Demographic Characteristics of the Included Published Studies

Study	Han et al 2013. ¹¹	Zhang et al 2017. ¹²	Woillard et al 2011 ¹³	Zhu et al 2018. ¹⁴	Ling et al 2020. ¹⁵
Mean age ± SD (range) (years)	38 (19–65)	39 (19–64)	55 (18–69)	38.26 ± 9.95	39 (18–68)
Mean weight ± SD (range) (kg)	59.0 ± 10.2	60.2 (44.0–107.0)	65 (46–97)	57.02 ± 9.92	60 (34–95)
Mean Hematocrit ± SD (range) (%)	35 ± 7.8	39.1 (18.4–60.7)	32.3 (20.9–46.6)	33.77 ± 7.83	30.9 (18.8–49.6)
CYP3A5 *1*1/ *1*3	32	39	1	57	213
CYP3A5 *3*3	48	44	31	84	121
No. of patients	80	83	32	141	234
No. of samples	2788	2109	145	1232	936
No. of PK dots/ patients	34.85	25.41	4.53	8.74	4
Bioassay	MEIA	EMIT	LCMS	CMIA	EMIT

Abbreviations: CMIA, chemiluminescence immunoassay; EMIT, enzyme-multiplied immunoassay; MEIA, microparticle enzyme-linked immunoassay; LCMS, Liquid chromatography–mass spectrometry.

Predictive Performance Assessment

The predictive performance expressed by MPE and MAPE is presented in [Figures 3](#) and [4](#). The model of Zhang et al and the model of Han et al resulted in an underprediction at MPE of −2.31 and −0.06, respectively. The rest of the models showed a higher estimation than the observed values. Using a Bayesian approach, the predictive results of PopPK models have been improved by reducing MPE values. The models of Woillard et al and Zhu et al showed good accuracy with MPE of −0.01 and −0.15, respectively. The model of Zhang et al still tends to predict a much smaller value than the observed value with an MPE of −2.18. The model of Ling et al resulted in overestimation. In contrast, the model of Han et al predicted lower concentrations than the observed values.

When using the a priori approach, all models give poor predictive results with a high MAPE (37.68–80.07%). Three-fifths of the models are acceptable with 20% < MAPE < 50%. The much lower MAPE value reflects the improved forecasting ability of the PopPK model using a Bayesian approach. Three models by Han et al, Woillard et al, and Zhu et al gave good estimation with a MAPE of 16.06%, 14.81%, and 19.29%, respectively. Ling et al’s model indicated an acceptable prediction with a MAPE of 28.58%.

Goodness-of-fit plots were generated to visually compare the observed concentrations with the predicted concentrations of the PopPK model, thereby enabling the validation of the models. [Figure 5](#) shows how well the predicted concentration fits the observed concentration using a Bayesian approach.

The models of Woillard et al, Zhu et al bring relatively good results exhibiting a good fit between the predicted and the observed concentration. Zhu’s model had the same characteristics as ours with Asian patients, POD, age, weight, HCT, CYP3A5 polymorphisms, and Tac immunoassays. Models of Zhang et al, Ling et al, and Han et al have poor predictions.

Influence of CYP3A5 Genotype on Tacrolimus Trough Concentrations

The model of Zhu was used to simulate the data from Vietnamese patients to evaluate the influence of the CYP3A5 genotype on Tac C₀. The simulation results showed that Tac C₀ were significantly higher in patients not expressing CYP3A5 (p<0.001, [Figure 6](#)).

Discussion

Vietnam currently lacks a formula to calculate Tacrolimus dosage based on CYP3A5 genotype and pharmacokinetic data specific to Vietnamese patients. This study aims to fill that gap by evaluating published Tacrolimus population

Table 3 Summary of Structural, Statistical, and Covariate Models of the Included Published Studies

Study	Structural Model	Pharmacokinetic Parameters and Covariate Relationships	Inter-Subject Variability	Residual Variability	Model Evaluation
Han et al 2013. ¹¹	I-CMT First-order absorption and elimination	$K_a = 4.5 \text{ h}^{-1}$ $CL/F(L/h) = 22.9 \times e^{(0.17(CYP3A5*1*3)+0.0525(CYP3A5*3*3))} \times e^{(0.297(LowHct)+0.117(NormalHct))} \times POD^{-0.00762}$ $V/F(L) = 716 \times e^{0.355 \times \frac{WTkg}{59.025}}$	49.8 48.7	Prop: 40.0%	RMSE, Bootstrap
Zhang et al 2017. ¹²	I-CMT First-order absorption and elimination	$K_a = 4.5 \text{ h}^{-1}$ $CL/F(L/h) = 22.4 \times e^{(-0.0526 \times \frac{83}{POD})} \times e^{-0.32 \times CYP3A5} \times (39.1/HCT)^{0.548}$ $V/F(L) = 179 \times POD^{0.842}$ CYP3A5 = 0 if patients did not express CYP3A5, others CYP3A5 = 1	18.8 43.7	Add: 2.33 ng/mL	GOF, VPC, Bootstrap
Woillard et al 2011. ¹³	2-CMT Erlang's delay and absorption time First-order elimination	$K_{tr} = 5.11 \text{ h}^{-1}$ $M_{tt} = 0.78 \text{ h}$ $K_a = 7.31 \text{ h}^{-1}$ $CL/F(L/h) = 21.2 \left[(HCT/35)^{-1.14} \right] \times (2^{CYP3A5})$ $V1/F = 140.94 \text{ (L)}$ $Q/F \text{ (L/h)} = 79$ $V2/F \text{ (L)} = 271$ CYP3A5 = 0 if patients did not express CYP3A5, others CYP3A5 = 1	24 32.6 28 31 54 60	Prop: 11.3% Add: 0.71 ng/mL	VPC
Zhu et al 2018. ¹⁴	I-CMT First-order absorption and elimination	$K_a = 3.089 \text{ h}^{-1}$ $CL/F = 27.2 \times \left[(WT/70)^{0.75} \right] \times \left[(HCT/0.35)^{-0.501} \right] \times \left[(POD/180)^{0.0306} \right] \times CYP3A5(L/h)$ CYP3A5 = 0.753 if patients did not express CYP3A5, others CYP3A5 = 1 $V/F = 240 \text{ L (constant)}$	28.8	Prop: 18.8% Add: 2.5 ng/mL	Bootstrap
Ling et al 2020. ¹⁵	I-CMT First-order absorption and elimination	$K_a = 4.5 \text{ h}^{-1}$ $CL/F(L/h) = 23.3 \times (HCT/0.309)^{-0.445} \times [(0.897 \text{ if } POD > 10) \text{ or } (1 \text{ if } POD \leq 10)] \times 0.657^{CYP3A5}$ CYP3A5 = 0 if patients did not express CYP3A5, others CYP3A5 = 1 $V/F \text{ (L)} = 240$	21.9	Prop: 24.4% Add: 1.40 ng/mL	GOF, Bootstrap

Abbreviations: Add, additive; CL/F, the clearance; CMT, compartment; CYP, cytochrome P450; CYP3A5*1*3 and CYP3A5*3*3, alleles of CYP3A5; GOF, goodness of fit; HCT, hematocrit; K_a , absorption rate constant; K_{tr} , the absorption rate; M_{tt} , mean transit time; POD, post-operative day; Prop, proportional; Q/F, apparent intercompartmental oral clearance; RMSE, Root mean square error; V/F, apparent volume of distribution; V1/F, apparent volume of distribution of the central; V2/F, volume of distribution of peripheral compartment; VPC, visual predictive check; WTkg, body weight (kg).

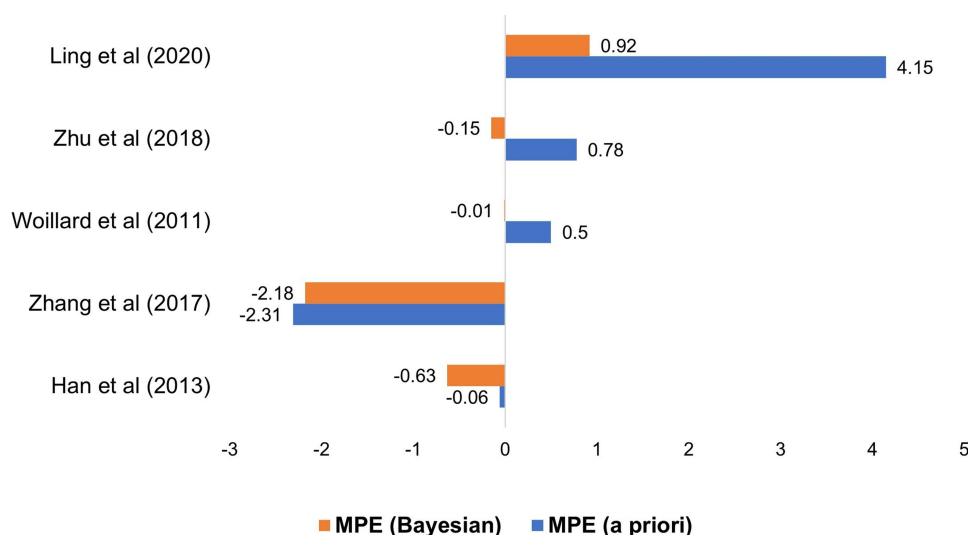


Figure 3 The MPE differences between Bayesian approach and priori approach.^{11–15}

Abbreviation: MPE, mean prediction error.

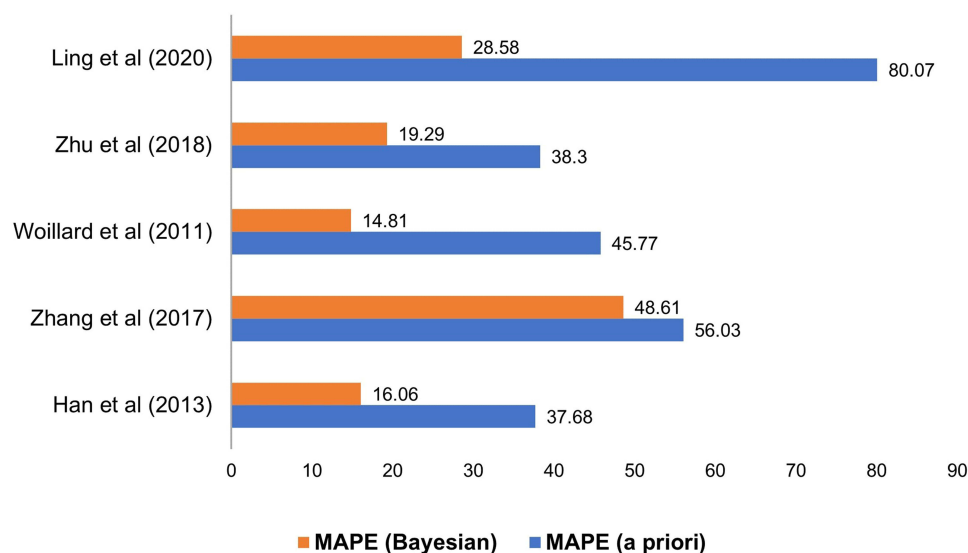


Figure 4 The MAPE differences between Bayesian approach and priori approach.^{11–15}

Abbreviation: MAPE, mean absolute prediction error.

pharmacokinetic (PopPK) studies and selecting an appropriate model to determine the influence of CYP3A5 genotype on Tacrolimus concentration (Tac C0) in the Vietnamese population. This study is a crucial step towards developing a model-informed precision dosing approach, which will assist pharmacists in prescribing the optimal initial and adjusted doses, thereby enhancing patient outcomes globally.

After a thorough systematic review, we carefully selected models that were applicable to our dataset, resulting in a collection of five final models for further analysis. When compared to our population, we observed similarities in terms of age, weight, and the prevalence of the CYP3A533 allele. Notably, the studies conducted by Woillard et al and Zhu et al showed promising predictive results that could be useful in clinical practice for predicting tacrolimus concentration (C0). Woillard's model utilized a two-compartment model with Erlang absorption and demonstrated the lowest mean absolute percentage error (MAPE) of 14.81%. However, it is worth mentioning that the study had a higher number of nonexpresser CYP3A5 *3/*3 carriers compared to only one expresser CYP3A5 *1/*3 carrier.

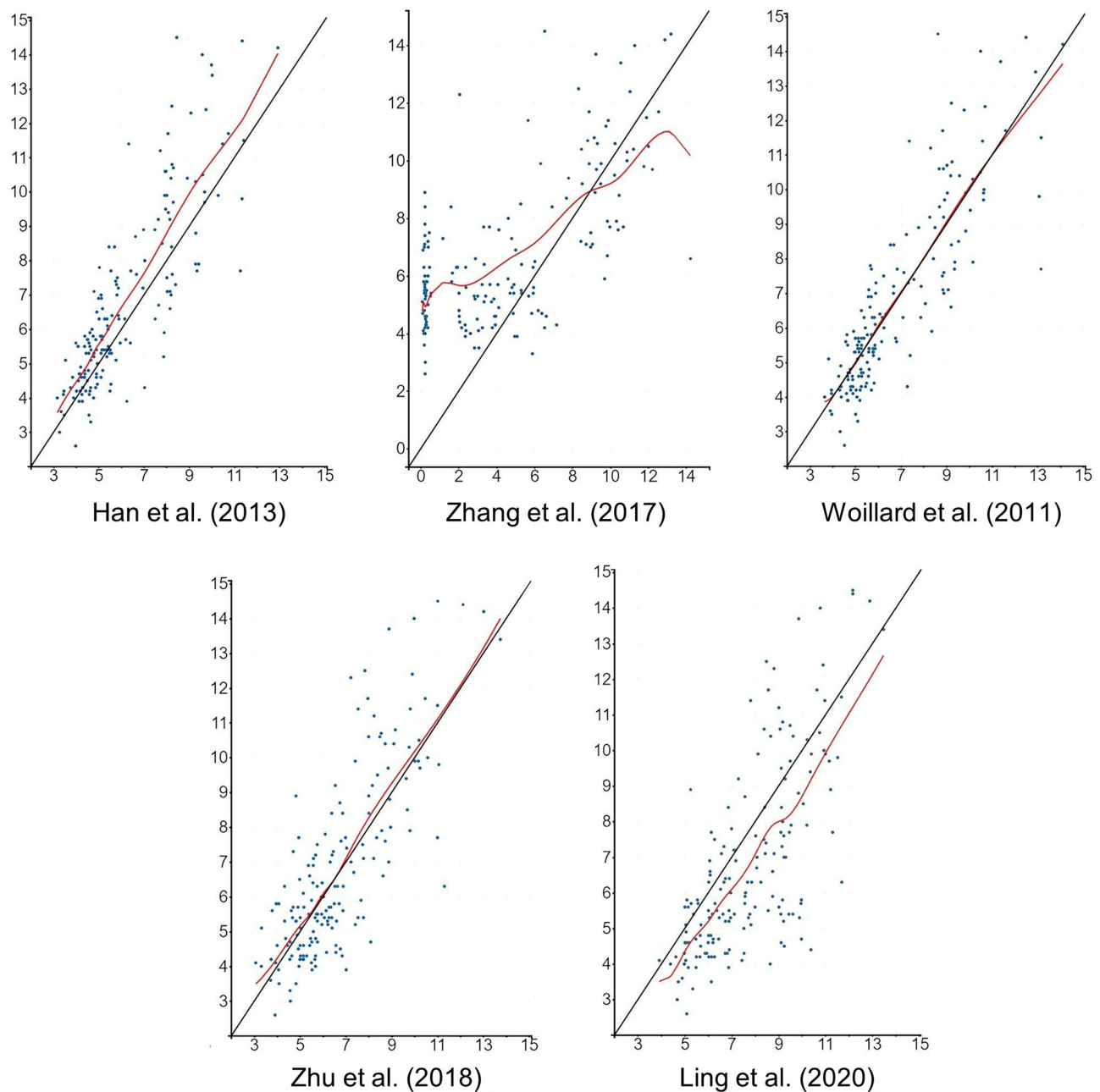


Figure 5 Individual-predicted concentrations against observed concentration using Goodness-of-fit plot.^{11–15}

Notes: Horizontal axis: Individual predictions of tacrolimus concentration (ng/mL), vertical axis: Observed tacrolimus concentration (ng/mL).

In contrast, Zhu's model exhibited numerous resemblances to our study, encompassing Asian demographics, post-operative day, age, weight, HCT, CYP3A5 polymorphisms, and Tacrolimus immunoassays. Consequently, Zhu's model was chosen for predicting target Tacrolimus concentrations. The impact of CYP3A5 genotype on tacrolimus clearance was identified in Zhu's equation $CL/F = 27.2 \times [(WT/70)^{0.75}] \times [(HCT/0.35) - 0.501] \times [(POD/180)^{0.0306}] \times CYP3A5(L/h)$. Our simulation results revealed significantly higher Tacrolimus C0 levels in CYP3A5 non-expressors. The CYP3A5*3 allele causes alternative splicing and protein truncation, resulting in the absence of CYP3A5 enzyme activity. Therefore, Tac metabolism in renal transplant recipients carrying CYP3A5*3*3 is much slower than that of CYP3A5 expressors, which is supported by a number of studies and meta-analyses such as the finding of Chauhan et al.¹⁶ Our findings are consistent with those of previous studies.^{6,16,17} In addition to CYP3A5, the post-operative day (POD) serves as a crucial covariate included in

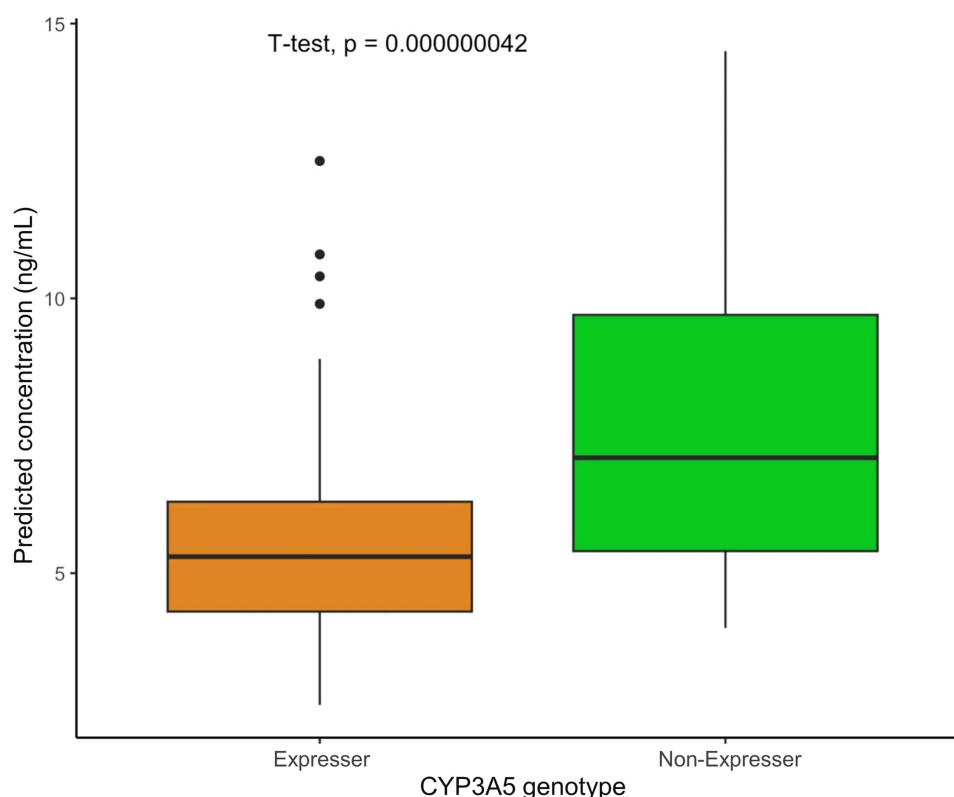


Figure 6 The difference on predicted concentrations between two groups of expressers versus non-expresser CYP3A5.

four out of the five examined models. However, there is some inconsistency in the effect of POD on tacrolimus clearance among these models. The studies by Han et al, Ling et al, and Staatz et al¹⁸ showed a decrease in tacrolimus clearance as PODs increased. Conversely, the models by Zhang et al and Zhu et al aligned with the findings of Antignac et al¹⁹ suggesting that an increase in tacrolimus clearance is associated with the recovery of gastrointestinal mobility and metabolism. In our study, most patients had a long average POD of 1426.6 days, leading to misestimations in the models of Zhang et al and Ling et al. Although the models of Han et al and Zhu et al did not exhibit consistent impacts of POD, both models demonstrated good predictive abilities. Hence, further research is needed to explore the influence of POD on tacrolimus clearance. Nevertheless, it is still regarded as one of the most significant covariates in tacrolimus population pharmacokinetic (PopPK) models for renal transplantation patients.

Numerous studies have demonstrated the significance of hematocrit (HCT) in influencing population pharmacokinetic (PopPK) models in kidney transplant patients. Specifically, tacrolimus has a strong binding affinity to erythrocytes in plasma, leading to higher HCT levels indicating an increased fraction of tacrolimus bound to erythrocytes and a decreased fraction in the plasma. In our study, all models considered HCT as a crucial covariate, and four models agreed that higher HCT levels were associated with a decrease in tacrolimus clearance. Moreover, the models developed by Han et al and Zhu et al incorporated patient weight as a covariate, which affected either the volume of distribution¹¹ or the clearance of tacrolimus.¹⁴ Both studies concurred that increased body weight was associated with an increase in tacrolimus volume distribution, likely due to the drug's lipophilic properties.

In comparison to the recent study conducted by Methaneethorn et al on Thai patients, which showcased effective predictive performance using Bayesian methods and two-compartment models, it is crucial to highlight that their research did not take into account the influence of CYP3A5 genotype as a covariate.¹⁰ Conversely, our study holds a distinct advantage over external investigations as we performed an external evaluation using both one- and two-compartment models, and notably, all of the models we assessed incorporated CYP3A5 as a covariate.

On the other hand, our study had certain limitations. Firstly, we did not include other patient factors such as CYP3A4, BSA, and corticosteroid concentration. The fixed dose of corticosteroid, specifically prednisolone 5 mg, prevented us from investigating its effect in this analysis. Although we assessed the genetic polymorphism of the CYP3A4 gene in phase one, the frequency of the CYP3A422 allele, which is associated with decreased CYP3A4 activity, was below 2%. In South Asia, the rate of CYP3A422 allele was even lower, at <0.01%.²⁰ Hence, we made the decision not to analyze the CYP3A4 genotype. Additionally, there was variation in Tac bioassay methods across studies. This could introduce inconsistencies when applying population pharmacokinetic (PopPK) models to predict concentration scores in a patient population that is different from the original population used to construct the model.²¹ However, the CMIA method used in our study is currently the most commonly used method for quantitative analysis of Tacrolimus C0 levels.

Based on the findings of this study, we can confidently assert that the application of population pharmacokinetic (PopPK) models using the Bayesian approach enables the accurate prediction of individual tacrolimus concentration levels. This, in turn, allows for the optimization of anti-rejection therapy for kidney transplant patients. In conclusion, further evaluation of population pharmacokinetic models for tacrolimus is warranted, and the development of early dose adjustment strategies in clinical practice is essential to enhance treatment outcomes and minimize adverse effects in kidney transplant recipients.

Conclusion

The incorporation of the CYP3A5 phenotype into Zhu's structural model has significantly enhanced our ability to predict Tacrolimus trough levels in the Vietnamese population. This study's results underscore the valuable role of CYP3A5 phenotype in optimizing the forecast of Tac concentrations, offering a promising avenue to assist health-care practitioners in their clinical decision-making and ultimately advance patient care outcomes.

Ethics Approval

All methods were carried out in accordance with the Declaration of Helsinki. The study received ethical approval from the Ethics Committee in Biomedical Research 103 Military Hospital (No. 04/CNChT-HĐĐĐ). Participants were informed, and their consent was obtained for the research. All kidneys were donated voluntarily with written informed consent and these were conducted in accordance with the Declaration of Istanbul.

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Disclosure

The authors declare no conflicts of interest in this work.

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