

Population Pharmacokinetic Modelling for Nifedipine to Evaluate the Effect of Parathyroid Hormone on CYP3A in Patients with Chronic Kidney Disease

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Purpose: Parathyroid hormone (PTH) can induce the downregulation of CYP3A in chronic kidney disease (CKD). Nevertheless, the effect of PTH on CYP3A-mediated clearance pathways from a clinical perspective remains unclear.

Methods: This study employed population pharmacokinetic (PopPK) modeling to delineate potential changes in CYP3A activity in patients with CKD. Pharmacokinetic data for nifedipine, a typical CYP3A substrate, as well as covariate information, were prospectively collected from 157 patients with a total of 612 concentrations. PopPK data analysis was performed using a nonlinear mixed-effects model.

Results: The pharmacokinetics of nifedipine were optimally described according to a one-compartment model with zero-order absorption and first-order elimination. The estimated population parameters (and interindividual variability) were apparent clearance (CL/F) 49.61 L/h (58.33%) and apparent volume of distribution (V/F) 2300.26 L (45.62%), and the PTH level negatively correlated with CL/F. In comparison with the reference level, it was observed that the dosage of nifedipine should be reduced with the maximum boundary value of PTH, after a Monte Carlo simulation.

Conclusion: This study provides insight into the effects of PTH on CYP3A-mediated clearance pathways. Moreover, PTH could be used as a guide for the appropriate administration of CYP3A eliminated drugs in patients with CKD.

Keywords: chronic kidney disease, parathyroid hormone, CYP3A, population pharmacokinetic, nifedipine

Introduction

Chronic kidney disease (CKD) is one of the most common diseases worldwide, with the number of incidences steadily increasing.¹ Impaired kidney function, observed in CKD patients, can alter the elimination of a drug from the kidney.^{2,3} CKD may also affect drug disposition by altering the enzyme function in extrarenal organs including the liver and the intestines.⁴ It has recently been reported that, in patients with CKD, the metabolism of CYP450 in the liver and intestine is altered, causing pharmacokinetic changes and an increase in the occurrence of adverse drug events.⁵ As such, regulatory agencies recommend conducting clinical trials for nonrenally eliminated drugs. This is to satisfy the requirements for potential dosage adjustments in CKD patients, on the account of kidney function stratification, which is considered a “worst-case scenario”.⁶ However, there are no justified and generalized instructions for dedicated CKD

study designs. Also, the dosage adjustment of nonrenally eliminated drugs is still not a conventional practice observed with CKD patients.

CKD is often concomitant with secondary hyperparathyroidism (SHPT), and the level of parathyroid hormone (PTH) in peripheral circulation significantly increases.⁷ PTH is secreted by the parathyroid gland and is widely distributed in the liver, kidney, small intestine, and other internal organs. As such, the hormone participates in the regulation of multiple protein functions.^{8–12} It was also reported that PTH may be the main factor in the downregulation of CYP3A in CKD.¹³ CYP3A is one of the most vital metabolic pathways and involves the metabolism of 50–60% of drugs on the market,¹⁴ including midazolam, nifedipine, tacrolimus, and cyclosporine.

Recently, using the SHPT rat model, primary rat hepatocytes, and a human colon carcinoma cell line, Watanabe et al demonstrated that elevated serum PTH levels reduced CYP3A expression in both the liver and small intestine. This resulted in a considerable decrease in the activity of CYP3A, and a significant increase in the area under the curve (AUC) of midazolam.¹⁵ In a retrospective study of 12 subjects, it was proposed that surveying serum PTH levels could forecast the trough level for the initial tacrolimus administration. A significant positive correlation between serum PTH and tacrolimus trough concentration 4 days before renal transplantation was observed. Therefore, it was proposed that PTH may be an indicator of the initial tacrolimus dosage in kidney transplantation patients.¹⁶ In contrast, a study including 63 Japanese kidney transplant recipients demonstrated that PTH levels were not associated with CYP3A phenocopy. This phenocopy was assessed via the plasma concentration of 4 β -hydroxycholesterol, which is a biomarker of CYP3A activity.¹⁷ The contrasting findings were considered a result of limited clinical data availability. Therefore, further large-scale clinical trials are needed to understand the impact of PTH on CYP3A in CKD patients. In addition, both the influence of PTH on the pharmacokinetics of drugs eliminated by nonrenal pathways and the dosage adjustments for CKD patients should be investigated.

PopPK modeling is a model technique developed to represent the population of interest. The process of modeling is to discriminate covariates that may account for potential sources of variability.¹⁸ A prospective observational study was conducted with 157 CKD subjects treated with nifedipine (a CYP3A substrate) to investigate the population pharmacokinetics of the drug and to clarify the effect of PTH on hepatic CYP3A. In addition, the role of PTH in characterizing the pharmacokinetics of drugs predominantly metabolized by CYP3A quantitatively in CKD patients was also explored.

Materials and Methods

Patient Recruitment and Data Collection

The investigational protocol was approved by the Medical Ethics Committee of the Third Xiangya Hospital of Central South University. The study was conducted in accordance with the legal requirements of the Declaration of Helsinki, and with the contemporary Chinese guidelines for Good Clinical Practice. This study was registered at <https://register.clinicaltrials.gov> (NCT03695107). The subjects were patients with CKD who received nifedipine tablets from the Department of Nephrology, The Third Xiangya Hospital, Central South University, from August 2017 to April 2019. All patients signed an informed consent form before inclusion. Nifedipine tablets used in this study were formulated for controlled release (CR, 30 mg/tablet) and were produced by Bayer, Germany.

The study included Chinese male or female patients (≥ 18 years old) who were diagnosed by clinicians as CKD accompanied by hypertension and were treated with nifedipine tablets. Besides, those patients with dialysis treatment prior to the study were excluded. Pharmacokinetic, demographic, and covariate data, including physical examination and laboratory tests, were collected retrospectively from patient medical records.

Sample Collection and Bioanalytical Assay

Patients with CKD and hypertension were treated with nifedipine for 7 days. The sparse blood samples were collected at predose (C_0 , trough concentration), 3–4 h post-dose (C_1 , concentration of time point in absorption phase), 6–8 h post-dose (C_2 , concentration of time point in elimination phase), and 24 h post-dose (C_3 , trough concentration) on the 7th day.

The blood samples were centrifuged at $3000 \times g$ for 10 min at 4°C , and the plasma was stored in the dark at -80°C until analysis. Nifedipine plasma concentrations were determined using a high-performance liquid chromatography-tandem mass spectrometry method. Before analysis, the plasma samples were thawed and vortexed. Ten microliters of a 100 ng/mL solution of nifedipine- d_6 (internal standard) was added, followed by 200 μL of acetonitrile. The mixture was then subjected to vortex oscillation for 30 s, followed by centrifugation at $13,000 \times g$ at 4°C for 10 min. After which, 100 μL of supernatant was obtained, and 10 μL of the sample was injected for analysis.

Chromatographic separation was performed using a liquid chromatograph (Agilent 1260, USA) equipped with an Agilent eclipse XDB- C_{18} (2.1 mm \times 150 mm, 5 μm) at 40°C . The mobile phase was a mixture of methanol (containing 0.1% $\text{NH}_3 \cdot \text{H}_2\text{O}$) and water (containing 5 mM ammonium acetate) (35:65, v/v) at a flow rate of 0.4 mL/min. Mass spectrometry was performed using a triple quadrupole mass spectrometer (Agilent 6460, USA) in the positive electrospray ionization mode. The fragmentation voltage was 100 V and the collision energy was 1 eV for nifedipine (parent ion m/z 347.1 \rightarrow son ion m/z 315.1). For nifedipine- d_6 (parent ion m/z 353.1 \rightarrow son ion m/z 318.1), the fragmentation voltage was 80 V, and the collision energy was 1 eV. The parameters of the ion source were as follows: gas temperature, 300°C ; gas flow, 11 L/min; nebulizer, 15 psi; and capillary, 4000 V. The results showed that the linear range of nifedipine was 1–200 ng/mL. The lower limit for the quantification of nifedipine in human plasma was 1 ng/mL. The RSD of intra- and inter-day precision of nifedipine in plasma samples (1 ng/mL) was 5.88% and 19.42%, respectively.

DNA Extraction and Genotyping Analysis

The DNA for genomic analysis was extracted using a commercially available EZNA[®] SQ Blood DNA Kit II. Through the Sanger dideoxy DNA sequencing method with the ABI 3730xl sequencer (ABI Co., Sangon Biotech Co. Ltd. Shanghai, China), *CYP3A4*1G* rs2242480,^{19,20} *CYP3A4* rs4646437,²¹ *CYP3A5*3* rs776746,²² *NR1I2* rs2276707,^{23–25} *NF- κ B* rs28362491,^{24,25} *IL-3* rs181781,²¹ and *MDR1-C3435T* rs1045642^{26,27} were detected, all of which may influence the expression of CYP3A and/or play important roles in nifedipine disposal.

Development of the Population Pharmacokinetic Model

Based on the concentration of nifedipine, the first-order conditional estimation-extended least squares (FOCE-ELS) was calculated via the Phoenix NLME software and a nonlinear mixed effect model method.

The model parameters were assumed to follow log-normal distributions, and the inter-individual variability for each structural parameter was modeled using Eq. (1): $P_i = P_{TV} * \exp(\eta_i)$.

Here, P_i represents a parameter for the i th individual, P_{TV} is the typical value of the parameter, and η_i is a random variable with a mean of zero and a variance of ω^2 .

A log transformation of the data was required, and the residual variability was modeled using an additive error, as shown in Eq. (2): $C_{\text{Obs}} = C_{\text{Pred}} + C_{\text{Eps}}$

Here, C_{Obs} is the observed value, C_{Pred} is the predicted value, and C_{Eps} is the intra-individual variability with a mean of zero and a variance of σ^2 .

Population Pharmacokinetic Covariate Model Selection

In the basic PK structural model, covariates were introduced: $P_{TVij} = P_{TVj} \times (\text{COVR}_{ik} / \overline{\text{COVR}_K})^{\theta_{jk}}$. Among them, P_{TVij} is the j th parameter value of the i th subject, P_{TVj} is the typical population value of the j th pharmacokinetic parameter, COVR_{ik} is the k th covariate of the i th subject, and $\overline{\text{COVR}_K}$ is the median value. The deviation degree of individual parameter value from the population typical value when there was a unit change between the individual covariate and its median value was represented by θ_{jk} .

The covariates of sex, age, BMI, PTH, Hb, renal function, liver function, combination therapy, and genotypes of *CYP3A4*, *CYP3A5*, *NR1I2*, *NF- κ B*, *IL-3*, and *MDR1*, were analyzed in the model by means of a stepwise approach. The identification of significant covariates was conducted: an increase of more than 3.841 in the objective function value (OFV) was considered significant ($P < 0.05$, $\text{df} = 1$) for inclusion, and a decrease of more than 7.879 in the OFV was considered significant ($P < 0.005$, $\text{df} = 1$) for backward exclusion.

The following graphs were prepared to evaluate the goodness-of-fit (GOF): observed (OBS) versus population predicted concentrations (PRED), OBS versus individual predicted concentrations (IPRED), conditional weighted residuals (CWRES) versus time, and CWRES versus PRED.

Model Evaluation

The final PopPK model was evaluated as a whole, including the model fit parameters and GOF plots. A predicted-corrected visual predictive check (pc-VPC) was then used to test the final model based on 1000 simulation predictions. And bootstrapping was performed 1000 times to verify the final model.

Monte Carlo Simulation

Taking the nifedipine 30 mg/tablet once a day as an example, the median level of significant covariates for the subjects was used as the reference. Considering the range of influencing factors associated with the subjects in the model, the AUC between 0 and infinity ($AUC_{0-\infty}$) of which the corresponding equation used was $AUC_{0-\infty} = Dose/CL$ was investigated, and each covariate at the boundary value and each scenario simulated 1000 sets of virtual data. Other scenarios included the minimum boundary value, maximum boundary value, and factor interaction with the minimum boundary value. Pharmacokinetic parameters were calculated, and descriptive statistical and graphical analyses were performed.

The AUC of the dose-adjusted drug exposure in each simulation scenario was compared with that of the reference. The adjusted doses were 7.5 mg (1/4, tablet), 15 mg (1/2 of tablet), and 22.5 mg (3/4 of tablet). Using a computer simulation and adjusting the administered dose, the adjusted dosage was determined to be in accordance with the reference.

Results

Patients and the Frequency of CYP3A4, CYP3A5, NR1I2, NF- κ B, IL-3, and MDR1 Genotypic Variants

Data were prospectively collected from 157 patients with CKD. The median age was 54 years (range, 24–84 years), and the median body mass index was 23.4 kg/m² (range 15.81–36.70 kg/m²). A total of 612 blood concentration–time measurements were collected (Figure 1). The number of nifedipine concentrations per patient ranged from two to four. The demographic characteristics are summarized in Table 1.

All DNA samples were analyzed, and deviation from the anticipated proportions of genotypes in the population predicted by Hardy-Weinberg equilibrium²⁸ was not observed. The distribution frequencies of the genotypes of *CYP3A4*, *CYP3A5*, *NR1I2*, *NF- κ B*, *IL-3*, and *MDR1* in each group are listed in Table 2.

Population Pharmacokinetic Modelling

Through the data obtained from 157 subjects and 612 concentrations, a base model was established, and the one-compartment model was investigated, based on the nifedipine concentration time curve and literature reports.²⁹ The results indicated that OFV (5141.5) and AIC (5155.5) of zero-order absorption and first-order elimination, respectively, were smaller than those of the other models (Table S1); the fitting values were closer to the observed values. Therefore, the one-compartment model with zero-order absorption and first-order elimination was selected as the base model.

Most of the concentration data collected in this study were in the range of 10–100 ng/mL. The residual data fitted by the additive residual model were evenly distributed. Therefore, the additive error model was chosen as residual error model. The CV of each parameter in the one-compartment model with zero-order absorption and first-order elimination was less than 10%. The inter-individual variation of parameters apparent volume of distribution (V/F), the elimination rate constant (K_e), and the zero-order absorption rate constant (K_0) were 51.58%, 27.01%, and 63.02%, respectively. The results are presented in Table S1.

Population Pharmacokinetic Covariate Modeling

It was found that age, hemoglobin (Hb), and PTH had significant effects on apparent clearance (CL/F), while alanine aminotransferase (ALT) had significant effects on the apparent volume of distribution (V/F). These covariates with

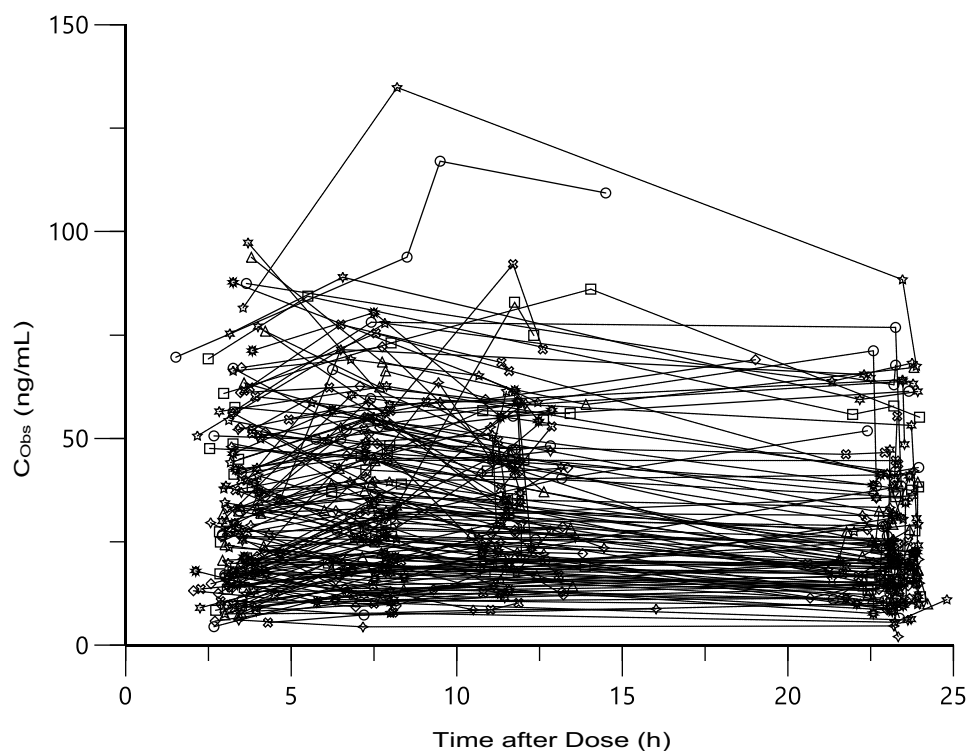


Figure 1 Plot of nifedipine concentrations versus the actual sampling time after dose.

significant influences were added to the model, and the final fitting results were obtained. In this study, PTH displayed a significant statistical impact on CL/F by reducing the OFV by 7.879 units ($P < 0.005$) in the base model. In addition, a decrease of 7.879 units ($P < 0.005$) in the OFV was also observed depending on the age or Hb level. Patients ages 24 to 84 years, and those with an increase in PTH or Hb level, achieved lower CL than those with higher levels.

Covariate analysis for the inter-individual variation of parameters demonstrated that ALT reduced the OFV by 7.879 units ($P < 0.01$). Patients with higher ALT levels had higher V/F compared to those with lower ALT levels.

The expression of PK parameters in the final model was as follows:

$$V/F = tvV/F * (ALT/14)^d V/FdALT * exp(nV/F)$$

$$CL/F = tvCL/F * (Age/54)^d CL/FdAge * (Hb/94)^d CL/FdHb * (PTH/156.84)^d CL/FdPTH * exp(nCL/F).$$

$K_0 = tvK_0 * exp(nK_0)$, where tv^* is the typical population value and d^*d^* is the correction coefficient. $dV/FdALT^*$ is the correction coefficient of ALT to V/F, $dCL/FdAge^*$ is the correction coefficient of Age to CL/F, $dCL/FdHb^*$ is the correction coefficient of Hb to CL/F, $dCL/FdPTH^*$ is the correction coefficient of PTH to CL/F.

The final population pharmacokinetic model revealed that after introducing the covariates as age, Hb, PTH, and ALT, inter-individual variation of parameters decreased from 59.42% to 45.64%, and CL/F decreased from 63.60% to 58.32%. These parameters were set as follows: $tvV/F = 2300.26$ L, and $tvCL/F = 49.61$ L/h. The results are shown in [Tables S2](#) and [3](#).

Model Evaluation

In the final model, both PRED and IPRED displayed good visual agreement with observed values. [Figure 2](#) shows basic goodness-of-fit plots for the base and final population pharmacokinetic models.

Most of the CWREs were between -2 and 2 and were evenly distributed above and below the coordinate $y = 0$. The predicted values for the different time (time), PRED, and subjects were well fitted with the measured values. Therefore, the final model adequately represents the data, as shown in [Figure 3A–C](#).

Table 1 Descriptive Statistical Analysis of Covariates (n = 157)

Covariate	Median (Min-Max) or Ratio
Continuous covariates	
AGE (yr)	54.00 (24–84)
BMI (kg/m ²)	23.40 (15.81–36.70)
GFR (mL/min/1.73m ²)	16.85 (4.84–73.93)
PTH (pg/mL)	156.84 (9.34–687.27)
Hemoglobin (g/L)	94.00 (40–177)
Hematocrit (%)	29.30 (12.82–73)
Red Blood Cell (10 ¹² /L)	3.17 (0.36–6.38)
ALT (U/L)	14.00 (1–81)
AST (U/L)	16.00 (7–72)
Total bilirubin (μmol/L)	6.90 (2.34–35)
Blood urea nitrogen (mmol/L)	17.16 (3.80–46.85)
Serum creatinine (μmol/L)	478.00 (35–2017)
Cystatin C (mg/L)	3.12 (0.66–8.22)
Vitamin D ₂ (ng/mL)	13.93 (3.39–47.29)
Categorical covariates	
Gender (male/female)	63:94
KDIGO phases (Phase 2/Phase 3/Phase 4/Phase 5)	11:20:62:64
WHO BMI classification (≤18.5/18.5–25/25–30/≥30 (kg/m ²))	13:98:39:7
Diabetes mellitus (no/yes)	114:43
Statins (no/yes)	111:46
Proton pump inhibitors (no/yes)	101:56

Note: Data presented as median (min-max) or ratio.

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; ALT, alanine transferase; AST, aspartate transferase; KDIGO, Kidney Disease Improving Global Outcomes; WHO, World Health Organization.

Table 2 Allelic and Genotype Frequency of *CYP3A4*, *CYP3A5*, *NR1I2*, *NF-κB*, *IL-3*, and *MDRD1* in Chinese Patients with CKD (n = 157)

SNP	Genotype	n	Frequency (%)	Allele	Frequency (%)
<i>CYP3A4</i> *1G (rs2242480)	CC	89	56.69	C	74.52
	CT	56	35.67	T	25.48
	TT	12	7.64		
<i>CYP3A4</i> (rs4646437)	CC	113	71.97	C	85.03
	CT	41	26.11	T	14.97
	TT	3	1.92		
<i>CYP3A5</i> *3 (rs776746)	AA	14	8.92	A	30.25
	AG	67	42.68	G	69.75
	GG	76	48.40		
<i>NR1I2</i> (rs2276707)	CC	44	28.02	C	51.91
	CT	75	47.77	T	48.09
	TT	38	24.21		
<i>NF-κB</i> (rs28362491)	ATTG+/+	55	35.03	ATTG+	57.32
	ATTG±	70	44.58	ATTG-	42.68
	ATTG-/-	32	20.38		
<i>IL-3</i> (rs181781)	AA	9	5.73	A	31.85
	AG	82	52.23	G	68.15
	GG	66	42.04		
<i>MDRD1</i> -C3435T (rs1045642)	CC	62	39.49	C	0.62.74
	CT	73	46.50	T	37.26
	TT	22	14.01		

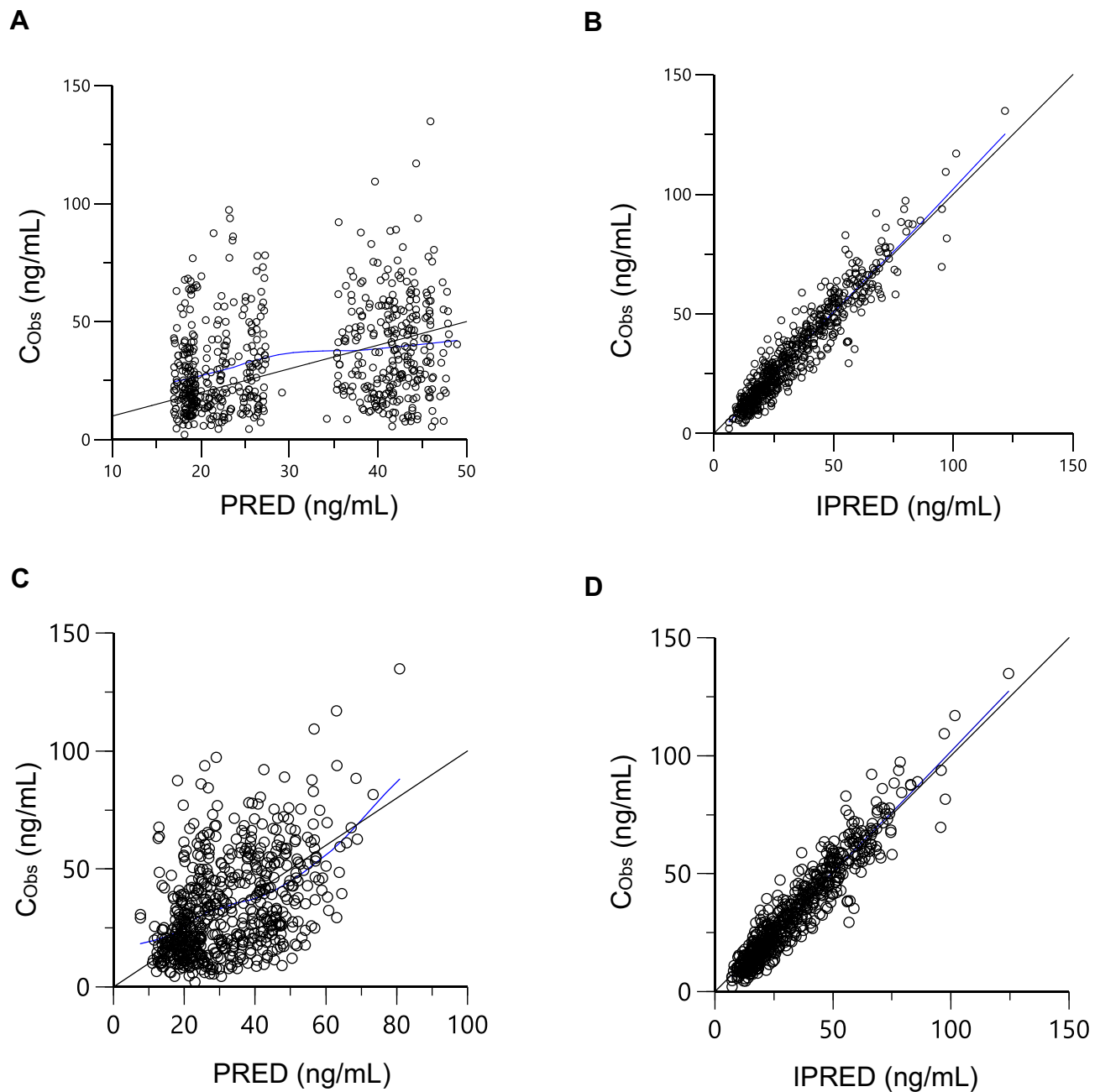


Figure 2 Goodness-of-fit plots for the base and final model. (A) C_{Obs} versus PRED for base model; (B) C_{Obs} versus IPRED for base model; (C) C_{Obs} versus PRED for final model; (D) C_{Obs} versus IPRED for final model.

Abbreviations: C_{Obs} , observed concentration; PRED, predicted concentration; IPRED, individual predicted concentration.

The CWREs of the final model resided on the diagonal of $Y = X$ in the QQ diagram. The frequency distribution of the CWREs and subsequently the final residual model fundamentally conformed to a normal distribution. This indicated that model fitting was good (Figure 3D–E).

The final model demonstrated high stability, and all the 1000 replications ran successfully in the bootstrap for the final model. The median and 95% confidence intervals of the parameters from the bootstrap analysis were consistent with the estimation from the final model. This indicated that the parameters were estimated with good precision, and the final model was robust (Table 3).

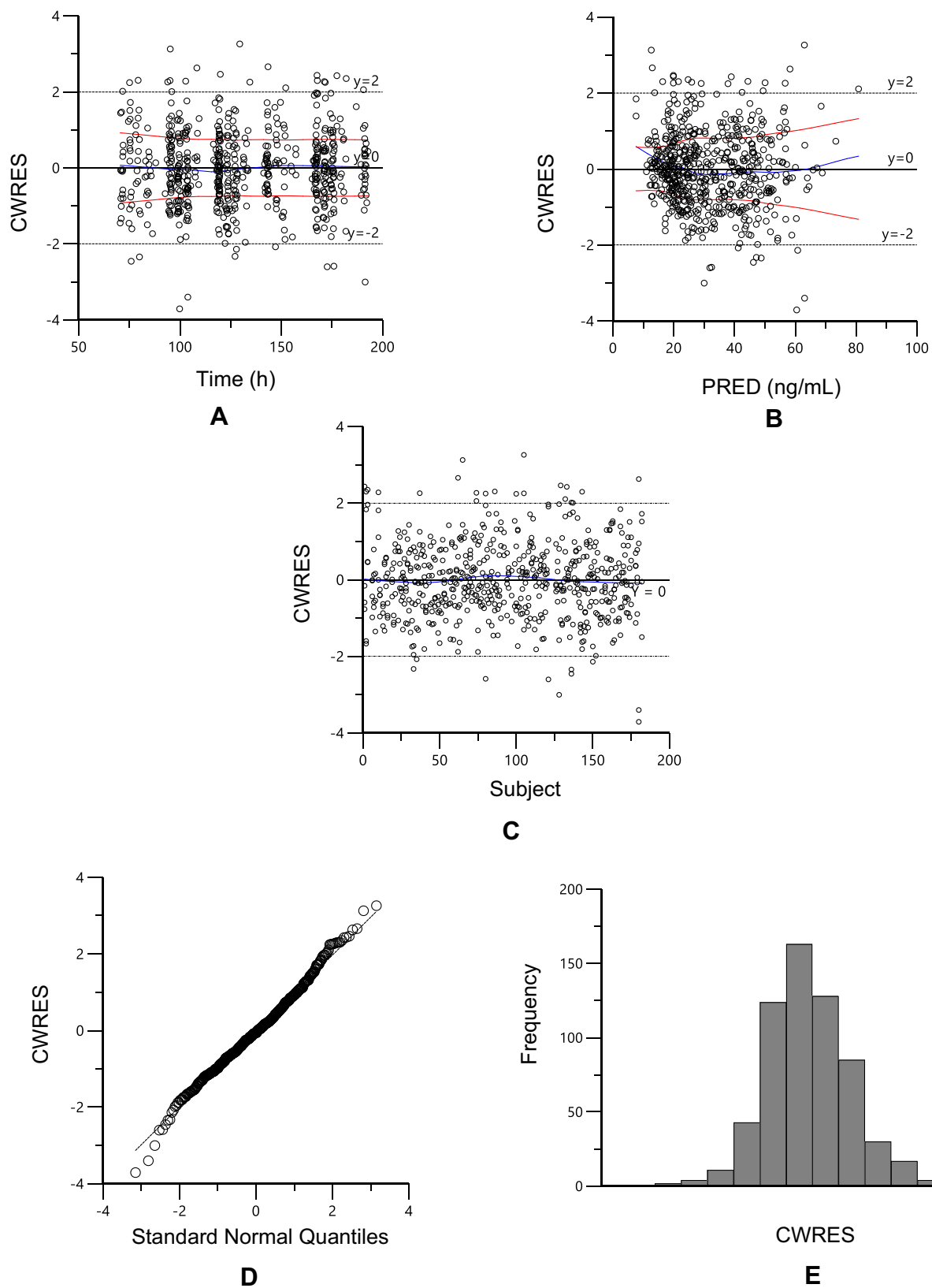


Figure 3 Distribution of conditional weighted residuals for the final model. **(A)** CWRES versus time; **(B)** CWRES versus PRED; **(C)** CWRES versus subject; **(D)** QQ diagram of CWRES; **(E)** histogram of CWRES. The blue line is the Loess trend line.

Abbreviations: CWRES, conditional weighted residuals; PRED, predicted concentration.

Table 3 The Comparison of Fitting Parameters Between Final Model and Bootstrap Verification

Parameter	Estimate	CV (%)	95% CI	IIV (%)	Mean of Bootstrap	Median of Bootstrap	95% CI of Bootstrap
tvV(L)	2300.26	2.41	2189.38– 2411.14	45.644	2336.09	2330.24	1892.23–2779.64
tvCL(L/h)	49.61	1.62	48.05–51.16	58.32	49.51	49.53	44.15–54.98
tvK ₀ (mg/h)	4.21	3.68	3.90–4.52	55.80	4.13	4.13	3.62–4.77
dVdALT	0.48	1.84	0.46–0.49		0.48	0.49	0.29–0.64
dCLdPTH	-0.22	-1.73	-0.22- -0.21		-0.20	-0.21	-0.29- -0.11
dCLdAge	-0.22	-1.79	-0.23- -0.21		-0.25	-0.22	-0.65- -0.19
dCLdHb	-0.35	-1.80	-0.37- -0.34		-0.41	-0.35	-0.93- -0.31
stdev0	8.12	1.71	7.85–8.39		8.07	8.10	7.08–9.03

Abbreviations: V, apparent distribution volume; CL, clearance; K₀, the zero-order absorption rate constant; stdev0, intra variation in additive residual effect model; IIV, inter individual variation; tv*, population typical value; d*d*, correction coefficient.

The pc-VPC of the final model of 1000 simulations grouped by renal function is shown in Figure 4. The observed concentration was included in the range of the confidence intervals, and the median and 95% confidence interval lines were located close to the center of the results. This suggests that the predictive power of the model is sufficient.

Dosing Regimen Simulation

Taking nifedipine 30 mg once a day, as an example, the median level of covariates for the subjects was set as the reference: age = 54 years, Hb = 94 g/L, and PTH = 156.84 pg/mL. The range for the influencing factors was age: 24–84 years, Hb: 40–177 g/L, and PTH: 9.34–687.27 pg/mL. The AUC was investigated to assess if each covariate was at the boundary value. Each scenario simulated 1000 sets of virtual data, and the PK parameters were calculated.

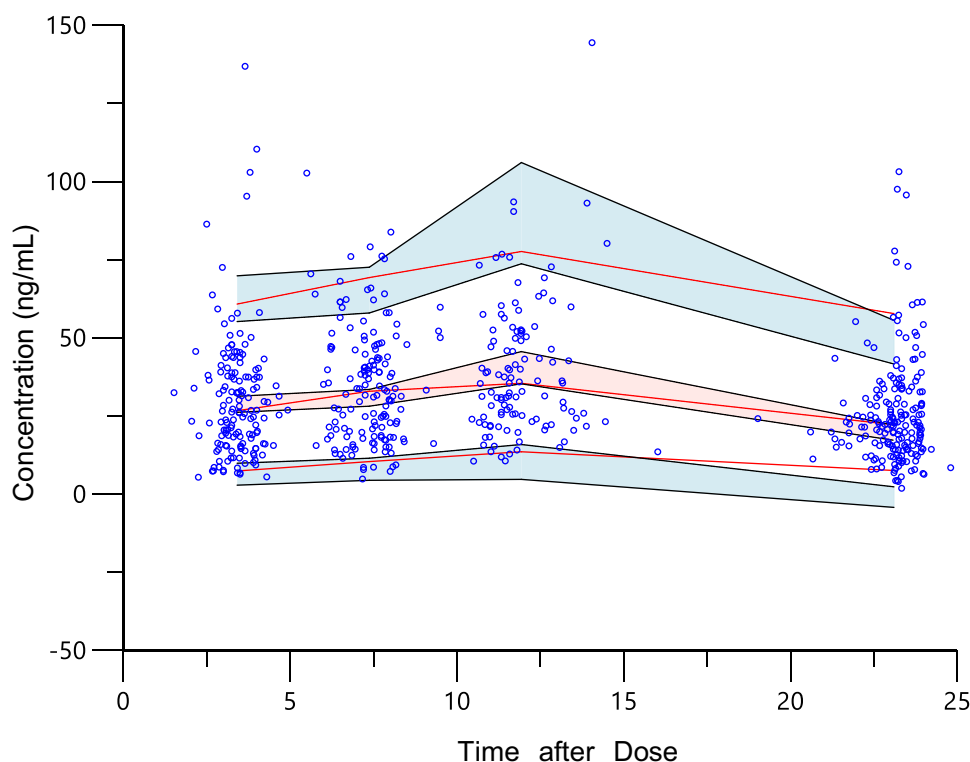


Figure 4 Predicted-corrected visual predictive checks or 1000 simulations. The pc-VPC chart generated by final model after 1000 Monte Carlo simulations. The red lines were 5%, 50%, and 95% percentile lines of measured values, and the shaded parts were 90% confidence intervals of predicted values of 5%, 50%, and 95% percentile lines. The percentile lines were fundamentally included in the 90% confidence interval of the predicted values. It was demonstrated that there was no deviation in the final prediction result of the model, and the trend of the model prediction was close to the measured value.

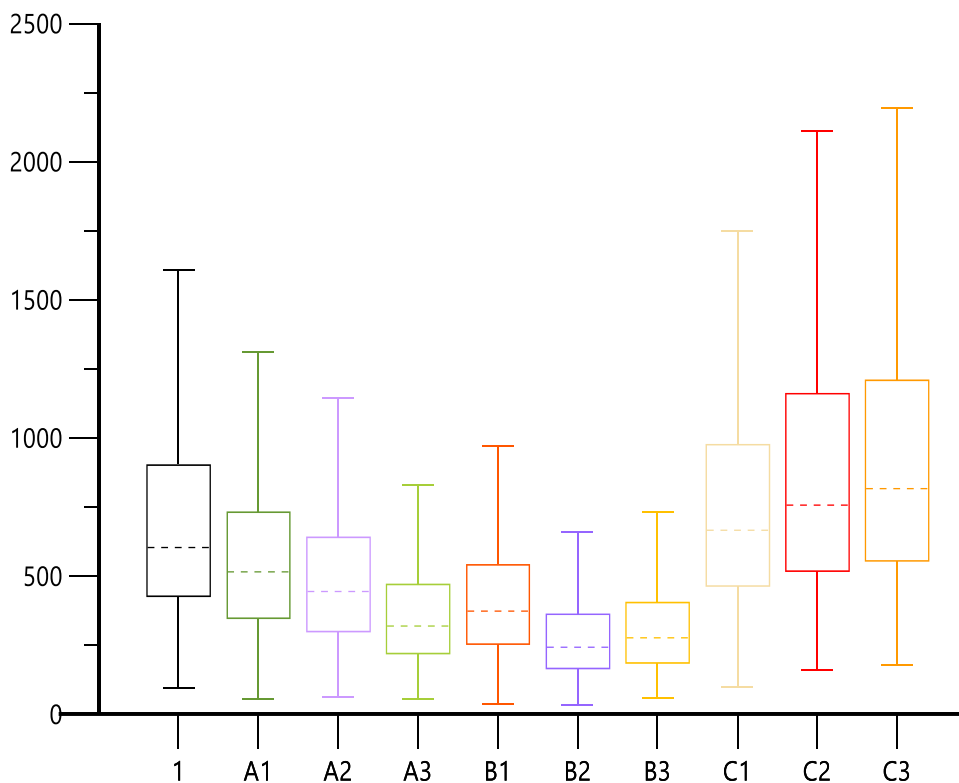


Figure 5 The box diagram of AUC simulated in different scenarios. The dotted line was the median level and the legend referring to Table 4. Scenario 1 was used as a reference. Scenarios A1, A2, and A3 were the minimum boundary values for age, Hb, and PTH, respectively. B1, B2, and B3 were scenarios with age and Hb; Hb and PTH; and age and PTH with minimum boundary value. Scenarios C1, C2, and C3 were the maximum boundary values of age, Hb, and PTH, respectively.

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The dose of nifedipine was adjusted for each simulation. The overall summary is presented in Table 4. Compared with the reference level, the dosage of nifedipine may be increased by 7.5, 15, and 22.5 mg (or 30 mg) with the minimum boundary values of age, Hb, and PTH, respectively. In addition, the dosage of nifedipine may be reduced by 7.5 mg, with the maximum boundary value of PTH. As observed in scenario B1–3, the dose might be increased by 22.5, 45, and 37.5 mg with the minimum boundary value of age and Hb, Hb and PTH, as well as age and PTH, respectively.

Table 4 Dosage Adjustment for Nifedipine in Different Scenarios

Scenery	Age (yr)	Hb (g/L)	PTH (pg/mL)	Recommended Dose
I	54	94	156.84	30 mg (not adjusted)
A1	24	94	156.84	37.5 mg
A2	54	40	156.84	45 mg
A3	54	94	9.34	52.5 mg or 60mg
B1	24	40	156.84	52.5 mg
B2	54	40	9.34	75 mg
B3	24	94	9.34	67.5 mg
C1	84	94	156.84	30 mg (not adjusted)
C2	54	177	156.84	30 mg (not adjusted) or 22.5 mg
C3	54	94	687.27	22.5 mg

Discussion

To the best of our knowledge, this is the first population pharmacokinetic study on nifedipine as a typical CYP3A substrate, in CKD patients. To determine the extent of the contribution of PTH to the changes in CYP3A expression and the pharmacokinetics of CYP3A eliminated drugs, we developed a PopPK model of nifedipine, by performing a prospective study of 157 Chinese CKD subjects. In this study, PTH demonstrated a significant negative correlation with CL in the PopPK model (also referring to Figure 6). In comparison with the reference, the dosage of nifedipine was reduced to the maximum boundary value of PTH after a Monte Carlo simulation.

PTH, as a middle molecule uremic toxin, may be the prime mediator involved in the downregulation of liver CYP450 in CKD rats.¹³ Therefore, successful clinical translation was brought into focus.^{30,31} It was observed that PTH exerted a suppressive effect on CYP3A expression via multiple signaling pathways including the NF- κ B/PXR pathway.¹⁵ However, as previously mentioned, reports on this finding from recent clinical trials are inconsistent.^{16,17} One explanation is that these were retrospective and observational studies with a limited number of enrolled patients. In addition, other covariates (additional physiological and genetic data) were not taken into account.¹⁶ In another a study of 48 subjects to examined CYP3A5 polymorphism and serum PTH level affect the tacrolimus blood concentration/dose (C/D) ratio before kidney transplantation in patients with end-stage renal failure, a significant positive correlation was found between tacrolimus C/D and PTH concentrations. Meanwhile, the multivariable linear regression analysis identified serum PTH level as significant factors associated with tacrolimus C/D.³² However, these analyses were performed on account of a single dose-normalized blood tacrolimus concentration, and not clearance. Therefore, it could not be inferred that the fluctuation of tacrolimus blood concentration was a result of reduced metabolic capacity.³² Our study evaluated whether serum PTH level influence the clearance of nifedipine in view of multiple blood levels, where the effects of serum PTH levels and CYP3A activity were confirmed.

For genetic factors, CYP3A genetic polymorphisms including *CYP3A5**3 rs776746,²² *CYP3A4**1G rs2242480,^{19,20} *CYP3A4* rs4646437,²¹ genetic polymorphisms of NF- κ B/PXR metabolism pathway proteins including *NFKB1* rs28362491^{24,25} and *NRII2* rs2276707,^{23–25} and immune-related genes including *IL-3* rs181781²¹ may influence the expression of CYP3A and play important roles in nifedipine metabolism. In addition, the multidrug resistance gene *MDR1*, which encodes P-gp, was reported to be involved in the transport of nifedipine.^{26,27} However, in our study

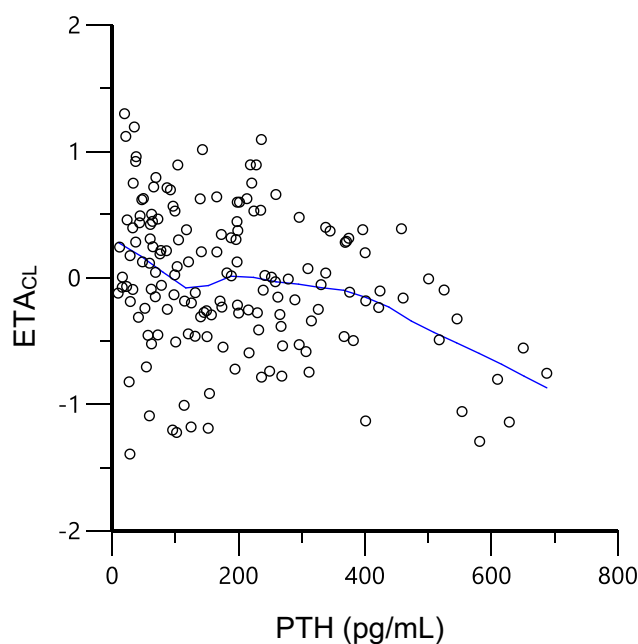


Figure 6 The relation between clearance and PTH. Green line, LOESS line.

population, the investigated polymorphisms did not influence nifedipine CL/F. For confirmation, these analyses should be repeated in other cohorts.

The physiological and pathological state of an individual is the most important factor that affects drug response. Injuries to the liver and kidney can impact drug disposal, leading to significant changes in the pharmacokinetic and pharmacodynamic properties of the drugs.^{33–35} This was observed in our PopPK model with CKD patients. Similar to PTH, Hb and CL/F were negatively correlated. This may be consistent with other findings in these reports,^{36,37} which raised this possibility that low hemoglobin values obtained from low hematocrit values, potentially leading to a decrease in bound nifedipine, while an increase in free nifedipine stimulates metabolic enzyme disposal and causes an increase in CL/F. However, hematocrit did not have significant covariates in the final model of CL/F. This finding arouses our interest and future exploration of it is also required.

Moreover, it was observed that there was no significant relationship between the severity of CKD and CYP3A4/5-mediated clearance via systematic and quantitative assessment.³⁸ These conflicting results may be ascribed to the classification of CKD subjects primarily based on measured creatinine clearance or GFR. In this study, CYP3A clearance was not significantly correlated with serum creatinine or GFR. However, it was demonstrated that PTH may be a superior index to characterize the elimination pathway of CYP3A, particularly in the case of nonrenally eliminated drugs.

To validate these findings, however, further large-scale studies with more covariates and multicenter clinical trials are required. This will provide a better explanation for the variation among individuals.

Conclusion

In conclusion, a population pharmacokinetic model of nifedipine was developed. This model adequately described the genetic and non-genetic factors in patients with CKD. This PopPK model confirmed the suppressive effect of PTH on the clearance of nifedipine (a substrate of CYP3A4) and may offer insights into the role of PTH in the characterization of CYP3A. This study may contribute to the design of and the optimal administration schedule for using CYP3A substrates in CKD patients.

Data Sharing Statement

All the relevant data are shown in the manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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