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ORIGINAL RESEARCH

A Step Toward Precision Dosing of Escitalopram in Chinese Patients: An External Evaluation of Published Population Pharmacokinetic Models

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Objective: This study aims to evaluate the predictive performance of the published population pharmacokinetic (PopPK) model of escitalopram in Chinese patients using an external validation method.

Methods: PubMed, Embase, and Web of Science databases were searched to identify PopPK models. Clinical data collected from Chinese patients treated with escitalopram were used to evaluate these models. The predictive performance of the models was evaluated using both prediction-based diagnostic methods and simulation-based diagnostic methods.

Results: Ten published PopPK models were included in the external validation. A total of 241 serum concentration samples were collected from 193 Chinese patient. Among all evaluated models, the Poweleit 2023 model exhibited the optimal predictive performance, with the PE of −2.14% and the RMSE of 22.27% at the individual level, and corresponding values of 14.13% and 104.19% at the population level, followed the model by Liu 2022. While the predictive performance of the other models was unsatisfactory.

Conclusion: Published PopPK models of escitalopram showed wide variations in predictive performance among our patient cohort. External models should be accurately evaluated before their application in clinical practice.

Keywords: population pharmacokinetics, external evaluation, therapeutic drug monitoring, nonlinear mixed effects modeling

Introduction

Mental disorders account for approximately 20% of the global disease burden, with depression being the leading cause.[1] The incidence rate of mental disorders has been rising in recent years, driven by population growth and increasing aging.[2] Currently, antidepressants remain the cornerstone of clinical treatment for depression, among which escitalopram is widely used for its efficacy in alleviating symptoms.[3,4] Escitalopram, the S-enantiomer of citalopram, is one of the most commonly used selective serotonin reuptake inhibitors since it was launched in China in 2006.[5] This drug specifically binds to the primary reuptake inhibitory site of the serotonin transporter, effectively regulating the concentration of serotonin in the central nervous system, and thus exerting its pharmacological effects in treating depression and anxiety disorders.[6,7] Escitalopram has a high selectivity for the serotonin transporter, and its pharmacological activity is approximately 30 times that of R-citalopram.[8] It has an oral bioavailability of about 80%, reaches peak plasma concentration within approximately 4 hours, and has a half-life of 27–32 hours, allowing for once-daily dosing.[9–11] The drug is primarily metabolized in the liver by the cytochrome P450 system, and CYP2C19 plays a key role in inter-individual variability in metabolism and response.[9] Finally, the metabolites are mainly excreted through the renal pathway.[12]

Given the substantial inter- and intra-individual pharmacokinetic (PK) variability of escitalopram, therapeutic drug monitoring (TDM) is critical for optimizing efficacy and minimizing adverse risks.[13] Neuroimaging studies have

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demonstrated a relationship between escitalopram plasma concentrations and SERT occupancy: when blood concentrations exceed 20 ng/mL, SERT occupancy is stably maintained above 80%.[14,15] This 80% occupancy threshold is considered the minimum level required to sufficiently enhance serotonergic neurotransmission for clinical efficacy.[14] Clinical guidelines recommend the use of TDM to assess whether escitalopram concentrations achieve the therapeutic range.[13,16] While a range of 15–80 ng/mL has been recommended in guidelines,[13] a recent meta-analysis has refined the target range to 20–40 ng/mL.[16] Nevertheless, an excessively high level of drug exposure will increase the risk of QTc interval prolongation.[17] Beyond CYP2C19 polymorphism, factors including age, body weight, and hepatic/renal function further contribute to PK variability, collectively underscoring the necessity for personalized dosing strategies guided by TDM.[5,7,18]

PopPK modeling is a powerful tool for understanding sources of variability in drug exposure and supporting individualized dosing strategies.[19] In previous studies, numerous published PopPK models have been dedicated to quantifying the pharmacokinetic parameters of escitalopram and analyzing the covariates that lead to its variations.[5,20–27] By integrating population sample data, these models can estimate the initial dose before actual blood drug concentration monitoring, significantly enhancing the efficiency of treatment plan formulation.

However, the generalizability of existing models remains uncertain. The differences in demographic characteristics, genetic polymorphisms and concomitant medications among different research cohorts may affect model predictive performance. Although two PopPK models for escitalopram have been developed using data from Chinese patients, they show significant discrepancies in key pharmacokinetic parameters, particularly apparent oral clearance (CL/F), and predict different drug exposure levels.[5,27] Therefore, evaluating the predictive performance of PopPK models through external validation has become a crucial step in ensuring the reliability of application.

To evaluate these uncertainties and provide evidence for personalized escitalopram therapy in Chinese patients, this study aims to evaluate all published escitalopram PopPK models predictive performance using external validation methods. The results of this study are expected to provide a basis for establishing individualized treatment of escitalopram in Chinese patients, and promote the precision of psychotropic drug treatment.

Methods

Model Selection

The PopPK models for external validation were sourced from previously established escitalopram PopPK model repository (Escitalopram Personalized Dosing: A Population Pharmacokinetics Repository Method),[28] initially published with a literature search cutoff date of November 2022. To ensure comprehensiveness, we conducted a supplementary literature search using the same systematic strategy and inclusion/exclusion criteria (Studies were included if they were English-language articles involving human subjects, evaluated escitalopram as the study drug or modeled citalopram with escitalopram analyzed separately, and conducted pharmacokinetic/pharmacodynamic (PK/PD) or PopPK analyses with sufficient PK parameter reporting.) up to April 28, 2025.

The methodological quality of newly identified reports was rigorously evaluated using a 33-item checklist adapted from established PopPK guideline.[26,27] A predefined template was used to extract critical information from eligible studies, including: (1) Demographic characteristics; (2) Study design; (3) Modeling strategy; (4) Covariates, etc.

Validation Data Acquisition

Data Source

Retrospective data were extracted from electronic medical records and TDM databases at Xi'an Mental Health Center (2020–2023).

Patient Inclusion Criteria

(1) Adults (≥18 years) prescribed escitalopram for a psychiatric indication, with ≥1 steady-state trough concentration measurement.
(2) Complete dosing records (dose, frequency, administration time) and demographic data (sex, age, weight, height).

Sample Analysis

(1) Analytical Method: Plasma escitalopram concentrations were quantified using a validated HPLC-MS/MS method (lower limit of quantification: 3.0 ng/mL [linear range: 11.68–291.88ng/mL], precision CV <15%).
(2) Sampling Protocol: Blood samples were collected within 2 hours before the next dose, after at least five half-lives of stable escitalopram administration to ensure steady-state concentrations.

Data Curation

(1) Software: R (version 4.3.1, R Foundation) was used for data cleaning, standardization, and alignment with the PopPK repository's input format (see Section 4.1.3 of the original repository publication).
(2) Variables: Demographic, dosing, and laboratory data were harmonized to match covariate definitions in the selected PopPK models. If the covariates specified in the PopPK model were unavailable in the evaluation dataset, the mean or median values of the covariates described in the original studies were employed. Missing genotype data were categorized as either intermediate metabolizer (IM) genotype or assigned to a separate missing category.

Validation and Evaluation

Software and Computational Tools

(1) NONMEM (version 7.5, ICON Development Solutions) was used for model execution and Bayesian forecasting.
(2) PsN (version 4.9.0) and Xpose (version 4.7.0) facilitated diagnostic evaluations.
(3) R (version 4.3.1)

Model Implementation

(1) Parameter Fixation: All structural model parameters (including, clearance [CL], volume of distribution [Vd]) and covariate coefficients were fixed to values reported in the original repository.
(2) Prediction Method: Individual and population predictions were generated using maximum a posteriori Bayesian estimation (MAP), incorporating the external cohort's dosing regimens, covariates, and sampling times.

Performance Metrics

(1) Graphical Evaluation: Goodness-of-Fit (GOF) Plots: Observed vs population-predicted (PRED) and individual-predicted (IPRED) concentrations. Normalized Prediction Distribution Errors (NPDE): Quantile-quantile (Q-Q) plots and histograms to assess model-predicted distribution accuracy.
(2) Numerical Evaluation: Prediction error (PE), Mean prediction error (MPE), and Root mean square error (RMSE) were used to conduct numerical evaluation. The calculation formula as below:

$$\mathrm{PE_{ij}} = \frac{\mathrm{C_{obs,ij}} - \mathrm{C_{pred,ij}}}{\mathrm{C_{obs,ij}}} \times 100\%$$

$$\mathrm{MPE} = \frac{1}{N}\sum_{i=1}^{N} PE_{ij}$$

$$\mathrm{RMSE} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\mathrm{C_{obs,}}_{ij} - \mathrm{C_{pred,}}_{ij}\right)^2}$$

where N is the number of observed escitalopram concentrations, and $C_{obs,ij}$ is the ith measured concentration of jth subjects, and $C_{pred,ij}$ is the ith prediction concentration of jth subjects.

A PopPK model was considered acceptable if: Absolute median PE <30% (indicating minimal bias), RMSE ≤30% (reflecting adequate precision) and NPDE distribution aligned with theoretical normality (Shapiro–Wilk test p>0.05).[29,30]

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Results

PopPK Models Characteristics

A total of 10 PopPK studies of escitalopram (2009–2024) were systematically reviewed, encompassing diverse populations across China, the United States, Switzerland, and multinational cohorts. The characteristics of these included studies are summarized in Table 1. The studies involved 1121 subjects, ranging from healthy adults (n=33–176) to special populations such as pediatric psychiatric patients (n=288, median age 15 years), pregnant/postpartum women (n=33), and HIV-infected individuals (n=39). Age distributions varied substantially, with median/mean values spanning 15.0–77.8 years across cohorts. CYP2C19 phenotype stratification was reported in 9 studies, showing poor metabolizers (PM) proportion of 3–16% and ultrarapid metabolizers (UM) of 0–12%. Sampling strategies ranged from intensive designs (16 timepoints over 120 hours in Liu 2024) to sparse clinical sampling (≥24-hour intervals in Jin 2009–2010). Escitalopram doses varied from therapeutic ranges (5–60 mg/day) to overdose cases (median 135 mg, range 10–450 mg). Bioanalytical methods predominantly employed HPLC-MS/MS with quantification limits as low as 0.03 ng/mL (Poweleit 2023), while earlier studies used conventional HPLC with higher detection thresholds (3–5 ng/mL).

The PopPK parameters of the retrieved studies are presented in Table 2. All studies implemented first-order absorption-elimination kinetics, predominantly using one-compartment models (9/10 studies). Structural refinements included transit compartments (M1) and a two-compartment model with absorption lag-time (M4). Body weight and CYP2C19 phenotype were consistently identified as key covariates for CL and Vd, with weight-based allometric scaling exponents ranging from 0.333 to 0.774. Between-subject variability (BSV) for CL ranged from 29.6% to 74.4%, while residual unexplained variability (RUV) showed proportional errors of 6.4–46.5%. Model validation predominantly relied on internal techniques (bootstrap in 7 studies, visual predictive checks in 4 studies), with only M6 conducting external validation (n=149). Software utilization was homogeneous, with NONMEM's FOCE-I algorithm applied in 8 studies, contrasting with Bayesian estimation in M8.

Subject Characteristics

The external validation cohort included 193 subjects (241 drug concentration measurements), with a median age of 45 years (range: 32–58). Demographic characteristics of the cohort are detailed in Table 3. Anthropometric parameters showed median values of 164 cm for height, 60 kg for weight, and 22.08 kg/m^2 for BMI. Daily doses varied between 5 mg and 20 mg, reflecting real-world clinical dosing strategies. Figure 1 illustrates the dynamic changes in drug concentration over detection time (days). Of these, 157 (81.3%) had a single trough concentration measured, 28 (14.5%) had two measurements, and 8 (4.1%) had three or more measurements.

Prediction Performance Evaluation

Goodness-of-Fit

The GOF plots (Figure 2) illustrate the comparison between observed and predicted concentrations for individual predictions (IPRED-DV) and population predictions (PRED-DV). The IPRED-DV plots show a strong alignment with the line of identity for most models, such as M1, M2, and M3, indicating good predictive performance at the individual level. However, models like M5, M7, and M8 exhibit more deviation, particularly at higher concentrations, suggesting occasional over-prediction or under-prediction at extreme values.

In the PRED-DV plots, models like M2 and M3 show good correlation with the observed data, while other models display significant discrepancies, particularly at higher concentrations, where the predictions deviate more from the observed values. This indicates that population-level predictions for these models may require further refinement to better match the observed data across all concentration ranges.

Prediction Error

The individual prediction error (IPRED) assess model performance at the individual level, as illustrated in Figure 3A and Table 4. Most models fall within the acceptable range, indicating reasonable individual-level accuracy: M1 (median PE: −3.55%, RMSE: 21.90%) and M2 (median PE: −2.14%, RMSE: 22.27%) show minimal bias, with RMSE values well below the 30% threshold. Models M3 (RMSE: 22.83%), M4 (RMSE: 20.63%), M6 (RMSE: 17.96%), M8 (RMSE:

Table 1 Demographics and Clinical Characteristics of Included Escitalopram PopPK Studies

Study (Publication Year)	Country (Type of Study)	Number of Subjects (M/F)	Sample Counts	Sampling Schedule (h)	Age (Years); Mean ± SD; Median [Range]	Weight (kg); Mean ± SD; Median [Range]	CYP2C19 Phenotype	Subject Characteristics	Dose (mg) [Range]	Bioassay [LOQ] (mg/L)
M1	China	176 (130/46)	2775	Pre-dose and post-dose 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120 h	Study 1: 25.43±5.46; Study2: 23.43±5.61	Study 1: 62.04±8.25; Study 2: 61.27±7.18	Study1: PM:10; IM:40; EM:36; UM:0; Study2: PM:16; IM: 54; EM:18; UM:2	Healthy volunteer Adult	10	HPLC-MS/MS [0.1 ng/mL]
M2	USA	288 (81/207)	315	12h or 24h post-dose, through concentration	15 [10–18]	66.6 [22.9–223.1]	PM:8; IM:75; NM:124; RM:78; UM:3	Pediatric psychiatric patients	10 mg/d; [1–30 mg/d]	HPLC-MS/MS; [0.03ng/mL]
M3	China	106 (59/47)	337	Through concentration	45 [12–83]	61 [37–97]	EM:47; IM:49; PM:10	Psychiatric patients	10mg/d; [5–30mg/d]	HPLC [3ng/mL]
M4	South Korean	33 (21/12)	330	Pre-dose and post-dose 1,2,3,4,6,8,12,16,24,30,36,48 h	NR	NR	NR	Healthy volunteer Adult	20mg	HPLC-MS/MS
M5	Multi-center	33 (0/33)	80 blood samples; 104 breast milk samples	11.2 h and 10.3 h after the last SCIT or Racemic Citalopram intake, steady state	34 [21–43]	76 [60.8–120]	PM:4; IM:5; EM:12; UM:12	Pregnant and post delivery women	10 mg/d [5–20 mg/d]: 15mg/d [5–60 mg/d]	HPLC-MS/MS [0.1ng/mL]
M6	Switzerland	110 (55/55)	159	0.1 h–29 h after the last dose	HIV 48[36–56]; Uninfected 46[35–58]	HIV 77[62–85]; Uninfected 69 [56–81]	NR	39 HIV infected psychiatric patients; 71 uninfected psychiatric patients	SCIT: 20 mg [5–20mg]; CIT: 20 mg [10–40mg]	HPLC-MS/MS [1ng/mL]
M7	USA	81 (41/40)	R-citalopram 205; S-citalopram 205	Plasma samples were collected at weeks 3, 6, and 9, most are 2–6 h	77.8±8.2 [47–90]	71.5±17.2 [40–122.3]	PM:3; IM:17; EM:43; RM:3; Unknown:15	Alzheimer's disease patients	Starting 10mg, titrated up over 2 weeks to the target of 30 mg/d	HPLC [5 ng/mL]
M8	Australia	29 (5/24)	104	1.5–47.5h after ingestion	27 [16–51]	NR	NR	Overdose	135mg [10–450mg]	HPLC [1μg/L]
M9	Multi-center	USA:105 (47/58); Italy: 67 (7/60)	320 USA; 153 Italy	At weeks 4,12,24 and 36 through concentration	USA: 38.84±12.05 [20.4–64.67]; Italy: 40.58±11.20 [21–65]	USA: 81.6±20 [31.9–139.7]; Italy: 67.8±15.2 [40–116]	USA: PM:3; IM:28; EM:54; RM:4; Unknown:16; Italy: PM:0; IM:15; EM:23; RM:1; Unknown:28	Psychiatric patients	5,10,15,20	HPLC [2ng/mL]
M10	USA	73 (32/41)	185	At weeks 4,12,24 and 36 through concentration	39.47±11.35	81.83±43.81	NR	Psychiatric patients	10,15,20	HPLC [2ng/mL]

Notes: M1 (Liu et al[27]); M2 (Poweleit et al[26]); M3 (Liu et al[5]); M4 (Kim et al[22]); M5 (Weisskopf et al[25]); M6 (Courlet et al[20]); M7 (Akil et al[24]); M8 (Van et al[23]); M9 (Jin et al[18]); M10 (Jin et al).[21]
Abbreviation: NR, Not reported.

Table 2 Model Characteristics of Included Escitalopram PopPK Studies

Study (Publication Year)	Software (Algorithm)	Model Structure	Fixed Effect Parameters		Between-Subject Variability (%CV)	Residual Unexplained Variability Prop% Add (mg/L)	Internal Validation	External Validation (N=Number of Samples)
M1	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model with transit absorption compartments	Ka (h^{-1})	=3.26	102.47	Prop=11.9; Add=0.175ng/mL	Bootstrap VPC GOF	NR
			CL (L/h)	=13.2*(WT/62)$^{0.663}$*e$^{0.386}$(IF IM)/e$^{0.741}$(IF EM)	36.64			
			Vd (L)	=895*(WT/62)$^{0.774}$	17.29			
			MTT (h)	=0.892	46.58			
M2	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=0.892	-	Prop=20.3	Bootstrap GOF	NR
			CL (L/h)	=14.2*0.338(IF PM)/0.767(IF IM)/1.11(IF RM)/1.54(IF UM)*(BSA/1.73)*0.758(IF inhibitor)	42.6			
			Vd (L)	=428	34.1			
M3	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=0.6	-	Prop=16.94	Bootstrap GOF	NR
			CL (L/h)	=16.3*(1+0.0077*(AGE-45)*0.847(IF IM)/*0.479(IF PM)	29.61			
			Vd (L)	=815	48.48			
M4	NONMEM FOCE-I	First-order absorption and first-order elimination two-compartment model with alag-time	Ka (h^{-1})	=5.46	95.4	Prop=6.40	Bootstrap VPC GOF	NR
			CL (L/h)	=22.8	43.9			
			Vd (L)	=867*(WT/70)$^{0.741}$	19.9			
			Q (L/h)	=34.4	-			
			Vp (L)	=234	-			
			ALAG (h)	=0.98	-			
M5	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=0.87	-	Prop=33.50	Bootstrap VPC	NR
			CL (L/h)	=32.3*0.49(IF PM)*0.9*(IF 1 month after delivery)	31.2			
			Vd (L)	=1590	-			
M6	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=0.8	-	Prop=27	Bootstrap VPC	N=149
			CL (L/h)	=23.1*e$^{-0.19}$(IF inhibitor)	51			
			Vd (L)	=920	-			

M7	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=1	-	Prop=46.49	Bootstrap GOF	NR
			CL (L/h)	=22.1(IF EM/RM)/16.3(IF IM/PM)/16.8(IF MISS)*(AGE/60)$^{-1.33}$*(WT/70)$^{0.75}$	61.92			
			Vd (L)	=1390	86.81			
M8	WinBUGS	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=8.0	111.4	Prop=23.7; Add=0.002 mg/L	Gelman-Rubin diagnostic plot	NR
			CL (L/h)	=33.5	74.4			
			Vd (L)	=1285	63.2			
M9	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=0.8	78.9	Prop=28.90	GOF	NR
			CL (L/h)	=26(IF EM/RM)/19.8(IF IM/PM)/21.5(IF MISS)*(AGE/40)$^{-0.336}$*(WT/76)$^{0.333}$	48.5			
			Vd (L)	=947*(BMI/27)$^{1.11}$	62			
M10	NONMEM FOCE-I	First-order absorption and first-order elimination one-compartment model	Ka (h^{-1})	=0.74	88.9	Prop=15.2; Add=3.61 ng/L	GOF	NR
			CL (L/h)	=25.5	53.5			
			Vd (L)	=1000	64.3			

Notes: M1 (Liu et al[27]); M2 (Poweleit et al[26]); M3 (Liu et al[5]); M4 (Kim et al[22]); M5 (Weisskopf et al[25]); M6 (Courlet et al[20]); M7 (Akil et al[24]); M8 (Van et al[23]); M9 (Jin et al[18]); M10 (Jin et al).[21]

Abbreviations: CL, apparent clearance (L/h); Q, the interconpartment clearance; V, apparent volume of distribution (L); Vc, the apparent central compartment distribution volumes (L); Vp, the apparent peripheral compartment distribution volumes (L); Ka, absorption rate (h-1); F, bioavaliability; Tlag, lag time (h); MTT, mean transit absorption time; NT, transit absorption compartment; Pfast, Proportion of fast eliminators in population; FOCE, first order conditional estimation; FOCE-I, FOCE with the interaction; SAEM, stochastic approximation expectation maximization; GOF, goodness-of-fit plot; VPC, visual predictive check; NPDE, normalized prediction distribution errors; BW, body weight; BMI, body mass index; PMA, postmenstrual age; FFM, Fat-free Mass; Cmax, peak plasma concentration (mg/L); AUC, area under the plasma concentration-time curve; NR, not reported.

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Table 3 External Validation Dataset Demographic Characteristics

Characteristics	Mean ± SD/Number	Range
Individuals	193	/
Concentration points	241	/
Age (years)	42.93 ± 17.67	13–80
Height (cm)	164.43 ± 7.91	140-183
Weight (kg)	61.13 ± 11.91	34–105
BMI (kg/m^2)	22.55 ± 3.75	13.28–39.52
Amount (mg/d)	14.70 ± 4.65	5-20

20.54%), M9 (RMSE: 22.57%), and M10 (RMSE: 18.52%) also maintain IPRED RMSE < 30% and median PE with absolute values < 30%, confirming acceptable individual prediction accuracy. However, M5 exceeds acceptable thresholds: its IPRED RMSE is 33.27% (> 30%), and while its median PE (−27.24%) is close to the threshold, the elevated RMSE indicates less reliable error distribution for individual predictions.

For population predictions (PRED), model performance is more variable, as illustrated in Figure 3B and Table 4. M2 (median PE: 14.13%, RMSE: 104.19%) and M3 (median PE: −0.53%, RMSE: 101.48%) have median PE values within the acceptable range (absolute value < 30%) but exceed the RMSE threshold (RMSE > 30%), indicating large scatter in

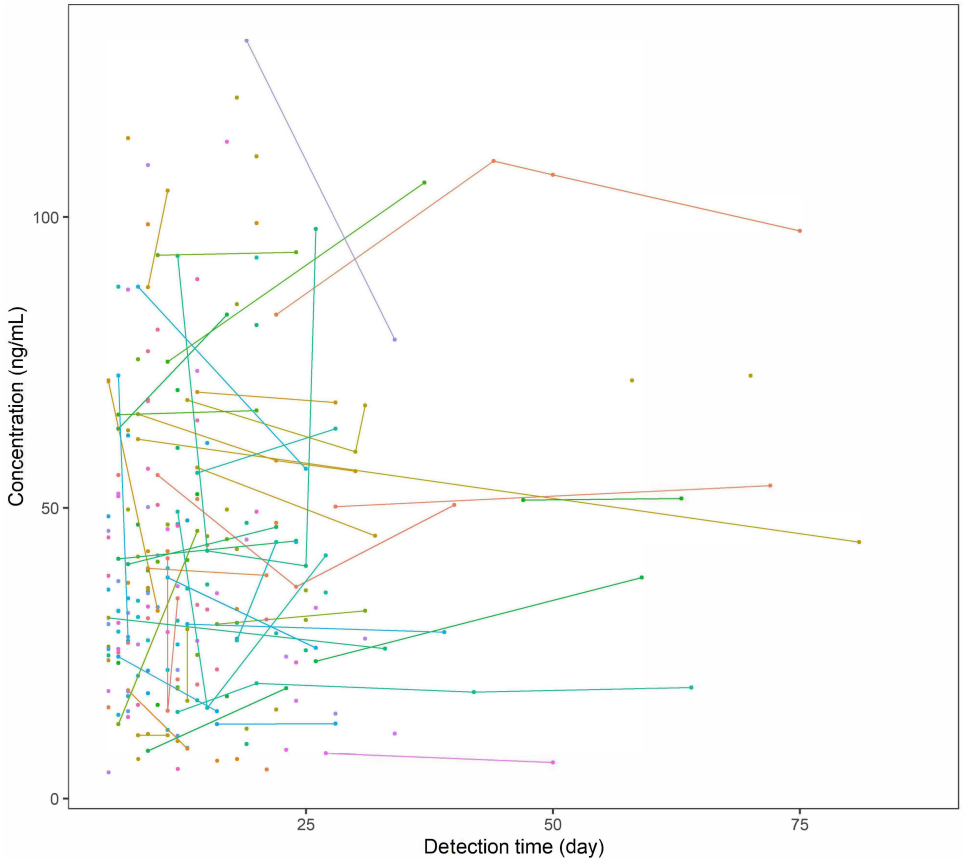

Figure 1 Escitalopram concentration versus time after dosing. Colored dots: Observed drug concentration from a subject at a single time point. Colored lines: Concentration-time profiles for individual subjects with multiple measurements.

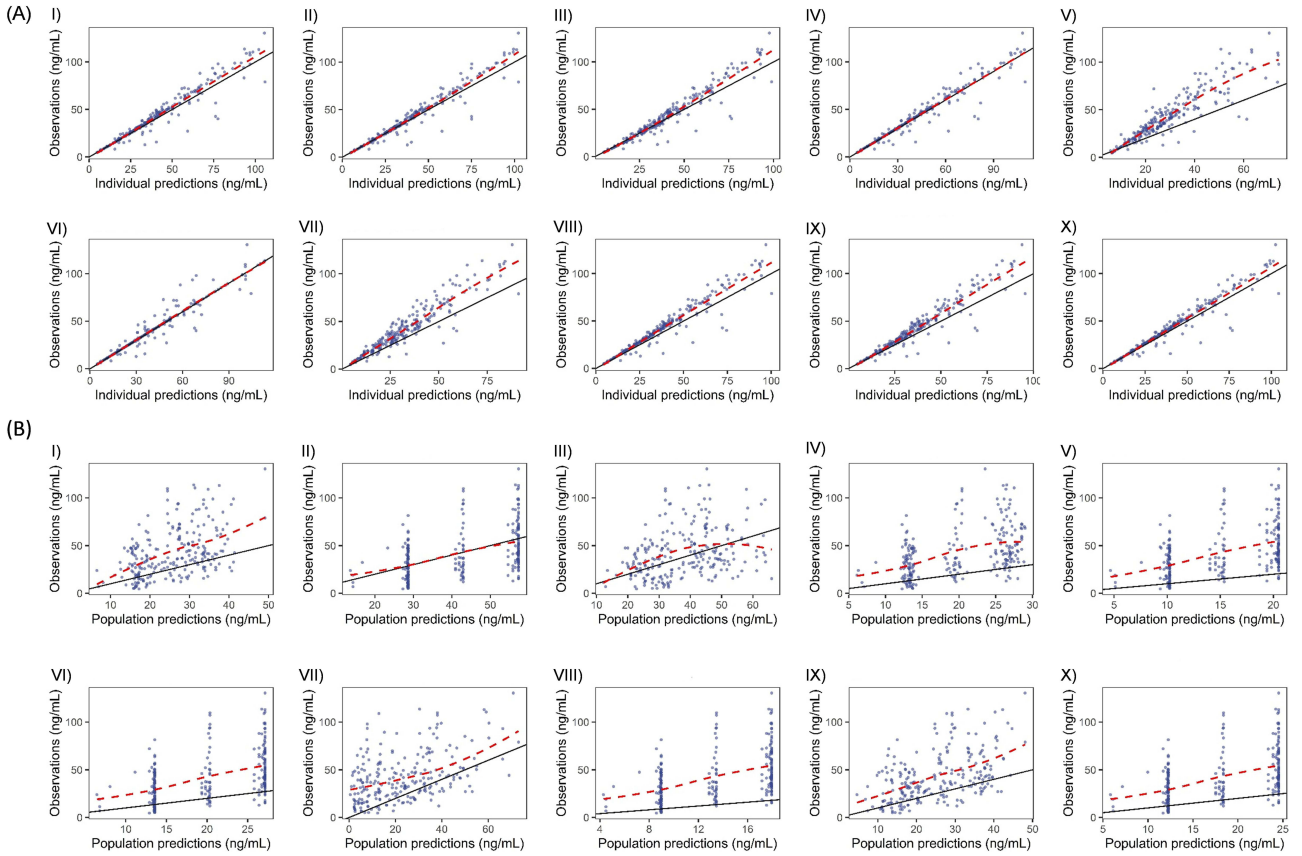

Figure 2 Goodness-of-Fit plots of observed versus individual (**A**) and population (**B**) predictions for the ten included escitalopram population pharmacokinetics models. Subplots I–X correspond to models M1–M10, respectively. The identity line is shown in black and a trend line (red) has been drawn for each model. Models are defined as follows: M1 (Liu et al[27]); M2 (Poweleit et al[26]); M3 (Liu et al[5]); M4 (Kim et al[22]); M5 (Weisskopf et al[25]); M6 (Courlet et al[20]); M7 (Akil et al[24]); M8 (Van et al[23]); M9 (Jin et al[18]); and M10 (Jin et al).[21]

population-level errors. Models M4 (median PE: −46.66%, RMSE: 56.55%), M5 (median PE: −60.04%, RMSE: 60.51%), M6 (median PE: −46.08%, RMSE: 56.35%), M7 (median PE: −45.63%, RMSE: 60.82%), M8 (median PE: −64.23%, RMSE: 63.47%), M9 (median PE: −31.46%, RMSE: 54.62%), and M10 (median PE: −51.14%, RMSE: 57.16%) exceed both thresholds: median PE (absolute value > 30%) and RMSE (> 30%). These models demonstrate substantial deviations between population predictions and observed data, highlighting the need for refinement.

Normalized Prediction Distribution Errors

The NPDE analysis (Figure 4) evaluates the distribution of normalized residuals across different models. The QQ plots and histograms reveal that models M2 and M3 exhibit a significantly better distribution of NPDEs, with both showing near-normal distributions and minimal skewness, indicating that these models are well-calibrated and provide unbiased predictions. The histograms for M2 and M3 align closely with the expected normal distribution, and the scatter plots of NPDE versus predicted concentrations (NPDE-DV) and time (NPDE-TIME) show random scattering around zero, further confirming the reliability of these models. In contrast, other models such as M4, M5, and M10 exhibit deviations in their NPDE distributions, where the QQ plots show slight departures from normality, and the histograms indicate a non-normal distribution of residuals. Additionally, the NPDE-TIME and NPDE-DV scatter plots for these models show more systematic deviations, suggesting that these models may have some degree of bias, especially at lower and higher concentration ranges or over time. These discrepancies point to potential areas for model refinement, particularly for improving prediction accuracy across the full range of data.

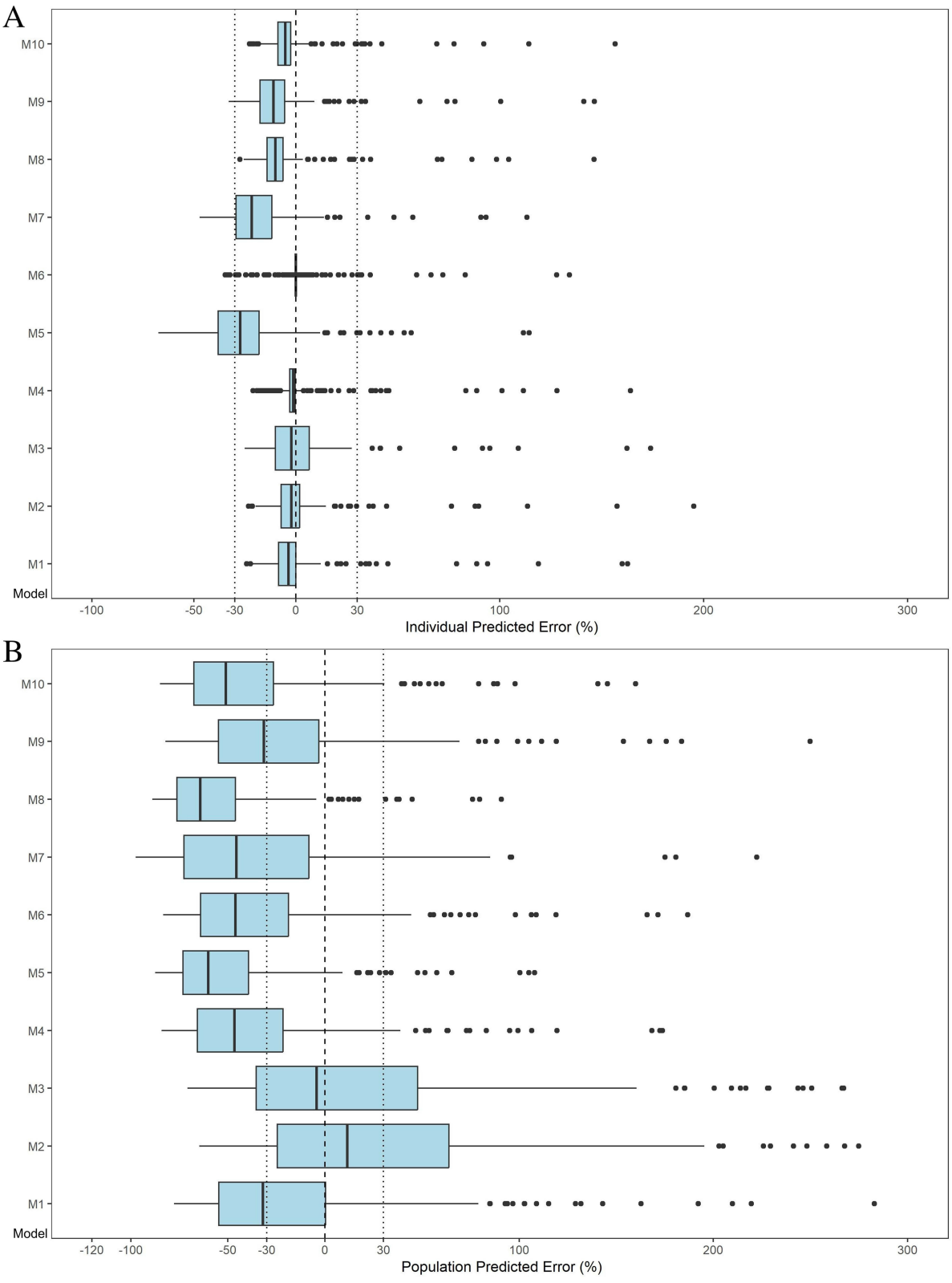

Figure 3 Prediction error (PE) distribution for the individual and population predictions of the included escitalopram population pharmacokinetics models (M1–M10). (**A**) Individual PE; (**B**) Population PE. Box elements: Lower hinge (25th percentile), midline (median), upper hinge (75th percentile). Whiskers: Extend to 1.5× interquartile range (IQR) below the 25th percentile and above the 75th percentile. Outliers: Data points beyond the whiskers. Reference lines: Vertical black dashed line indicates zero PE (unbiased prediction); black dotted lines denote ±30% PE thresholds (acceptable bias range). Models are defined as follows: M1 (Liu et al[27]); M2 (Poweleit et al[26]); M3 (Liu et al[5]); M4 (Kim et al[22]); M5 (Weisskopf et al[25]); M6 (Courlet et al[20]); M7 (Akil et al[24]); M8 (Van et al[23]); M9 (Jin et al[18]); and M10 (Jin et al).[21]

Table 4 Prediction Error of the Individual and Population Predictions to Observations for the Included PopPK Models

Model	IPRED			PRED		
	Median PE (%)	MPE (%)	RMSE (%)	Median PE (%)	MPE (%)	RMSE (%)
M1	−3.55	−0.46	21.90	−32.04	−16.16	59.48
M2	−2.14	0.86	22.27	14.13	40.72	104.19
M3	−2.15	1.00	22.83	−0.53	27.99	101.48
M4	−1.24	1.91	20.63	−46.66	−34.57	56.55
M5	−27.24	−24.15	33.27	−60.04	−50.10	60.51
M6	−0.01	1.60	17.96	−46.08	−33.41	56.35
M7	−21.73	−18.54	27.15	−45.63	−33.66	60.82
M8	−10.07	−6.86	20.54	−64.23	−55.90	63.47
M9	−11.06	−8.30	22.57	−31.46	−20.98	54.62
M10	−5.20	−2.36	18.52	−51.14	−39.77	57.16

Notes: M1 (Liu et al[27]); M2 (Poweleit et al[26]); M3 (Liu et al[5]); M4 (Kim et al[22]); M5 (Weisskopf et al[25]); M6 (Courlet et al[20]); M7 (Akil et al[24]); M8 (Van et al[23]); M9 (Jin et al[18]); M10 (Jin et al).[21]
Abbreviations: IPRED, Individual predictions; PRED, Population predictions.

Discussion

In precision medicine, PopPK models are increasingly applied, but require rigorous evaluation before clinical application, including internal and external validation.[31] External validation, which is the most robust assessment of predictive performance, uses independent datasets to evaluate how well a model generalizes to new patient populations and identifies factors affecting its extrapolability.[31] Although several PopPK models for escitalopram have been developed, their clinical utility remains uncertain without systematic external validation, particularly across different centers and populations.[5,18,20–27]

This study is the first to evaluate the predictive performance of published PopPK models for escitalopram, using data from the Chinese population as an external dataset. In the diagnostic evaluation based on prediction and simulation, significant performance differences were observed between the 10 published PopPK models. Overall, M2 exhibited the best predictive performance, and both performed well in terms of goodness-of-fit, control of individual prediction errors, and performance of NPDE normal distribution; within this model, body surface area (BSA) and CYP2C19 gene polymorphism were identified as the two primary covariates influencing the CL/F of escitalopram.[26]

External validation results indicate that the pharmacokinetic parameter of escitalopram can be adjusted relatively accurately using BSA as a body size parameter. Compared with body weight (BW), BSA demonstrates a significant advantage in predicting clearance values and can more accurately reflect the body's metabolic mass.[32] This superiority is attributed to the fact that BSA is less affected by abnormal adipose mass, thereby providing a more realistic representation of the effective tissue mass involved in drug metabolism.[33] Despite its good performance in predicting metabolic parameters, the application of BSA has certain limitations and is currently primarily used in pediatric patients.[32] Studies have shown that there is a specific power-law relationship between BSA and BW, typically expressed as BSA being proportional to the square of BW.[34] In adult populations, due to the relatively stable metabolic function and the small range of body size variations, the difference in the impact of choosing BSA or BW as a covariate on PK parameter adjustment is not significant.[32] Moreover, using BW as a covariate in clinical practice offers distinct advantages. It can be directly translated into weight-based dosage recommendations familiar to clinicians, which helps enhance the convenience and clinical applicability.[32]

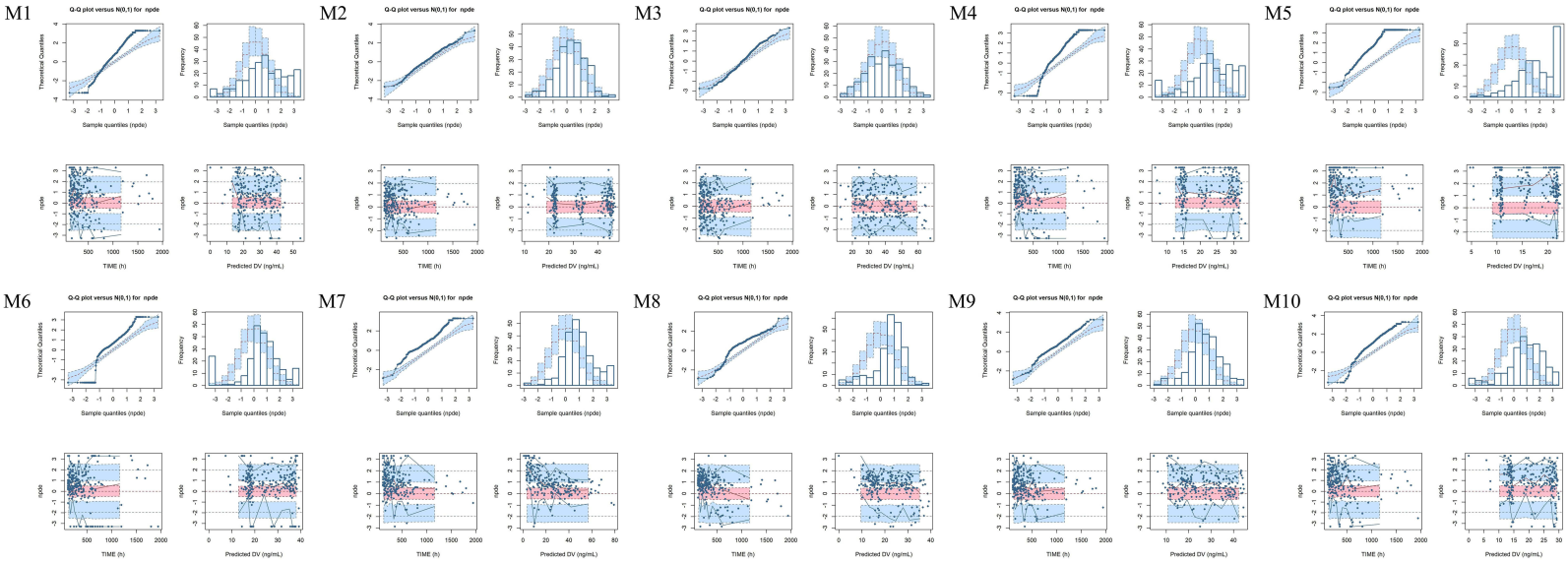

Figure 4 Normalized prediction distribution errors (NPDE) of the included escitalopram population pharmacokinetics models.

Notes: The QQ plot and histogram show the distribution of NPDE values, with a near-normal distribution indicating unbiased predictions. The NPDE versus predicted concentration (NPDE-DV) and NPDE versus time (NPDE-TIME) scatter plots assess the model's ability to predict drug concentrations without systematic bias across different concentration ranges and time points; the prediction interval is plotted as a colored area (blue for the 5th and 95th prediction intervals and pink for the median); Observations plotted as dots and the corresponding 5th, 50th and 95th of observation percentiles as solid lines. M1 (Liu et al[27]); M2 (Poweleit et al[26]); M3 (Liu et al[5]); M4 (Kim et al[22]); M5 (Weisskopf et al[25]); M6 (Courlet et al[20]); M7 (Akil et al[24]); M8 (Van et al[23]); M9 (Jin et al[18]); and M10 (Jin et al).[21]

The guidelines of the Dutch Pharmacogenomics Working Group (DPWG) recommend that the dosage of escitalopram for CYP2C19 PM populations should not exceed 50% of the normal maximum dose, while IM populations should receive 75% of the dose.[35] Although the influence of CYP2C19 genetic polymorphism on escitalopram metabolism is well-established, this study, like with many real-world observational studies,[5,20,26] did not include CYP2C19 genotyping as a covariate due to practical limitations in clinical data collection. Genomic testing for drug-metabolizing enzymes remains challenging, primarily constrained by high testing costs, inadequate healthcare reimbursement, and limited clinical awareness. Consequently, the data set was constructed using clinically feasible covariates that are more readily accessible and applicable in routine practice. Notably, CYP2C19 allele frequencies vary significantly across populations: the carrier frequency of the *2/*3 alleles in East Asian populations (29–35%) is 2–3 times higher than in Caucasian populations (12–15%).[36,37] In the Han Chinese population specifically, the distribution frequencies of CYP2C19 phenotypes are 34.8% (extensive metabolizers, EM), 50.3% (intermediate metabolizers, IM), and 14.9% (poor metabolizers, PM), with IM being the most prevalent.[38] Therefore, the CYP2C19 IM phenotype was incorporated as a fixed parameter in the model to account for potential genetic influences on escitalopram metabolism. Beyond pharmacokinetic variability, emerging research on molecular pathways, including the ESR2–BDNF axis in postpartum depression, underscores the importance of integrating pharmacogenomics and neurobiological insights into personalized dosing strategies.[39]

Although previous studies have shown that age, when included as a covariate in pharmacokinetic models, can significantly affect drug plasma concentrations,[5,18,24] this study found that the model developed based on adolescent populations (15 years old) still exhibited optimal predictive performance in populations with significant age stratification (such as adult groups at 43 years old).[26] This phenomenon suggests that age may not be the most critical covariate for the PK of escitalopram.

Due to the limitation of sparse data and the collection of only trough concentration samples in TDM, most models face data scarcity when describing the characteristics of absorption and distribution phases.[40] The absorption rate constant (Ka) and Vd are set as fixed values in most models for the aforementioned reasons, while all models involving escitalopram in this study also use a fixed Ka value for modeling. This approach essentially reduces the degrees of freedom of the model, simplifying the modeling process but potentially compromising the model's external generalizability.[41,42] When applied to external datasets, the strategy of fixing Ka values exacerbates parameter shrinkage effects, weakens model diagnostic efficiency, and increases sensitivity to data distribution shifts.[41,42] Therefore, we recommend prioritizing the optimization of modeling strategies for Vd and Ka parameters in future PopPK model development to enhance model universality and predictive accuracy.

This study has some limitations. First, as a single-center retrospective study, the limited sample size may lead to bias in the evaluation of the model's predictive performance. Therefore, future studies should consider adopting a multi-center prospective design to expand the sample size, which can improve the reliability of the model's predictive performance evaluation. Second, the model validation relying solely on trough concentration data fails to comprehensively cover the entire processes of drug absorption, distribution, metabolism, and excretion. As such, the external validation in this study was largely based on a one-compartment model, which might fail to adequately capture the drug's absorption and distribution processes within the body. Future research ought to employ richer sample datasets, encompassing data from multiple pharmacokinetic stages (including the absorption and distribution phases), to more thoroughly describe pharmacokinetic characteristics. Additionally, a key limitation of this study lies in the lack of CYP2C19 genetic variation data among patients. Due to the lack of genetic variation data of patients, all patients were assumed to have fixed genotypes. Consequently, it was impossible to evaluate the incorporated genetic factors, thereby restricting in-depth exploration of genetic polymorphisms. Future studies should conduct more thorough investigations by collecting blood samples for CYP2C19 genotyping, thereby developing more robust models.

This study highlights the critical role of external validation in enabling reliable clinical use of escitalopram PopPK models. Though multiple published PopPK models for escitalopram exist, their predictive performance differs markedly in independent dataset. Our findings confirm that PopPK models may fail to predict pharmacokinetics in new populations without rigorous external evaluation. Given the suboptimal predictive performance observed, future efforts should consider implementing model averaging approaches (MAA) or model selection algorithms (MSA) to improve dosing precision and enhance cross-population applicability.[43]

Conclusion

Among the ten published PopPK models evaluated, the model developed by Poweleit et al demonstrated the best overall predictive performance for individual-level pharmacokinetic predictions in the Chinese population during external validation, suggesting potential utility for clinical application.[26] However, it did not consistently outperform other models at the population level, indicating limitations in its generalizability. Overall, these findings underscore the challenges in recommending initial escitalopram doses based on existing PopPK models.

Ethics Approval and Consent to Participate

The investigation received ethical approval from the Xi'an Mental Health Center, and abided by the guidelines of the Declaration of Helsinki (Approval No. XAJWKY-2024011). The waiver of informed consent was granted by the institutional review board for the study involves retrospective data analysis, which does not adversely affect the rights and health of the subjects. Furthermore, all patient data have been anonymized to ensure confidentiality and privacy protection.

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Disclosure

There are no competing interests to declare.

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