POPULATION PHARMACOKINETICS MODELING OF LEVOFLOXACIN AFTER ORAL ADMINISTRATION IN HEALTHY INDONESIAN VOLUNTEERS

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ABSTRACT

Research on the application of population-based pharmacokinetic modeling in Indonesia remains limited. This study aimed to apply a population-based approach to characterize the pharmacokinetic profile of levofloxacin, a broad-spectrum antibiotic widely used in the treatment of infections.

A single 500 mg film-coated levofloxacin tablet was administered orally to 18 healthy volunteers (10 males and 8 females, aged 18–55 years). Eligibility was determined based on liver and kidney function, hematological and urine parameters, medical history, physical examination, blood pressure, heart rate, ECG, body weight, and the absence of viral infections (HCV, hepatitis B, and HIV). Blood samples were collected periodically over 24 hours post-dosing. Plasma concentrations of levofloxacin (Cp) were quantified using a validated bioanalytical HPLC method, evaluated for selectivity, accuracy, precision, stability, LLOQ, and linearity. Population pharmacokinetic modeling of Cp–time profiles was performed using Monolix (v. 2020 R1) and NONMEM (v. 7.43). Model selection compared one-compartment and two-compartment models, with and without absorption lag-time. Covariate analysis was conducted using automated searches in Monolix and PLTTools (NONMEM), including sex, age, weight, BMI, height, systolic and diastolic blood pressure, pulse, respiratory rate, albumin, bilirubin, SGOT, SGPT, urea, total creatinine, hemoglobin, lymphocytes, monocytes, eosinophils, basophils, hematocrit, red blood cells, and platelets.

A two-compartment model with absorption lag-time best described the pharmacokinetic profile of levofloxacin. Both Monolix and NONMEM provided comparable population and individual parameter estimates for CL (central clearance), Vd (central distribution volume), Q (inter-compartmental clearance), V2 (peripheral distribution volume), Ka (absorption rate constant), and lag-time. Age and height were identified as significant covariates, influencing Ka and Vd, respectively. Overall, both Monolix and NONMEM adequately described levofloxacin Cp data using a population-based modeling approach.

Keywords: Levofloxacin, population pharmacokinetics, Monolix, NONMEM, covariates

INTRODUCTION

Levofloxacin is a broad-spectrum fluoroquinolone antibiotic that exhibits greater activity than its predecessor, ciprofloxacin (Fu et al., 1992; Majalekar & Shirote, 2020). It is commonly used for the treatment of bacterial infections of the skin, sinuses, kidneys, bladder, and prostate, and is also effective against *Escherichia coli* infections (McGregor et al., 2008).

An ideal therapeutic process requires the implementation of therapeutic drug monitoring (TDM), which ensures that plasma drug concentrations remain within the optimal range to achieve the desired pharmacological effect (Parke & Charles, 1998; Sandström et al., 2001; Shaker et al., 2013). Although TDM has not yet been widely applied in Indonesia, its use in antimicrobial therapy has been reported (Mabilat et al., 2020). Levofloxacin, in particular, demonstrates considerable interindividual variability in its pharmacokinetics. Therefore, TDM plays a crucial role in facilitating its optimal clinical use (van den Elsen et al., 2018).

However, the main limitations of TDM are its high cost and the discomfort associated with repeated blood sampling. Conventional pharmacokinetic data analysis requires a sufficient number of sampling points to adequately represent the absorption, distribution, and elimination phases in each individual, which restricts its routine implementation.

To overcome this limitation, population-based pharmacokinetic modeling using nonlinear mixed-effects modeling has been developed since the 1970s. Unlike the conventional two-stage approach, this method analyzes the entire dataset across the study population, thereby enabling pharmacokinetic evaluation even when limited data are available for each subject. The population-based approach provides more comprehensive information on absorption, distribution, and elimination kinetics (Sheiner et al., 1972; Mould & Upton, 2012).

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Several studies have investigated the pharmacokinetics of levofloxacin (Furlanut et al., 2003; Ghimire et al., 2019), including those employing population-based modeling. Recently, we conducted population pharmacokinetic modeling of levofloxacin following intravenous bolus injection and oral administration in rabbits (Nugroho et al., 2021). In the present study, we sought to identify the most appropriate compartmental model (Wastney et al., 1998) to describe the pharmacokinetic profiles of levofloxacin in healthy Indonesian volunteers using a population-based approach. In addition, the influence of several covariates on pharmacokinetic parameters was examined. Two widely used population pharmacokinetic tools, Monolix and NONMEM, were employed for model development and evaluation (Dartois et al., 2007; Chan et al., 2011).

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MATERIALS AND METHODS

Materials

Levofloxacin hemihydrate 500 mg film-coated tablets (Cravit®) were obtained from PT Kalbe Farma (Jakarta, Indonesia). Analytical grade levofloxacin and ciprofloxacin were purchased from Sigma-Aldrich (Buchs, Switzerland). Potassium dihydrogen phosphate, glacial acetic acid, phosphoric acid, acetonitrile, and methanol (analytical grade) were purchased from Merck (Darmstadt, Germany).

Methods

1. Pharmacokinetic study of levofloxacin

Eighteen healthy volunteers (10 males and 8 females) received a single Cravit® film-coated tablet containing 512.29 mg of levofloxacin hemihydrate, equivalent to 500 mg of levofloxacin anhydrous. Health status was confirmed based on medical evaluation, including

liver and kidney function, hematological and urine parameters, medical history, physical examination, blood pressure, heart rate, ECG, body weight, and the absence of viral infections (HCV, hepatitis B, and HIV). Blood samples (7 mL) were collected at the following time points: 0, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dosing. Samples were obtained through a peripheral vein using an Abocath, followed by withdrawal with a syringe. Plasma was separated in vacutainer tubes containing citrate anticoagulant and stored at –20°C in aluminum-wrapped glass tubes until analysis. The study protocol was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia (Ref. KE/FK/483/EC).

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2. Liquid chromatographic system

Levofloxacin concentrations were measured using a validated bioanalytical HPLC method. A 150 µL plasma sample was transferred to a centrifuge tube, spiked with 50 µL of ciprofloxacin (internal standard), and mixed with 800 µL of acetonitrile. Samples were centrifuged at 5000 rpm for 10 minutes using a TA-15-24-2 rotor (8.61 cm diameter). The resulting supernatant was transferred into vials. The residue was extracted again with 1000 µL of acetonitrile and centrifuged at 5000 rpm for 10 minutes. The combined supernatants were evaporated to dryness. The residue was reconstituted with 1000 µL of mobile phase and homogenized with a mechanical stirrer for 1 minute. The solution was filtered using a microsyringe filter, transferred to an autosampler vial, and injected into the HPLC system (injection volume: 20 µL). Chromatographic separation was achieved with a C18 stationary phase and a mobile phase consisting of acetonitrile, methanol, and 25 mM phosphate buffer pH

3.0 (13:7:80, v/v), at a flow rate of 1.5 mL/min. Levofloxacin detection was performed at 280 nm using a UV detector.

3. Data Analysis

Population pharmacokinetic analyses were performed using Monolix (version 2020R1, stand-alone, Windows 10) and NONMEM (version 7.43), supplemented with PLTTools (version 6, shareware). One- and two-compartment disposition models with and without lag-time were tested. In Monolix, analyses were conducted using template models with the SAEM algorithm. In NONMEM, analyses used the ADVAN6 TRANS1 TOL=5 method with FOCE with interaction. Bootstrap analysis (Nakashima et al., 2015) with 500 replication was applied in NONMEM to estimate the standard errors of population parameter predictions, which were not directly provided.

The one-compartment model included absorption rate constant (Ka), clearance (CL), and volume of distribution (Vd), with or without lag time (Tlag). The two-compartment model included Ka, CL, Vd, intercompartmental clearance (Q), and peripheral volume of distribution (V2). Covariate analyses considered sex, age, body weight, height, BMI, systolic and diastolic blood pressure, pulse rate, respiratory rate, total protein, albumin, bilirubin, SGOT, SGPT, urea, creatinine, hemoglobin, WBC count, lymphocytes, monocytes, eosinophils, basophils, hematocrit, RBC count, and platelets.

Model adequacy was evaluated by: (1) Visual inspection of individual fits with population and individual prediction curves; (2) Correlation between observed plasma concentrations (DV) and population model-predicted concentrations; and (3) Correlation between DV and individual model-predicted concentrations. These diagnostic evaluations were

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considered essential to assess the adequacy of the modeling approach (Mohammed et al., 2012; Owen & Fiedler-Kelly, 2014; Zheng et al., 2014).

RESULTS AND DISCUSSION

1. Determination of the best structural model for the pharmacokinetic profiles of levofloxacin after oral administration

The first step in the population-based analysis of levofloxacin pharmacokinetics was to identify the most appropriate structural model to adequately describe the data. Four structural models were tested: A) oral model with one dispositional compartment; B) oral model with one dispositional compartment including absorption lag time (Tlag); C) oral model with two dispositional compartments; and D) oral model with two dispositional compartments including Tlag.

The Monolix results are presented in Figure 1. Goodness-of-fit evaluations are shown in Panel A (correlation between observed and population-predicted plasma concentrations, Cp), Panel B (correlation between observed and individual post hoc-predicted Cp values), and Panel C (a representative individual fit). These plots clearly indicate that Model D—the oral model with two dispositional compartments and absorption lag time—provided the best description of the Cp data.

Beyond graphical assessments, the adequacy of the models was further evaluated using log-likelihood–based criteria. Monolix provided the objective function value (OFV), Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), and the corrected BIC (BICc). These values are summarized in Table 1. The inclusion of two additional parameters (Q and Vd2) in Model D led to substantial decreases in all criteria

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compared with Model B. The reductions in OFV, AIC, BIC, and BICc were 47.27, 39.27, 35.70, and 30.29, respectively, strongly supporting the superiority of the two-compartment lag-time model over the one-compartment model.

Moreover, the NONMEM analysis yielded a similar conclusion regarding the adequacy of Model D in best describing the plasma concentration (Cp) profiles of levofloxacin. The results are presented in Figure 2, Panel A (correlation between the observed and predicted population Cp values), Panel B (correlation between the observed and predicted post hoc Cp values), and Panel C (a representative example of individual fitting). These plots collectively demonstrate the adequacy of Model D in capturing the observed Cp data.

The log-likelihood–based parameter values obtained from NONMEM analyses (i.e., OFV, AIC, BIC, and BICc), shown in Table 1, further support the adequacy of Model D. The decreases in OFV, AIC, BIC, and BICc from Model B to Model D were 51.29, 45.29, 42.61, and 37.2, respectively. These reductions highlight the superiority of the two-compartment disposition model with absorption lag time in describing the levofloxacin data.

The determination of the levofloxacin pharmacokinetic profile using this two-compartment disposition model with absorption lag time is consistent with our previous investigation in rabbits (Nugroho et al., 2021). In contrast, several pharmacokinetic studies in humans, both in patients and healthy volunteers, have reported that a one-compartment disposition model provides an adequate fit (Kervezee et al., 2016; Tanigawara et al., 1995). Such discrepancies may be attributed to several factors, including differences in study focus. Unlike the present study, those investigations did not systematically compare

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alternative pharmacokinetic models.

2. Analyses of covariates in the pharmacokinetic profiles of levofloxacin

After identifying the best structural model, covariate analyses were conducted to further refine the population-based modeling of levofloxacin plasma concentration (Cp) data.

In Monolix, covariate selection was performed using the statistical test and proposed model features. Based on the lowest p-values for correlations between covariates and model parameters, AGE was identified as a significant covariate for Ka, while HEIGHT was identified for Vd. Both covariates were incorporated as log-transformed values. The goodness-of-fit evaluation after incorporating these covariates is presented in Figure 3 (Part I). Compared with the covariate-free model, the correlation between observed and predicted Cp values improved, as indicated by a more random distribution of data points around the line of identity. A comparison between Figure 1, Panel A (Model D) and Figure 3 clearly shows this improvement.

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In NONMEM, automated univariate covariate searches in PLTTools were employed, using an exponential screening process. The selection was based on statistical criteria, including p-value, slope, and correlation coefficient (r). Consistent with Monolix, AGE and HEIGHT were identified as significant covariates for Ka and Vd, respectively. As with the Monolix results, incorporating these covariates led to a more random distribution of residuals around the identity line (Figure 3, Part II).

Interestingly, in this study HEIGHT exerted a more prominent influence on

population-based Vd than WEIGHT or other covariates. Typically, WEIGHT is the variable most often reported to correlate with Vd or related pharmacokinetic parameters (Maharaj et al., 2021; Zheng et al., 2018). Whether this finding reflects a unique characteristic of the healthy Indonesian volunteer population or is due to other factors remains uncertain, and further studies are required to confirm this observation.

Based on these results, the oral two-compartment model with lag time (Tlag), incorporating AGE and HEIGHT as covariates, was considered the best model for describing the levofloxacin pharmacokinetic profile. The estimated population parameter values (Ka, Vd, CL, Q, and Vd2) are presented in Table 2, while individual parameter estimates from post hoc analyses are summarized in Table 3. Both population and individual results demonstrated strong agreement between Monolix and NONMEM, underscoring the comparable performance of the two software platforms. This finding highlights the potential of Monolix as a user-friendly and freely available alternative to NONMEM for academic use.

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Furthermore, both Monolix and NONMEM produced consistent estimates of pharmacokinetic parameters (mean ± SD): Tmax of 0.72 ± 0.16 and 0.76 ± 0.15 hours, and Cmax of 6.31 ± 1.34 and 6.59 ± 1.48 µg/mL, respectively. These values are comparable with previous reports. For instance, Wagenlehner et al. (2006) reported a Tmax of 1.4 ± 0.5 hours and a Cmax of 6.1 ± 1.2 µg/mL in 14 volunteers receiving a single dose of levofloxacin. Similarly, Galán-Herrera et al. (2009) investigated two tablet formulations in healthy volunteers, reporting Tmax values of 1.31 ± 0.50 and 1.21 ± 0.67 hours, and Cmax values of 9.33 ± 2.43 and 9.32 ± 2.58 µg/mL for the test and reference formulations, respectively. Such comparisons confirm the adequacy and external validity of the

population-based pharmacokinetic analyses performed in this study using both Monolix and NONMEM.

CONCLUSION

The plasma concentration–time profiles of levofloxacin in healthy Indonesian volunteers following oral administration were adequately described by a population pharmacokinetic model using a two-compartment open model with absorption lag time. AGE and HEIGHT were identified as significant covariates influencing the pharmacokinetic parameters in the population-based analyses. Monolix demonstrated comparable performance to NONMEM in describing the levofloxacin data. The estimated Tmax and Cmax values obtained from both Monolix and NONMEM were consistent with those reported in previous studies, thereby confirming the adequacy of the population-based approach. These findings underscore the potential of Monolix as a freely available and user-friendly alternative to NONMEM, which may encourage broader adoption of population-based pharmacokinetic modeling in Indonesia.

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Table 1. The likelihood parameter values in population-based modeling of levofloxacin pharmacokinetic profiles following peroral administrations using Monolix and NONMEM.

	Monolix				NONMEM			
Criterion	1 Comp	1 Comp - Tlag	2 Comp	2 Comp - Tlag	1 Comp	1 Comp - Tlag	2 Comp	2 Comp - Tlag
-2 x log-likelihood (OFV)	833.84	654.73	812.17	607.46	340.62	173.34	318.25	122.05
Akaike Information Criteria (AIC)	849.84	674.73	836.17	635.46	356.62	193.34	338.25	148.05
Bayesian Information Criteria (BIC)	856.96	683.63	846.86	647.93	363.74	202.24	347.15	159.63
Corrected Bayesian Information Criteria (BICc)	870.50	699.88	865.81	669.59	377.28	218.49	366.11	181.29

Table 2. Population pharmacokinetic parameter estimates of levofloxacin obtained using Monolix and NONMEM.

Parameter	Monolix		NONMEM	
	Mean	SE	Mean	SE*
Ka	4.04	0.52	3.83	0.03
Vd	48.26	12.3	48.63	0.33
Cl	9.00	0.39	8.91	0.02
Vd2	47.45	13.26	45.75	0.31
Q	62.12	52.69	44.04	0.31
T_{lag}	0.20	0.024	0.18	0.001
Ka.Age	1.61	1.07	2.24	0.03
Vd.Height	3.79	1.31	1.60	0.06

* Estimated based on the Bootstrap analyses (n=500)

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Table 3. Individual pharmacokinetic parameter estimates of levofloxacin obtained using Monolix and NONMEM.

ID	Tlag		ka		Cl		Vd		Q		Vd2	
	Monolix	NONMEM	Monolix	NONMEM	Monolix	NONMEM	Monolix	NONMEM	Monolix	NONMEM	Monolix	NONMEM
1	0.23	0.25	3.52	3.45	8.30	8.20	50.66	50.69	61.63	44.04	46.64	46.92
2	0.15	0.16	6.77	5.70	10.82	10.90	46.27	39.48	40.49	44.04	55.62	60.81
3	0.31	0.31	3.12	3.44	10.67	10.40	59.06	70.07	64.22	44.04	78.68	76.49
4	0.28	0.30	2.53	2.68	8.87	8.80	49.66	42.37	36.34	44.04	46.95	55.32
5	0.20	0.17	3.70	4.02	11.52	11.21	64.41	98.24	142.72	44.04	60.21	37.35
6	0.39	0.46	3.74	3.84	7.93	7.98	43.55	38.18	41.74	44.04	44.33	50.48
7	0.16	0.18	4.37	4.43	9.51	9.49	58.94	55.37	46.25	44.04	54.69	60.74
8	0.19	0.21	3.59	3.63	8.48	8.57	51.80	51.48	62.46	44.04	34.58	33.43
9	0.14	0.14	3.61	3.82	8.42	8.33	71.26	82.87	86.65	44.04	45.73	37.39
10	0.18	0.17	3.47	3.27	8.91	9.04	61.47	65.07	77.61	44.04	58.05	54.12
11	0.26	0.27	6.30	5.90	8.89	8.88	44.33	50.36	64.28	44.04	51.29	49.50
12	0.09	0.07	10.17	7.93	7.81	7.85	42.40	53.50	107.87	44.04	46.03	36.85
13	0.25	0.30	4.61	4.82	9.40	9.42	44.25	44.76	46.87	44.04	36.57	37.24
14	0.26	0.27	2.49	2.87	8.63	8.60	48.82	64.26	72.06	44.04	69.15	60.52
15	0.22	0.24	3.84	3.84	11.03	10.93	42.49	44.25	52.77	44.04	59.54	62.38
16	0.14	0.14	2.92	3.42	8.34	8.25	37.48	46.87	75.19	44.04	35.38	28.21
17	0.13	0.13	3.88	4.03	8.35	8.32	34.67	36.08	52.00	44.04	35.25	34.59
18	0.37	0.38	4.91	4.63	7.46	7.51	34.78	35.08	66.13	44.04	25.76	24.08

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Table 4.. Estimated values of Tmax and Cmax of levofloxacin analyzed using Monolix and NONMEM.

Parameter	Monolix estimation, n=18	NONMEM estimation, n=18	Wagenlehner et al. study, n=14 (2006)	Test formulation, n=25 (Galan-Herrera et al., 2009)	Reference formulation, n=25 (Galan-Herrera et al., 2009)
Tmax (hour)	0.72 ± 0.16*	0.76 ± 0.15*	1.4 ± 0.5	1.31 ± 0.50	1.21 ± 0.67
Cmax (μg/mL)	6.31 ± 1.34*	6.59 ± 1.48*	6.1 ± 1.2	9.33 ± 2.43	9.32 ± 2.58

* The estimated values of Tmax and Cmax (mean ± SD) in Monolix and NONMEM were calculated from simulated Cp profiles (in 18 subjects) based on individual predicted pharmacokinetic parameters (Tlag, Ka, CL, Vd, Q, and Vd2) using the *linpk* package in R software.

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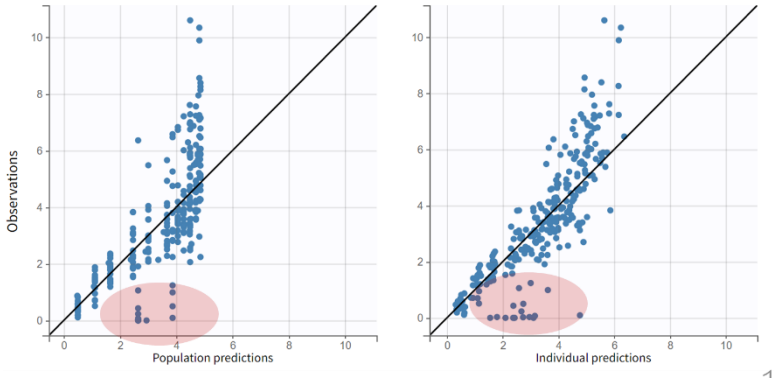
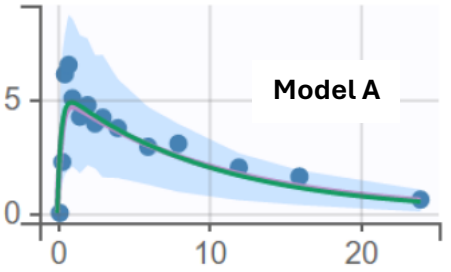
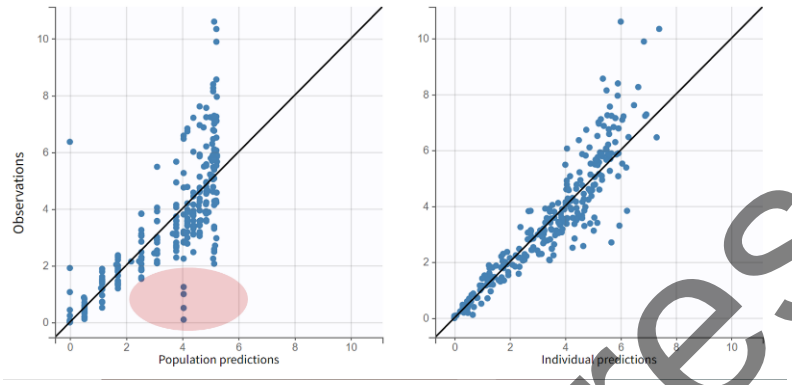
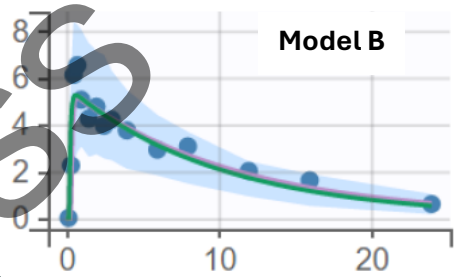
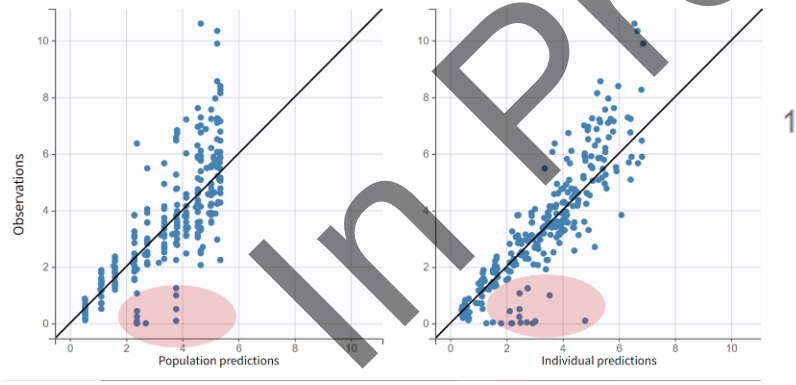
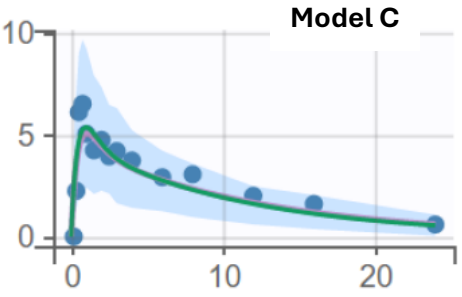

Observations
Population predictions
Individual predictions

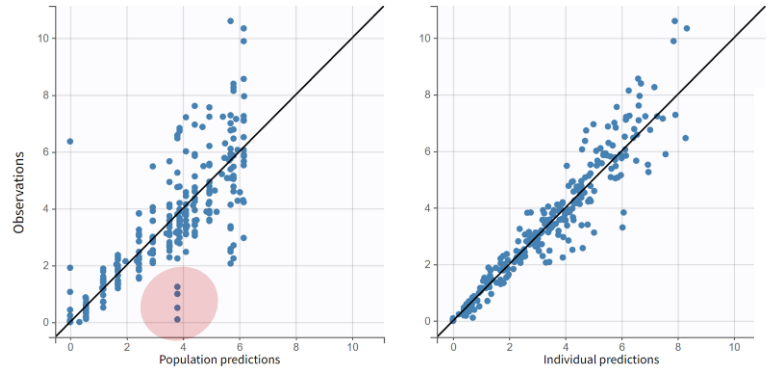

Model A


Observations
Population predictions
Individual predictions


Model B


Observations
Population predictions
Individual predictions


Model C


Observations
Population predictions
Individual predictions

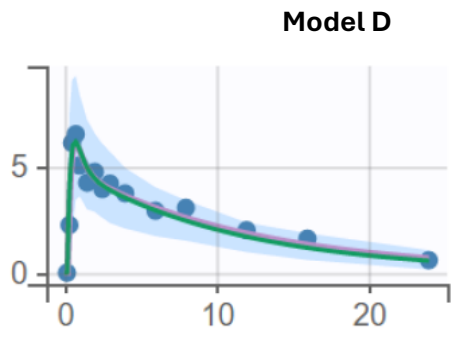

Model D

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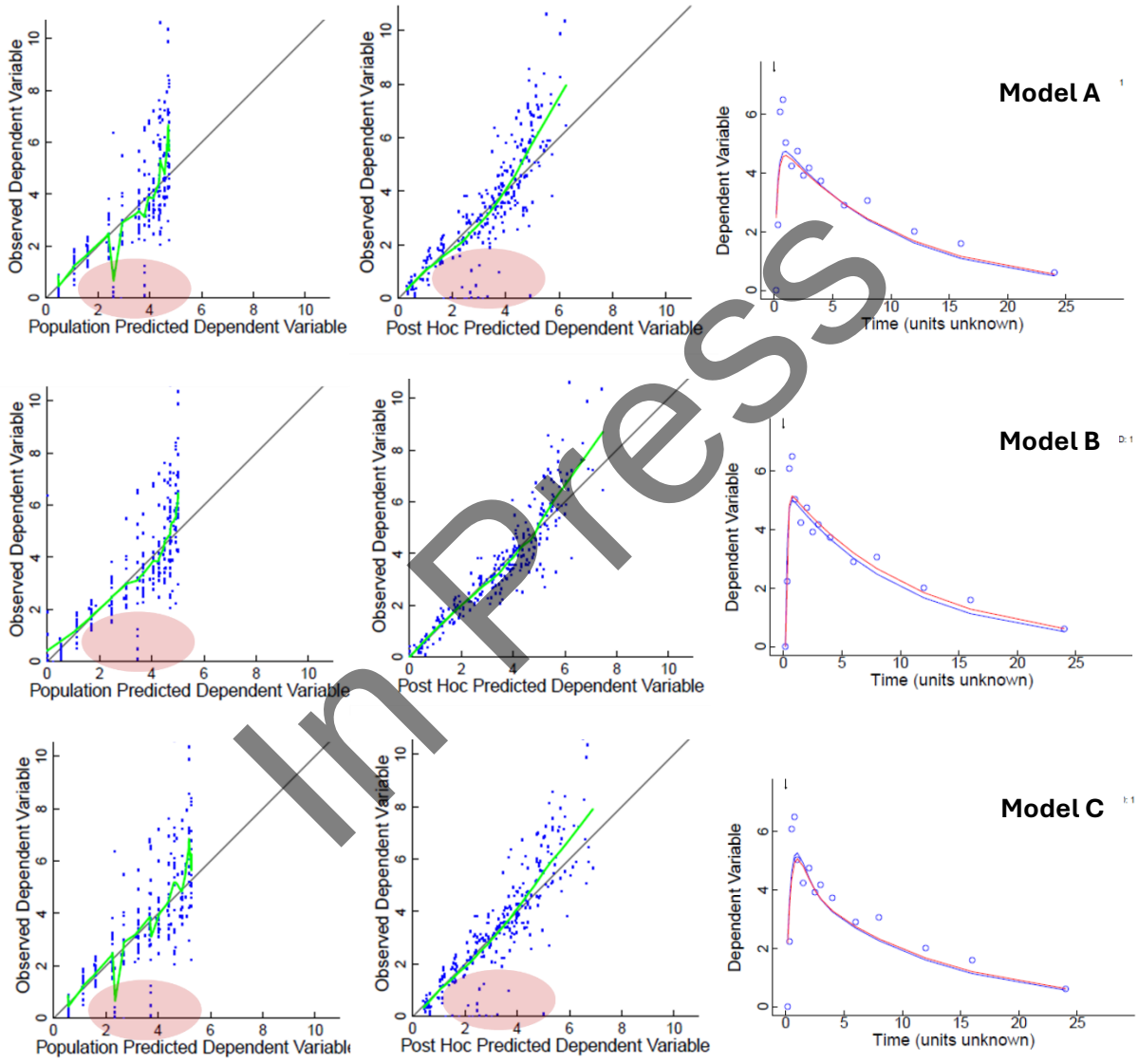
Figure 1. Population modeling of levofloxacin pharmacokinetic profiles based on Models A, B, C, and D using Monolix. Panel A and Panel B: correlations between the observed and predicted population Cp values, and between the observed and predicted post hoc individual Cp values, respectively. Panel C: a representative example of the individual data analysis. The red spot indicates a data fitting discrepancy.



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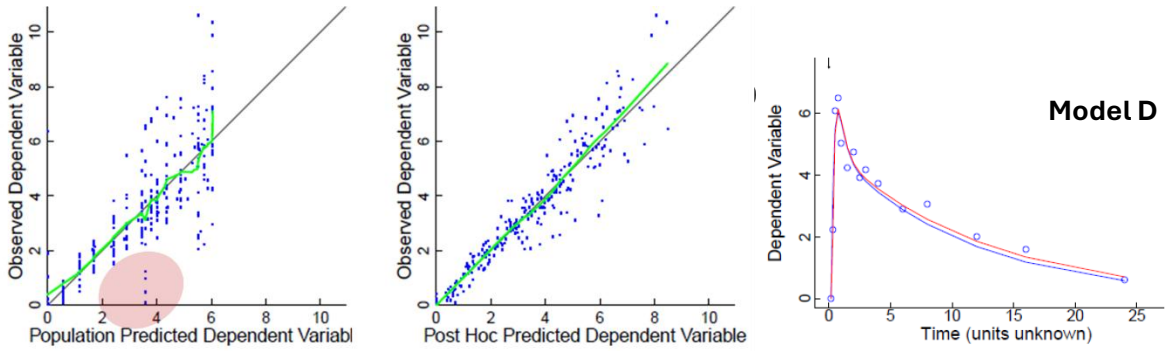

Figure 2. Population modeling of levofloxacin pharmacokinetic profiles based on Models A, B, C, and D using NONMEM. Panel A and Panel B: correlations between the observed and predicted population Cp values, and between the observed and predicted post hoc individual Cp values, respectively. Panel C: a representative example of individual data analysis. The red spot indicates a data fitting discrepancy.

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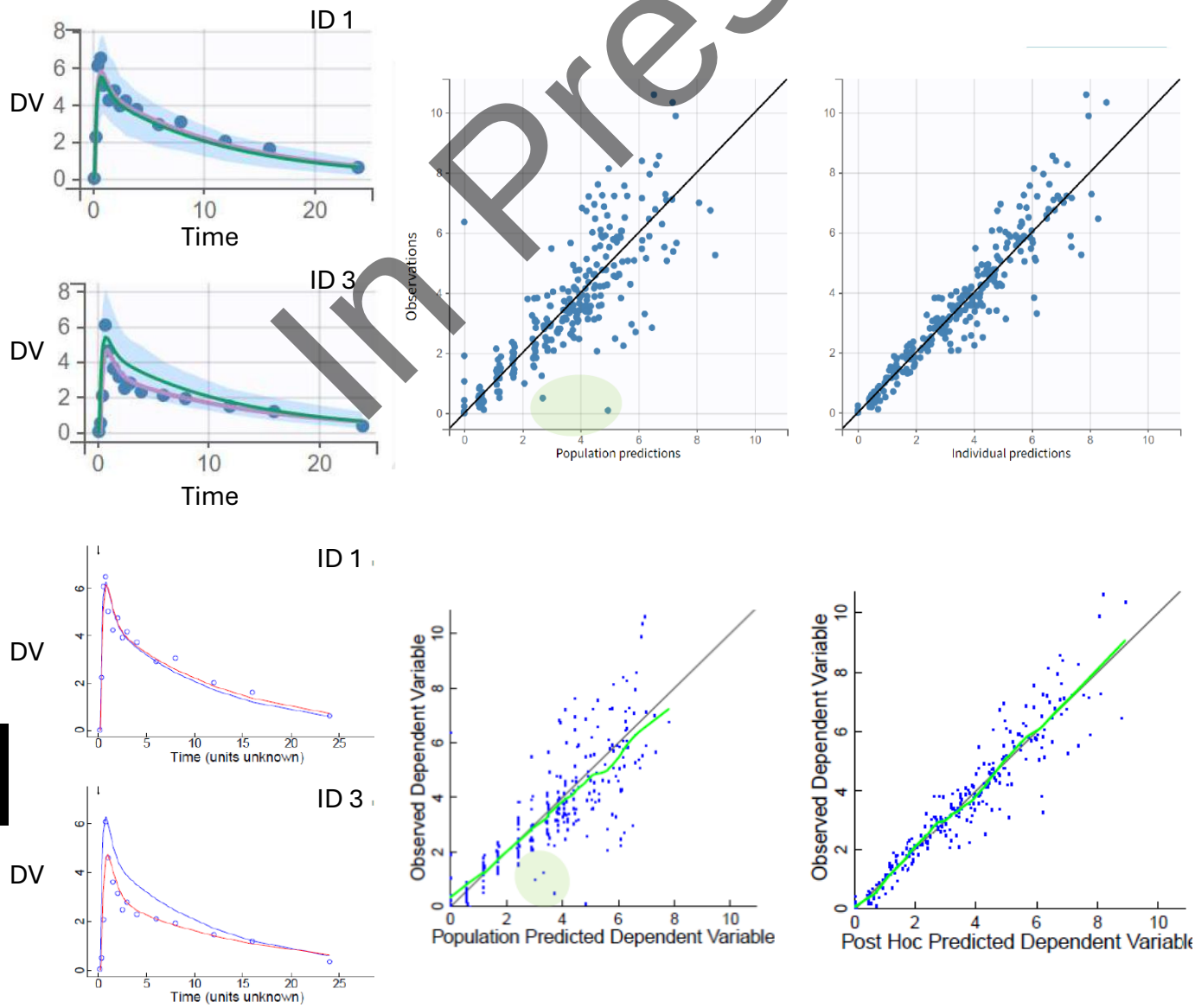

Figure 3. Population modeling of levofloxacin pharmacokinetic profiles based on Model D using Monolix (Part I) and NONMEM (Part II), with Age and Height included as covariates for Ka and Vd, respectively. Panel A: a representative example of individual data analysis. Panel B: correlations between the observed and predicted population Cp values and between the observed and predicted post hoc individual Cp values. The green spot indicates an improvement in data fitting.

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