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ORIGINAL RESEARCH

Parametric Population Pharmacokinetics Model Repository of Rifampicin: Model-Informed Individualized Therapy

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Introduction: Rifampicin is a crucial first-line anti-tuberculosis drug that has been extensively studied through population pharmacokinetic (popPK) analyses. This study aims to construct a comprehensive rifampicin popPK model repository to support model-informed individualized therapy.

Methods: A systematic review was conducted using PubMed, Web of Science, and Embase databases up to September 2023 to retrieve popPK model articles on rifampicin. Extracted data included basic information, dosing regimens, sampling strategies, model parameters, and covariate details. Non-English studies, non-parametric models, and duplicates were excluded. The repository was built using R package mrgsolve, and a Shiny application was developed for simulation and individualized dosing predictions.

Results: A total of 29 studies were included in the rifampicin model repository: 23 on adults, 5 on pediatrics, 1 on both populations, and 1 on pregnant women. Most rifampicin popPK models were one-compartment linear elimination models, with transit compartment or lagged absorption models improving drug absorption fitting. An allometric growth model based on fat-free mass (FFM) might improved model fit. Postmenstrual age (PMA) significantly impacted elimination in pediatric patients. All models underwent internal validation, with three studies validated externally. Significant variations in exposure predictions were observed among models, indicating challenges in achieving therapeutic targets under standard treatment.

Discussion: The model repository provides a comprehensive resource for exploring various models and their application in different populations, supporting individualized rifampicin therapy. Further research is needed for special populations and to determine whether weight or FFM is more rational for dosing. External validation is essential for model development.

Keywords: rifampicin, model-informed precision dosing, population pharmacokinetics

Introduction

Despite significant therapeutic advances in the global fight against tuberculosis (TB), a notable proportion of patients still experience treatment failure due to issues related to drug safety and efficacy, with drug resistance remaining a persistent challenge.[1] According to the World Health Organization's standard treatment regimen, rifampin (RIF) is a crucial first-line anti-TB drug. It binds to the beta subunit of the mycobacterial DNA-dependent RNA polymerase enzyme, inhibiting transcription.

Pharmacokinetics (PK) plays an essential role in optimizing the therapeutic potential of drugs. For medications with a narrow therapeutic window or a high risk of developing resistance, such as rifampicin, strict control of drug exposure within the therapeutic window can reduce the occurrence of adverse events and delay the onset of resistance. The peak

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concentration (C_{max}) of RIF can be detected 2 hours after oral administration, with approximately 20–30% of free unbound RIF remaining in plasma.[2] RIF is approximately 70% bioavailable, and its absorption is modestly reduced by food intake.[3] Prior research has implicated factors such as the hepatic organic anion transporter SLCO1B1, arylacetamide deacetylase (AADAC), auto-induction, non-cytochrome P450 pathways, gender, age, body weight, dietary status, alcohol consumption, concomitant diseases (eg, HIV, diabetes mellitus), and concomitant medications as potential sources of variability in rifampicin exposure, although their clinical significance remains uncertain.[4–7] Due to the relatively narrow therapeutic range of rifampicin (8–24 mg/L) and the significant inter-individual variation in its PK properties, treatment outcomes may be affected, potentially contributing to the development of drug resistance.[8]

The recommended dosing for RIF is typically weight-based: 15 mg/kg (range 10–20) for children under 10 years old and 10 mg/kg for individuals 10 years and older. In clinical practice, RIF is usually administered orally at a standard dose of 600 mg.[9] However, relying solely on body weight for dose adjustment or evaluating efficacy based solely on C_{max} within 2 hours after administration may be insufficient. Population pharmacokinetic (popPK) modeling addresses these limitations by systematically quantifying interindividual variability in drug disposition through demographic, genetic, and physiological determinants of absorption, distribution, metabolism, and excretion (ADME).[10] These models face inherent challenges stemming from heterogeneous data sources - geographic disparities, ethnic diversity, lifestyle patterns, and comorbidity profiles often lead to divergent covariate selections across studies. While demonstrating strong predictive performance within their original study populations, such models encounter generalizability constraints when extrapolated to external cohorts. Using popPK's maximum a posteriori Bayesian simulation method, Area under the concentration curve (AUC) and C_{max} exposure for patients can be predicted by combining drug concentration measurements with the matched model, allowing for the development of comprehensive dose adjustment strategies for individual patients. Notably, the clinical relevance of selected covariates (even when overlapping between models) requires rigorous validation, particularly given the potential discordance in covariate inclusion strategies across different modeling frameworks.

Previous reviews of RIF popPK models have been limited by search strategies and timeframes, which have led to the omission of certain models and a lack of comprehensive exposure comparisons between the models included.[11] Additionally, no user-friendly clinical tools have been developed to facilitate individualized dosing in routine practice. To address these gaps, this study aims to systematically review and summarize existing RIF popPK models, identify key covariates influencing PK variability, compare PK profiles between models, and establish a comprehensive RIF popPK model repository for further analysis. Furthermore, we aim to develop a Shiny application for RIF model simulations to enable individualized dose adjustments and enhance clinical decision-making. Special attention will be given to the application of popPK models in vulnerable populations, such as children and pregnant women, where dosing optimization remains a critical challenge.

Methods

Search Strategy

A systematic search of PubMed, Web of Science, and Embase databases was conducted from their inception to September 23, 2023, for the initial retrieval. To ensure the inclusion of the most recent and relevant studies, a supplementary search was performed up to February 26, 2025. The search terms included MeSH terms (Medical Subject Headings) and Entry terms. Two authors conducted the literature screening work in parallel. The paper management software used was EndNote (Version 20; Thomson Scientific, Box Hill, Victoria, Australia).

Inclusion criteria were as follows:

(1) Study population: human (with the majority being TB patients);
(2) Modelling approach: parametric nonlinear mixed-effects model;
(3) Languages: published in English.

Exclusion criteria were as follows:

(1) Type of paper: reviews or methodology articles;
(2) Duplicated studies;
(3) Model established with nonparametric methods;
(4) Lack essential PK parameters;
(5) Complex PK features: auto-induction.

The inclusion and exclusion criteria were established based on the standards for constructing the model repository, aiming to facilitate horizontal comparison of similar models and ensure the reproducibility of the models.

Data Extraction

Two authors independently extracted the following information from eligible articles: (1) baseline data, including demographic data and laboratory test data (eg country, age, body weight, sex, etc).; (2) study characteristics: treatment regimens, sample counts, bioanalytical methods, the lower limit of quantification, etc.; (3) popPK characteristics: model parameters and formulation, structural models, covariates, methods used to identify and incorporate covariates, inter-individual variability, inter-occasion variability (IOV), and residual unexplained variability (RUV).

Literature Quality Assessment

The assessment of the quality of the included studies was performed by utilizing a 33-item checklist, consisting of 5 categories, according to a previously published popPK assessment method.[12–14] This checklist was designed to assess the essential components necessary for the reporting of clinical pharmacokinetic (PK) studies. For each item, one point received if the involved study met the criteria, whereas incomplete data were assigned 0.5 points. If the item did not meet the criteria, it was assigned 0 points. To evaluate the quality of each population pharmacokinetic (popPK) study, compliance was calculated using the following equation i:

$$Compliance(\%) = \left(\frac{sum\ of\ items\ reported}{sum\ of\ all\ items}\right) * 100\% \tag{1}$$

Comparison of the Retrieved Study

In our study, we summarized the covariates that affect both clearance (CL) and volume of distribution (Vd). However, since CL is considered the most critical pharmacokinetic parameter, we placed particular emphasis on examining how covariates affect rifampicin clearance. To facilitate comparison, continuous covariates were standardized to the same range, whereas binary covariates, such as HIV status, were coded as 0 for negative and 1 for positive. The minimum and maximum CL values were determined based on the range of covariates identified in each study. The median covariate values were normalized against to the reference value of CL, and the effect of covariates on CL was expressed as a percentage of the CL range divided by the CL reference value for each study. A forest plot was used to summarize and compare the identified covariates' impact on CL. The covariate effects were calculated as follows: the maximum effect was determined using Equation ii, and the minimum effect was determined using Equation iii:

$$Covariate\ max\ effect = \left(\frac{The\ Maximum\ CL}{Reference\ CL}\right) * 100\% \tag{2}$$

$$Covariate\ min\ effect = \left(\frac{The\ Minimum\ CL}{Reference\ CL}\right) * 100\% \tag{3}$$

A change in CL within the 80% to 125% range was considered clinically insignificant according to bioequivalence standards.[12,13,15]

Monte Carlo Simulation

To assess the statistical and structural models of the popPK studies, Monte Carlo simulations of concentration-time profiles were performed, and visual predictive distributions (VPDs) were generated. It was assumed that the published models were sufficient to describe the data, and a predictive distribution of the simulated rifampicin concentration for each model would adequately represent the original data and its significant features. The MrgSolve package (version 1.1.1, https://mrgsolve.org) was utilized for solving and simulating ODE-based models. One thousand virtual patients were simulated for each identified study, and the concentration-time profiles were plotted using R software (version 4.2.2) according to the popPK model.

The VPDs incorporated the effects of body weight (BW)/Fat-free Mass (FFM), and postmenstrual age for neonates. Virtual patients were defined as infants (14/11kg, 2 years) or adults (60 kg/46 kg). The conversion between BW and FFM was referenced from the study by Kyle et al, and the age group stratification was used solely for horizontal comparison of exposure within the same population.[16] Oral administration of 600 mg QD for adults or 150 mg QD for infants, based on existing treatment standards.[8,9,17] The PK studies of RIF, as summarized in the earlier research by Abulfathi et al,[18] indicate that the half-life of RIF post-administration ranges from 0.6 to 6.5 hours. In some individuals, there may be accumulation with repeated dosing. Considering the maximum half-life of 6.5 hours, it can be assumed that steady-state is achieved after 5 to 6 doses. Therefore, in this simulation, RIF is assumed to be administered consecutively for 7 doses, and the PK profile of the last dose is observed to assess its systemic exposure.

Model Simulation Software

Using the Shiny package (version 1.7.1. https://CRAN.R-project.org/package=shiny) and MrgSolve package, a rifampicin model repository was integrated into a simulation app. This app allows users to input patient age, BW/ FFM, sex, select the target model, and input the intended dosing regimen. Through Bayesian simulation techniques, we generated exposure predictions that reflect the typical values within a population, along with prediction intervals that account for IIV and IOV as reported in the literature.

Results

Study Identification

A total of 2278 studies were initially identified, comprising 628 articles from PubMed, 561 articles from Embase, 1089 articles from Web of Science. Subsequently, 30 articles were selected for the model repository. A supplementary search conducted up to February 26, 2024, identified one additional study, resulting in a final total of 31 articles included in the analysis. The flowchart illustrating the screening process for the initial search is provided in the supplementary material (Figure S1), and the detailed search strategy is summarized in Table S1.

The quality assessment results of retrieved studies are shown in Figure 1 and Table S2. The quality evaluation was generally good, with an average compliance of 88.31% (78.8–93.9%). There was no significant publication bias observed. However, most studies did not report: (1) missing data handling methods (22/31); (2) statistical methods and software (18/31); (3) covariate inclusion description was incomplete (15/31); (4) schematic of the final model (22/31); and (5) summary of the model-building process and the derived final model (30/31).

Literature Characteristics

Basic Characteristics

The publication years of the included studies ranged from 2008 to 2024. The majority of subjects across the studies were diagnosed with tuberculosis, with 24 studies focused on adults,[5,19–42] 6 on pediatrics,[43–48] 1 on pregnant women,[22] and 1 on both adults and pediatrics.[36] In addition, 13 studies enrolled patients with HIV, and 4 studies included patients with diabetes. Plasma RIF concentrations were determined using either liquid chromatography with ultraviolet detection or mass spectrometry, with lower limits of quantification ranging from 0.008 to 0.5 mg/L. Detailed characteristics of the included studies are provided in Table 1. Savic did not report key demographic information for inclusion of pediatric patients and did not conduct follow-up simulation comparisons.[48]

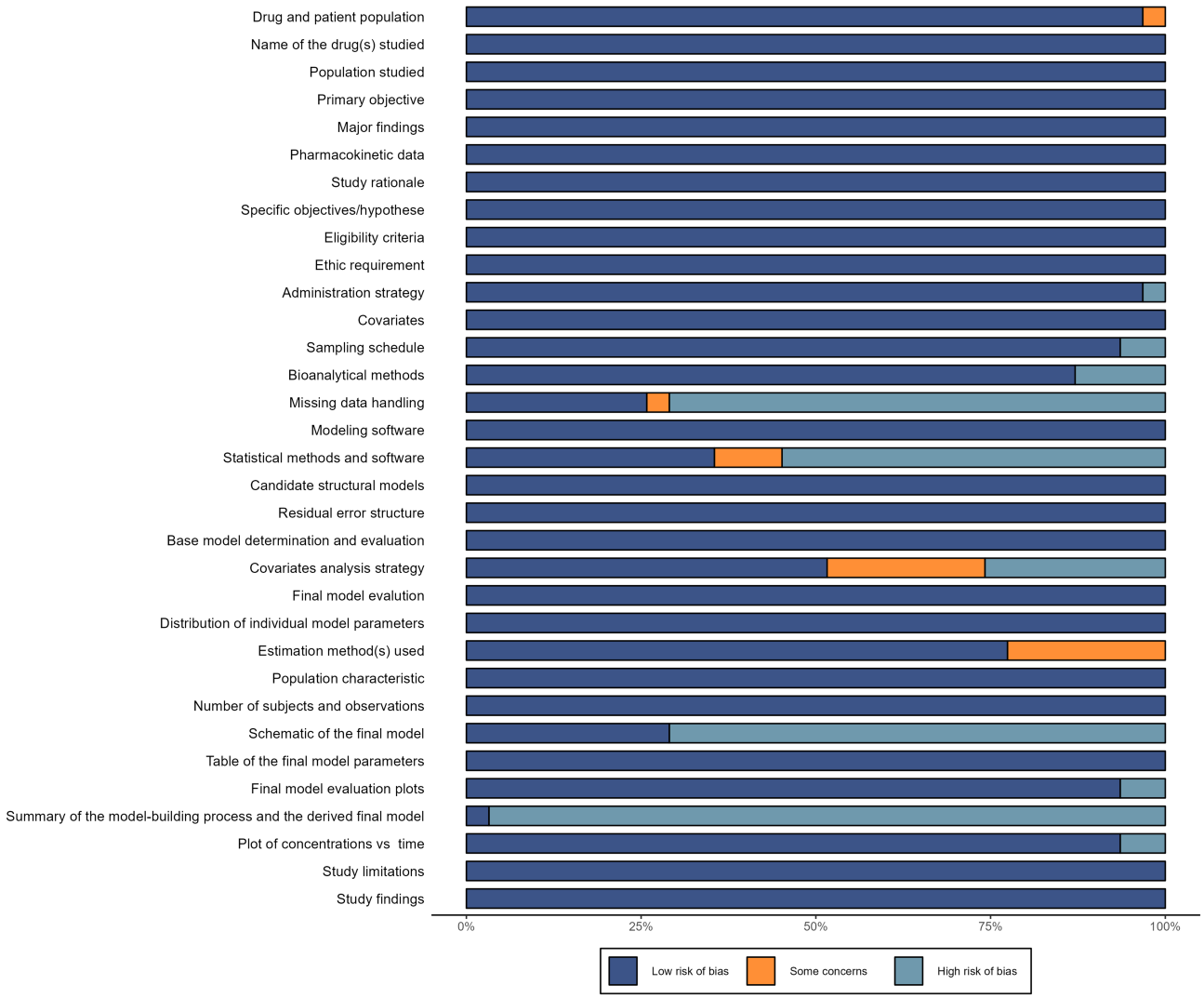

Figure 1 Risk-of-bias assessments of rifampicin popPK studies.

Population Pharmacokinetic Characteristics

Twenty-seven popPK models were conducted using NONMEM (Icon, Dublin, Ireland), 3 studies based on Monolix (Lixoft, Antony, France), and 1 study based on Phoenix NLME (Certara Inc, Princeton, USA). The first-order conditional estimation with the η-ε interaction (FOCE-I) was the most commonly used algorithm. Twenty-eight studies described the PK of RIF using a one-compartment model with first-order absorption and elimination, while only three studies used a two-compartment model. At high doses, the systemic exposure of RIF exhibits a dose-dependent increase.[41] Most models included transit compartments or lag time (Tlag) during the absorption period. The allometric growth model was used in all pediatric popPK models, and PMA had a significant effect on CL. The model characteristics and PK parameters of all studies are presented in Table 2.

Inter-individual variability (IIV) was described by an exponential model in all studies. Residual unexplained variability (RUV) was described by proportional models in 8 studies, additive models in 6, and combined proportional and additive models in 16 studies. All proportional RUV values were less than 50%, whereas additive RUV ranged from 0.0032 to 2.256. Some studies reported the existence of inter-occasion variability (IOV) in Ka, bioavailability (F), Tlag, and model transit time (MTT).

All models were evaluated internally with visual predictive check (VPC), bootstrap, and goodness-of-fit (GOF) plots as the most commonly used methods. One study employed the normalized prediction distribution error (NPDE). Only

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Table 1 Characteristics of Included RIF popPK Studies

Study (Publication year)	Country	Number of subjects (M/F)	Sample counts	Sampling Frequency	Sampling schedule (h)	Age (Years) Mean ± SD Median [Range]	Weight (Kg) Mean ± SD Median [Range]	Fat-Free Mass (Kg) Mean ± SD Median [Range]	Subject characteristics	Dose [Range]	Bioassay [LOQ] (mg/L)
Abdelgawad (2022)[19]	South Africa	108 (65/43)	632	5.85	0, 1, 2.5, 4, 6, 8 (day 3)	36.0 [32.0–42.0]	56.0 [49.0–62.0]	43.0 [38.0–49.0]	Pulmonary tuberculosis HIV Adult	300	LC-MS/MS 0.117
Aruldhas (2019)[43]	India	41 (29/12)	284	7.28	1, 0.5, 1, 1.5, 2, 2.5, 4, 6 (steady state)	7.0 [3.5–13.0]	19.5 [13.7–33.7]	NR	Pulmonary tuberculosis Children	6–10 kg: 75 11–17 kg: 150 18–25 kg: 225 26–30 kg: 300	HPLC-UV 0.04
Chang (2015)[20]	South Korea	54 (20/34)	206	3.81	1, 2, 4, 6 (day 7)	55.0 [20.0–92.0]	53.96 ± 8.563	NR	Pulmonary tuberculosis Diabetes Mellitus Adult	450–600	LC-MS/MS NA
Chirehwa (2016)[21]	South Africa	61 (28/33)	1342	22.00	0, 1, 2, 4, 6, 8, 12 (days 1, 8, 15 and 29)	32.0 [18.0–47.0]	55.2 [34.4–98.7]	42.2 [28.0–57.6]	Pulmonary tuberculosis Adult	30–37 kg: 300 38–54 kg: 450 55–70 kg: 600 >70 kg: 750	NA 0.1
Denti (2016)[22]	South Africa	33 (0/33)	183	5.55	0, 2, 4, 6, 8 (days 1 and 42)	28.0 [26.0–30.0]	67.0 [60.0–77.0]	NR	Pulmonary tuberculosis Pregnancy HIV Adult	600	LC-MS/MS 0.117
Denti (2022)[44]	Malawi South Africa	180 (106/74)	841	4.67	NR	2.03 [0.219–11.9]	10.9 [3.20–28.8]	8.4 [2.76–22.7]	Pulmonary tuberculosis HIV Children	40–300	LC-MS/MS 0.117
Gao (2021)[23]	ChiNR	217 (147/70)	1272	5.86	1, 2, 4, 6, 8 (day 14)	41.0 ± 10.6	52.13 ± 9.7	NR	Pulmonary tuberculosis Diabetes Mellitus Adult	450–600	LC-MS/MS 0.01
Horita (2018)[45]	GhaNR	113 (63/48)	558	4.94	0, 1, 2, 4, 8	5.0 [2.17–8.25]	14.3 [9.7–20.1]	NR	Pulmonary tuberculosis HIV Children	132–378	LC-MS/MS 0.117
Jeremiah (2014)[24]	Tanzania	100 (58/42)	574	5.74	2, 4, 6 (days 7 and 60)	35.0 [29.5–40.0]	NR	NR	Pulmonary tuberculosis HIV Adult	<50 kg: 450 >50 kg: 600	LC-MS/MS 0.117
Jing (2016)[25]	ChiNR	54 (35/19)	95	1.76	0, 1, 2, 4, 6, 8, 10, 12	46.9 ± 20.3	58.6 ± 9.0	NR	Pulmonary tuberculosis Adult	150–450	HPLC 1.25
Karballaei (2022)[26]	Iran	29 (NR)	406	14.00	0, 1, 2, 4, 8, 12, 24	55.0 [27.0–81.0]	NR	NR	Pulmonary tuberculosis Adult	1200	HPLC-UV 0.1

Kim (2021)[27]	South Korea	105 (70/35)	300	2.86	0, 0.5, 1, 2, 4, 6, 9, 12	55.4 ± 18.6	NR	NR	Pulmonary tuberculosis Adult	450–600	HPLC 0.1
Kloprogge (2020)[28]	Malawi	154 (107/47)	NR	3.00	0, 2, 6 (day 14 or 21)	30 [17.0–61.0]	52 [34.0–74.0]	NR	Pulmonary tuberculosis HIV Adult	150	HPLC-UV 0.015
Marsot (2017)[29]	France	62 (46/16)	103	1.66	Steady state	57.4 [20.0–89.0]	72.3 [46.0–119.0]	NR	Pulmonary tuberculosis Adult	300	HPLC-UV 0.5
Medellin (2020)[30]	Mexico	56 (32/24)	329	5.88	0.3, 0.6, 1, 1.5, 2, 2.5, 4, 6, 8, 12	47.5 [20.0–72.0]	55.5 [33.5–108.0]	NR	Pulmonary tuberculosis Diabetes Mellitus Adult	<50 kg: 450 >50 kg: 600	HPLC [0.1]
Milán (2013)[31]	Mexico	94 (57/37)	602	6.40	0.3, 0.6, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24	37.67 [18.0–91.0]	59.96 [34.0–89.0]	NR	Pulmonary tuberculosis Adult	<50 kg: 450 >50 kg: 600	HPLC [0.1]
Mukonzo (2020)[32]	Uganda	25 (21/4)	150	6.00	0, 1, 2, 4, 6, 12 (>day 21)	24.0 [20.0–39.0]	54.0 [53.0–60.0]	NR	Pulmonary tuberculosis Adult	450–600	LC-MS/MS [0.2]
Nishimura (2020)[34]	Japan	138 (110/28)	662	4.80	1, 2, 3, 4, 5, 6, 7, 8 (>day 14)	58.0 [21.0–90.0]	51.5 [32.0–58.0]	NR	Pulmonary tuberculosis Adult	300–450	HPLC [0.02]
Panjasawatwong (2020)[46]	VietNRm	100 (56/44)	512	5.12	2 points randomly drawn at 1, 2, 3, 4, 5, 6, 8, 12, 18, or 24 (day 1, 14, 30, 90)	3.0 [0.167–15.0]	10.9 [4.0–43.0]	NR	Pulmonary tuberculosis HIV Children	10 mg/kg	LC-MS/MS [0.008]
Perumal (2022)[35]	South Africa	101 (67/34)	692	6.85	0, 2.5, 6, 24	36.0 [30.5–41.5]	57.7 [52.7–62.7]	49.6 [45.2–54.1]	Pulmonary tuberculosis Adult	2–4 drug FDC	[0.04]
Savic (2015)[48]	Indonesia	53 (NR/NR)	234	4.42	0, 1, 2, 4, 6, 12	NR	NR	NR	Pulmonary tuberculosis Adult	450 mg oral 600 mg IV	NA
Schipani (2016)[36]	Malawi	115 (NR/NR)	608	5.29	0.5, 1, 2, 3, 4, 6, 8 (>day 14)	33.0 [14.0–65.0]	49.0 [30.0–87.0]	NR	Pulmonary tuberculosis HIV Adult & Children	150	HPLC [0.5]

(*Continued*)

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Table 1 (Continued).

Study (Publication year)	Country	Number of subjects (M/F)	Sample counts	Sampling Frequency	Sampling schedule (h)	Age (Years) Mean ± SD Median [Range]	Weight (Kg) Mean ± SD Median [Range]	Fat-Free Mass (Kg) Mean ± SD Median [Range]	Subject characteristics	Dose [Range]	Bioassay [LOQ] (mg/L)
Sekaggya (2019)[5]	Uganda	249 (157/97)	1085	4.36	1, 2, 4 (days 14, 56, 84 and 168)	35.0 [29.0–40.0]	52.0 [47.5–59.0]	NR	Pulmonary tuberculosis HIV Adult	<55 kg: 450 55–70 kg: 600 >70 kg: 750	HPLC-UV [0.5]
Seng (2015)[37]	SiNRpore	34 (24/10)	1066	31.35	1, 2, 4, 6, 8, 10, 12, 18, 24 (days 14 and 28)	34.0 [22.0–56.0]	63.2 [45.8–86.1]	NR	Healthy volunteer Adult	600	HPLC-MS/MS [0.025]
Sloan (2017)[38]	Malawi	174 (121/53)	NR	3*	0, 2, 6 (day 14 or 21)	30.0 [17.0–61.0]	52.0 [34.0–74.0]	NR	Pulmonary tuberculosis HIV Adult	300/450/600	HPLC-MS [0.5]
Soedarsono (2023)[39]	South Korea	210 (136/74)	300	1.43	0–24h after the last dose	43.0 [18.0–77.0]	50.0 [32.0–82.0]	44.2 [32.6–59.5]	Pulmonary tuberculosis Diabetes Mellitus Adult	NR	HPLC-MS [0.2]
Wilkins (2008)[40]	South Africa	261 (102/159)	2913	11.16	0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 (days 7, 14, 21 and 28)	36.0 [29.0–44.0]	50.0 [43.7–56.0]	NR	Pulmonary tuberculosis HIV Adult	<50 kg: 450 >50 kg: 600	HPLC-UV [0.3]
Zvada (2014)[47]	South Africa	67 (NR/NR)	629	9.39	0.75, 1.5, 3, 4, 6	2.17 [0.417–1.99]	10.5 [4.9–21.8]	NR	Pulmonary tuberculosis HIV Children	49–218	LC-MS/MS [0.1]
Naidoo (2019)[33]	South Africa	58 (41/17)	574	9.90	0, 2.5, 6, 24 (day 28 and/or 56 and day 168)	37.0 [31.0–42.0]	56.9 [51.1–65.2]	46.8 [42.5–50.3]	Pulmonary tuberculosis HIV Adult	<55 kg: 450 >55 kg: 600	LC-MS/MS [0.04]
Hoa (2024)[42]	South Korea	869 (562/307)	917	1.06	0–24h after the last dose	59 [18.0–96.0]	58.4 [28.8–109.0]	NR	Pulmonary tuberculosis Adult	450/600	LC-MS/MS [0.2]
Svensson (2018)[41]	South Africa	83 (59/24)	913	11.00	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 (days 7 and 14)	31.0 [18.0–59.0]	53.9 [40.2–84.2]	44.2 [32.6–59.5]	Pulmonary tuberculosis Adult	450–1800	0.13

Note: Sampling frequency = Sample counts / Number of subjects.
Abbreviation: NR, not reported.

Table 2 Population Pharmacokinetic Parameters of Retrieved Studies

Study (Publication year)	Software (Algorithm)	Model	Fixed effect parameters		Between-subject variability (%CV)#	Between-occasion variability (%CV)#	Residual unexplained variability prop % add (mg/L)	Internal Validation	External Validation (N=number of samples)	Model Application
Abdelgawad (2022)[19]	NONMEM 7.4 (FOCE-I)	one-comp model with first-order elimination and transit-comp absorption	CL	=8.82*(FFM/43)^0.75*(BRC/6.0)^(−0.333)	42.4	-	prop.err: 17.2% add.err: 0.0234 FIX	GOF VPC	NR	Dose recommendations based on Cmax and AUC0-24
			Vd	=56.8*(FFM/43)	-	-				
			Ka	=1.38	-	119				
			F	=1	-	21.3				
			MTT	=0.342	-	93.8				
			NN	=12 FIX	-	-				
Aruldhas (2019)[43]	NONMEM 7.3 (FOCE-I)	one-comp model with first-order elimination and transit-comp absorption	CL	=8.11*(BW/19.5)^0.75	-	-	add.err: 0.0967	Bootstrap GOF VPC	NR	Dose recommendations based on Cmax and AUC0-24
			Vd	=44.7*(BW/19.5)	42	-				
			Ka	=(NN+1)/MTT	-	-				
			F	=1	68	-				
			MTT	=0.932	52.2	-				
			NN	=9 FIX	-	-				
Chang (2015)[20]	NONMEM 7.2 (FOCE-I)	one-comp model with first-order elimination and transit-comp absorption	CL	=6.10+((BMI/20.3)*6.22)	53.7	-	prop.err: 0.12 add. err: 1.42	GOF VPC	NR	NR
			Vd	=48.0+(DM*16.2)	32.8	-				
			Ka	=1.31+(DM*1.56)	49.9*	-				

(*Continued*)

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Table 2 (Continued).

Study (Publication year)	Software (Algorithm)	Model	Fixed effect parameters		Between-subject variability (%CV)#	Between-occasion variability (%CV)#	Residual unexplained variability prop % add (mg/L)	Internal Validation	External Validation (N=number of samples)	Model Application
Chirehwa (2016)[21]	NONMEM 7.3 (FOCE-I)	Well-stirred liver model with transit comp	CL0, int, max	=93.2*(FFM/42) ^0.75	22.5	21.9	prop.err: 10.8 add. err: 0.064	VPC	NR	Dose recommendations based on Cmax and AUC0-24; and probabilities of target attainment: AUCτ/MIC≥271 mg/L
			Vd	=50.1*(FFM/42)	14.2	-				
			Ka	=1.96	-	81.2				
			MTT	=0.71	-	62.7				
			NN	=19.3	-	-				
			F	=1 FIX	-	11				
			CLss, int, max	=176*(FFM/42) ^0.75	-	-				
			t1/ 2ind (day)	=4.5	-	-				
			VH	=1 FIX	-	-				
			QH	=50 FIX	-	-				
			fu	=0.2 FIX	-	-				
			Km (mg/ L)	=3.35	-	-				
			CLint, max	=CL0,int,max +(CLss,int,max-CL0,int,max)*(1-e(-ln(2)*t/t1/2ind)	-	-				
			CLint	=(CLint,max*CH)/ (CH+Km)						
			EH	=(CLint*fu)/ (CLint*fu+QH)						
			CLH	=QH*EH	-	-				

Denti (2016)[22]	NONMEM 7.3 (FOCE-I)	one-comp model with first-order elimination and transit-comp absorption	CL	=16.2*(BW/66) ^0.75*(1-Prgancy*0.14)	30.4	-	prop.err: 13.1 add. err: 0.0585 FIX	Bootstrap GOF VPC	NR	Effect of pregnancy status on RIF exposure
			Vd	=43.3*(BW/66)	-	-				
			Ka	=1.67	-	78.2				
			F	=1 FIX	-	28				
			MTT	=1.31	-	34.4				
			NN	=54.6	-	-				
Denti (2022)[44]	NONMEM (FOCE-I)	one-comp model with saturable hepatic clearance elimination and transit-comp absorption	CL	=54.5*(FFM/9) ^0.75*(PMAy^3.22/ (PMAy^3.22 +1.04^3.22))	41.8	-	prop.err: 13.7 add. err: 0.023 FIX	Bootstrap VPC	NR	Dose recommendations based on Cmax and AUC0-24; and probabilities of target attainment: AUCτ
			Vd	=12.3*(FFM/9)	-	-				
			Ka	=1.82	-	111				
			F	=1 FIX; if Age≥ 2.72 =0.655+((1–0.655)/ 2.72)*Age	-	45.1				
			MTT	=0.589	-	58.8				
			NN	=9.70	-	-				
Gao (2021)[23]	Phoenix NLME 8.0 (FOCE)	one-compartment open model with first-order absorption and elimination	CL	=9.4*(BW/50) ^0.76*(1–0.15*SEX)	28.5	-	prop.err: 6.3 add. err: 0.07	GOF VPC	N=61	Effect of SEX on RIF exposure; and Proportions of model-simulated Cmax below the lowest reference level: Cmax<8 mg/L
			Vd	=37.0*(BW/50) ^0.66	14.6	-				
			Ka	=0.82	14.2	-				
Horita (2018)[45]	Monolix2016R1 (SAEM)	one-compartment model with sequential zero- and first-order absorption and first-order elimination	Fr	=0.0878	108	-	prop.err: 20.2 add. err: 0.0476	GOF VPC	NR	Dose recommendations based on Cmax and AUC0-24
			D0	=0.342	91.4	-				
			CL	=7.53*(BW/14.3) ^0.75	54.7	-				
			Vd	=13.8*(BW/14.3)	21.7	-				
			Ka	=0.645	46.4	-				

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Table 2 (Continued).

Study (Publication year)	Software (Algorithm)	Model	Fixed effect parameters		Between-subject variability (%CV)#	Between-occasion variability (%CV)#	Residual unexplained variability prop % add (mg/L)	Internal Validation	External Validation (N=number of samples)	Model Application
Jeremiah (2014)[24]	NONMEM 7.2 (FOCE-I)	one-comp model with first-order elimination and transit-comp absorption	CL	=CL7+(CLss-CL7)*(1-e(-log(2)/t1/2)*t)	24.0	-	prop.err: 13.7 add. err: 0.0417	VPC	NR	NR
			CL7	=13.9*(FFM/43)^0.75	-					
			CLss	=16.5*(FFM/43)^0.75	-	-				
			t1/2 (day)	=6 FIX	-	-				
			Vd	=55.8*(FFM/43)	-	-				
			Ka	=1.77	-	67.6				
			MTT	=1.50	-	34				
			NN	=27.6	-	MTT-BIO correlation: −25.2				
			F	=1 FIX	-	31.1				
Jing (2016)[25]	NONMEM 5 (FOCE-I)	one-compartment open model with first-order absorption and elimination	CL	=4.02	64.5	-	add.err: 6.55	GOF	NR	NR
			Vd	=57.8	20.9	-				
			Ka	=1.61 FIX	-	-				
Karballaei (2022)[26]	Monolix2021R1 (SAEM)	one-compartment open model with mixed first-order absorption and elimination	Ka1	=1.1	85	-	prop.err: 49 add. err: 0.15	GOF VPC	NR	Probabilities of target attainment: AUCτ≥600ug*h/mL and Cmax>32-40mg/L
			Ka2	=0.46	46	-				
			Fr	=0.68	357	-				
			Tlag2	=2.92	299	-				
			CL	=0.08	52	-				
			Vd (L/kg)	=0.68	9.7	-				

Kim (2021)[27]	NONMEM 7.3 (FOCE-I)	two-compartment open model with first-order absorption and elimination	CL	=11.4*(BW/60)^1.14	64.2	-	prop.err: 20.43	GOF VPC	NR	Effect of SLCO1B1 genotype on RIF exposure, CL, clinical outcomes and adverse events
			Vd	=17.8	70.2	-				
			Q	=2.78	CL-Vd correlation: 0.927	-				
			Vp	=80.7	-	-				
			Ka	=0.436 FIX	-	-				
Kloprogge (2020)[28]	NONMEM	one-comp model with first-order elimination and transit-comp absorption	CL	=13.7*(BW/70)^0.75*(1+SEX*0.183)	40.08	-	prop.err: 19.40	VPC	NR	Effect of alcohol status on RIF exposure and clinical outcomes
			Vd	=39.7*(BW/70)	84.52	-				
			Ka	=0.277 FIX	-	-				
			MTT	=0.326 FIX	27.05 FIX	-				
			NN	=1.5 FIX	-	-				
Marsot (2017)[29]	NONMEM	one-comp model with first-order elimination	CL	=13.7–8.6*Fusidic acid	53.1	-	add.err: 2.256	GOF VPC NPDE Bootstrap	NR	NR
			Vd	=61.1–37.3*Fusidic acid	34.9	-				
			Ka	=1.15 FIX	-	-				
Medellin (2020)[30]	NONMEM 7.3 (FOCE-I)	one-comp model with first-order elimination and tlag, sequential zero and first order absorption	Tlag	=0.24	-	-	add.err: 1.14	Bootstrap VPC	N=15	Dose recommendations based on Cmax and AUC0-24
			D0	=0.62	131.1	-				
			Ka	=1.24	110.5	-				
			CL	=5.96	38.5	-				
			Vd	=0.7*BW	26.8	-				
Milán (2013)[31]	NONMEM 6	one-comp model with first-order elimination	CL	=8.17*(1+SEX*0.4)	31.9	-	prop.err: 7.74	NR	N=77	NR
			Vd	=50.1*(1+SEX*0.29)	16.7	-				
			Ka	=2.70	92.9	-				

(*Continued*)

Table 2 (Continued).

Study (Publication year)	Software (Algorithm)	Model	Fixed effect parameters		Between-subject variability (%CV)#	Between-occasion variability (%CV)#	Residual unexplained variability prop % add (mg/L)	Internal Validation	External Validation (N=number of samples)	Model Application
Mukonzo (2020)[32]	NONMEM 7.3	two-compartment open model with first-order elimination and Tlag in absorption	CL	=19.8831	38.22	-	prop.err: 13.86 add.err: 0.0032	GOF VPC	NR	Probabilities of target attainment: Cmax~8-24mg/L
			Vd	=0.5383	255.65	-				
			Q	=19.6854	0 FIX	-				
			Vp	=19.3284	0 FIX	-				
			Tlag	=0.7748	-	-				
			Ka	=0.4682	9.22	-				
Nishimura (2020)[34]	NONMEM 7 (FOCE-I)	one-comp model with first-order elimination and tlag, sequential zero and first order absorption	Tlag	=1.43	12.96	-	prop.err: 4.95	Bootstrap GOF VPC	NR	NR
			D0	=1.58*FOOD	78.23	-				
			F	=1*(1+FOOD*0.32)	0.00063	-				
			Ka	=0.248*(1 +FOOD*0.21)	24.98	-				
			CL	=15.2*(BW/51.5) ^0.978	38.92	-				
			Vd	=2.09	151.66	-				
Panjasawatwong (2020)[46]	NONMEM 7 (FOCE-I)	one-comp model with first-order elimination and transit absorption	MTT	=1.25	85	-	add.err: 0.513	VPC	NR	Probabilities of target attainment: AUCτ≥86.4mg*h/L in plasma and 17.3 mg*h/L in CSF
			NN	=2 FIX	-	-				
			Ka	=1.24	-	-				
			CL	=3.22*(BW/10.9) ^0.75*(PMAm^1.38/ (PMAm^1.28 +6.81^1.38))	19.4	-				
			Vd	=12.3*(BW/10.9)	23	-				

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Perumal (2022)[35]	NONMEM 7.4 (FOCE-I)	one-comp model with first-order elimination and tlag, first order absorption	Tlag	=0.38	88.9	-	prop.err: 36.3 add. err: 0.008	VPC	NR	NR
			F	=1-0.253*PXR +0.193*MOX	43.1	-				
			Ka	=1.64	89.2	-				
			CL	=25.5*(FFM/49.6) ^0.75	9.1	-				
			Vd	=90.1*(FFM/49.6)	-	-				
Savic (2015)[48]	NONMEM 7.3 (FOCE-I)	two-compartment open model with first-order elimination and absorption	F	=0.6	-	-	prop.err: 28.0 add. err: 2.18	NR	NR	Dose recommendations based on AUC0-24
			Ka	=0.644	-	-				
			CL	=5.71	34 CL-Vd correlation: 0.53	-				
			Vd	=24.9	60	-				
			Q	=9.46	-	-				
			Vp	=12.4	-	-				
Schipani (2016)[36]	NONMEM 7.2	one-comp model with first-order elimination and tlag, first order absorption	F	=1*0.517^Child	-	-	prop.err: 48.0	GOF VPC	NR	Effect of body weight and age on RIF exposure
			Ka	=0.236	-	-				
			CL	=23.9*(BW/70) ^0.75*(AGE/33) ^0.517	46.6	-				
			Vd	=44.6*(BW/70)	87.4	-				
Sekaggya (2019)[5]	Monolix2016R1	one-comp model with first-order elimination and tlag, first order absorption	F	=1 FIX	-	36.4	prop.err: 48.0	VPC	NR	Dose recommendations based on AUC0-24
			Tlag	=0.83		48.2				
			Ka	=1.99	-	50.7				
			CL	=(12.2+20*week) * (FFM/43)^0.75	46.6	-				
			Vd	=58*(FFM/43)	87.4	-				

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Table 2 (Continued).

Study (Publication year)	Software (Algorithm)	Model	Fixed effect parameters		Between-subject variability (%CV)#	Between-occasion variability (%CV)#	Residual unexplained variability prop % add (mg/L)	Internal Validation	External Validation (N=number of samples)	Model Application
Seng (2015)[37]	NONMEM 7.2 (FOCE-I)	one-comp model with first-order elimination with two transit-comp absorption	KTR	=KA	-	-	prop.err: 26.4	Bootstrap GOF VPC	NR	NR
			F	=1 FIX	51.09	57.18				
			NN	=2 FIX	-	-				
			Ka	=2.15	57.71	-				
			CL	=10.3*(BW/70)^0.75	30.13	41.23				
			Vd	=30.9*(BW/70)	-	-				
Sloan (2017)[38]	NONMEM 7.2 (NA)	one-comp model with first-order elimination with transit-comp absorption	CL	=19.6*1.2^SEX	27.57	-	prop.err: 22	VPC	NR	NR
			Vd	=23.6	63.01	-				
			Ka	=0.277 FIX	-	-				
			NN	=1.5 FIX	-	-				
			MTT	=0.326 FIX	26.57 FIX	-				
Soedarsono (2023)[39]	NONMEM 7.4 (FOCE-I)	one-comp model with first-order elimination transit absorption	Ka	=0.37	-	-	add.err: 0.29	Bootstrap GOF VPC	NR	Effect of SLCO1B1*15 and age on RIF exposure
			CL	=7.85*(AGE/40)^(−0.55)*(1+SLCO*0.24)*(FFM/44)^0.75	78.1	-				
			Vd	=30.9*(FFM/44)	-	-				
Wilkins (2008)[40]	NONMEM 6	one-comp model with first-order elimination with transit-comp absorption	MTT	=0.424	60.1	67.9	prop.err: 22.2 add. err: 0.0923	GOF VPC	NR	RIF exposure comparison with other literature
			NN	=7.13	156	-				
			Ka	=1.15	66.3	-				
			CL	=19.2	52.8 CL_Vd correlation: 0.217	22.5				
			Vd	=53.2	43.4	-				

Zvada (2014)[47]	NONMEM 7 (FOCE-I)	one-comp model with first-order elimination with transit-comp absorption	MTT	=1.04	-	63.72	prop.err: 23.4 add. err: 0.122/0.630	VPC	NR	Dose recommendations based on AUC0-24 across different age and weight bands
			NN	=8.04	-	-				
			F	=1 FIX	-	69.34				
			Ka	=KTR	-	-				
			CL	=8.15*(BW/12.5) ^0.75*(1/(1 +(PMAw/58.2) ^-2.21))	57.1	50.1				
			Vd	=16.2*(BW/12.5)	65.88	-				
Naidoo (2019)[33]	NONMEM 7.3 (FOCE-I)	one-comp model with first-order elimination with two transit-comp absorption	MTT	=0.53	-	-	prop.err: 37.4 add. err: 0.008 FIX	VPC	NR	Exposure simulation
			NN	=34.6	-	-				
			F	=1 FIX	-	65.88				
			Ka	=1.57	-	-				
			CL	=22.8*(FFM/47) ^0.75	23.45	46.15				
			Vd	=77.4*(FFM/47)	-	-				
Hoa (2024)[42]	NONMEM 7.4.1 (FOCE-I)	one-comp model with first-order elimination	CL	=6.05*(1 +SLCO*0.17)*(BW/ 60)^0.75	25.9	-	prop.err: 18 add. err: 1.77	Bootstrap GOF VPC	359	Dose recommendations based on SLCO1B1 genotype Exposure comparison with different model
			Vd	=36.5*(BW/60)	41.7	-				
			Ka	=1.52	118.7	-				

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Table 2 (Continued).

Study (Publication year)	Software (Algorithm)	Model	Fixed effect parameters		Between-subject variability (%CV)#	Between-occasion variability (%CV)#	Residual unexplained variability prop % add (mg/L)	Internal Validation	External Validation (N=number of samples)	Model Application
Svensson (2018)[41]	NONMEM 7.2 (FOCE-I)	one-comp model with first-order elimination with transit-comp absorption	MTT	=0.513	61.81	75.1	add.err: 0.236	VPC	NR	High dose exposure
			NN	=23.8	88.26	-				
			Vmax	=525	54.77 Vmax_Km correlation: 0.389	-				
			Km	=35.3	59.83	43.47				
			F	=1*(1+0.504*(DOSE-450)/(67.0+(DOSE-450)))	-	39.62				
			Ka	=1.77	58.14	56.04				
			CL	=((VMAX/(KM+CP))*(BW/70)^0.75	-	-				
			Vd	=30.9*(BW/70)	28.04	-				

Abbreviations: CL, apparent clearance (L/h); Q, the intercompartment 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.

four studies performed external evaluations using an independent dataset, demonstrating acceptable predictability. Enhancing the predictive performance of popPK models requires rigorous external validation to ensure their applicability across different populations and clinical settings.

Covariates of Inclusion

The majority of studies sought to identify covariates that explain the IIV of rifampicin pharmacokinetics, focusing on those with potential clinical significance. A stepwise approach involving forward inclusion and backward elimination was used in 23 of the 31 studies for covariate screening. Notably, 8 studies used forward inclusion and 11 studies used backward elimination, The specific inclusion or exclusion criteria were not reported in 7 studies. A summary of all tested and identified covariates for CL and Vd is presented in Table 3. The excluded and included covariates for CL and Vd in each study are illustrated in Figure 2. BW and FFM significantly affected rifampicin CL in the majority of included models. However, in studies that directly compared BW and FFM, FFM provided a better fit. In children, PMA affected CL, other demographic and laboratory indices (BRC, sex, pregnancy status, concomitant drugs, administration duration, and SLCO1B1*15) might influence CL or Vd. Of the 22 studies using allometric scaling models, 8 used FFM and 14 used BW as the covariate.

The forest plot of covariate effects on CL (Figure 3) showed that pregnancy, BMI, BRC, and SLCO1B1 genotype might not have clinically significant impacts on rifampicin clearance. The combination of fusidic acid significantly affected RIF clearance. In studies that evaluated both FFM and BW as covariates, FFM provided a better fit for the allometric scaling models, particularly for rifampicin clearance. These studies consistently preferred FFM over BW, suggesting that FFM may better capture the variability in drug clearance. Other studies that considered only BW did not provide comparative analysis, and thus did not assess the potential advantages of FFM.

Exposure Comparison

The simulated concentration-time profiles of included popPK models are presented in Figure 4A–B. Based on the simulated PK profiles, the concentrations in most typical patients did not reach the therapeutic concentration range. Gender factors may introduce differences in rifampicin exposure, with simulation results from three studies indicating lower exposure in males than in females. However, variations in rifampicin exposure related to genetic polymorphisms in the SLCO1B1 gene were not considered clinically significant. There are substantial exposure differences among various models when subjected to the same dosing regimen, and understanding the origins of these exposure discrepancies between models is crucial. Due to issues such as the complexity of the model reported by Svensson and the inability to unify parameter units,[41] simulation reproduction could not be achieved, and the model exposure comparison was not included.

Model Application

The code for the RIF popPK repository and the Shiny app is available at Github (https://github.com/727397883/Rifampicin-PopPK-Repository). The graphical presentation interface of the shiny app is provided in the supplementary material (Figure S2).

Discussion

This study systematically reviewed existing population pharmacokinetic models of rifampicin and constructed a comprehensive rifampicin model repository using mrgsolve. Additionally, we developed a Shiny application based on this model repository to facilitate individualized dosing strategies. The article compiles extensive information from the studies, including study design, population characteristics, dosing regimens, sampling strategies, and bioanalytical methods, modeling techniques, as well as covariate models. It objectively compares the quality of reporting, inclusion of covariates among the models, while assessing the clinical significance of all included covariates. Bayesian simulation techniques are employed to compare exposure differences across studies in typical populations and evaluate the attainment of therapeutic targets under standard treatment regimens.

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Table 3 List of Tested and Significant Covariates in the Model

Study (publication year)	Tested covariates			Covariate selection criteria		Significant covariates			
	Demographic	Laboratory tests	Others	Forward inclusion	Backward elimination	CL	Vc	Q	Vp
Abdelgawad (2022)[19]	Age, Sex, BW, FFM, Height	TBIL, BRC, Lactate, ALT, AST	HIV status, Concomitant drugs	NR	P<0.001	FFM, BRC	FFM	/	/
Aruldhas (2019)[43]	Age, Sex, BW, BMI	NR	Concomitant drugs	P<0.05	P<0.01	BW	BW	/	/
Chang (2015)[20]	Age, Sex, BW, BMI	FBG, PP2, SCR, CrCL	DM status	P<0.05	P<0.01	BMI	DM	/	/
Chirehwa (2016)[21]	Age, Sex, BW, FFM, Height	ALB, CRE	Concomitant drugs	NR	NR	FFM	FFM	/	/
Denti (2016)[22]	Age, BW	NR	Concomitant drugs, Pregnant status, HIV status	P<0.05	NR	BW, Pregnancy	BW	/	/
Denti (2022)[44]	PMA, Age, BW, Height, FFM, Sex	SLCO1B1, AADAC	HIV status, Concomitant drugs, Administration method	NR	P<0.01	FFM, PMA	FFM	/	/
Gao (2021)[23]	Age, BW, Height, BMI, Sex	FBG, CRP, OGTT2h, BUN, UA, CRE, TBIL, ALT, AST, ALP, ALB	DM status, Smoking status, Alcohol consumption, Formulation	P<0.05	P<0.01	BW, Sex	BW	/	/
Horita (2018)[45]	Age, BW, Sex	SCR, SLCO1B1, eGFR	HIV status, Dose	P<0.1	P<0.05	BW	BW	/	/
Jeremiah (2014)[24]	Age, BW, Sex, FFM	SLCO1B1	HIV status, Smoking status, Alcohol consumption, Dose	NR	NR	FFM	FFM	/	/
Jing (2016)[25]	Age, Sex, BW	ALT, AST, MAST, GGT, ALP, CRE, BUN, UA	NR	P<0.1	P<0.05	NR	NR	/	/
Karballaei (2022)[26]	Age, BMI	eGFR	Concomitant drugs	NR	NR	NR	NR	/	/
Kim (2021)[27]	Age, Sex, BMI	CBC, Hb, PLT, BUN, CRE, TP; ALB, AST, ALT, SLCO1B1, Radiology findings	Concomitant drugs, DM status, Hypertension status, Chronic liver disease status, Smoking status	P<0.1	NR	BW	NR	NR	NR

Kloprogge (2020)[28]	Age, BW, Height, BMI, Sex	Hb, CBC, PLT, Urea, CRE, BIL, ALT	HIV status, Smoking status, Alcohol consumption, Dose, Adherence	P<0.05	P<0.01	BW, Sex	BW	/	/
Marsot (2017)[29]	Age, Sex, BW, Height	NR	Concomitant drugs, Type of infection	NR	NR	Fusidic acid	Fusidic acid	/	/
Medellin (2020)[30]	Age, Sex, BW, BMI, BSA	MDR1, SLCO1B1	Concomitant drugs, DM status	P<0.05	P<0.001	NR	BW	/	/
Milán (2013)[31]	Age, Sex, BW, Height	NR	Concomitant disease, Concomitant drugs, Addictions, Dose, Formulation	P<0.05	P<0.001	Sex	Sex	/	/
Mukonzo (2020)[32]	Age, BW, Sex	SLCO1B1	NR	P<0.05	NR	/	/	/	/
Nishimura (2020)[34]	Age, BW, Sex	ALT, AST, BUN, γGTP, TBIL, eGFR	NR	P<0.01	P<0.001	BW	/	/	/
Panjasawatwong (2020)[46]	Age, PMA, Sex, BW	Renal function, Liver function, Nutritional status, CNS inflammation markers	Disease severity, HIV status	P<0.05	P<0.01	BW, PMA	BW	/	/
Perumal (2022)[35]	Age, Sex, Race, BW, BMI, FFM	SLCO1B1, PXR	HIV status, Concomitant drugs	P<0.05	NR	FFM	FFM	/	/
Savic (2015)[48]	BW	NR	NR	NR	NR	BW	BW	NR	NR
Schipani (2016)[36]	Age, BW	NR	HIV status	P<0.05	P<0.01	BW, Age	BW	/	/
Sekaggya (2019)[5]	Age, BW, BMI, FFM	SLCO1B1	Formulation, Week	NR	NR	FFM, Week	FFM	/	/
Seng (2015)[37]	Age, BW, Height, Sex, Race	ABCB1, SLCO1B1, PXR, CYP3A4, CYP2B6, CAR	NR	P<0.05	P<0.01	BW	BW	/	/
Sloan (2017)[38]	Age, Sex, BW	SLCO1B1, AADAC, CES1	HIV status, Adherence, Dose	P<0.05	P<0.01	Sex	/	/	/
Soedarsono (2023)[39]	Age, Sex, BW, Height, FFM	SLCO1B1, ALB, AST, ALT, TBIL	Feeding status, DM status, Liver impairment, Renal disease, Dose	P<0.05	P<0.01	Age, SLCO1B1, FFM	FFM	/	/
Wilkins (2008)[40]	Age, BW, BMI, Height, Sex,	NR	Formulation, HIV status, Smoking status, Alcohol consumption, Concomitant drugs, Drugs of abuse, HIV status	P<0.05	P<0.01	/	/	/	/

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Table 3 (Continued).

Study (publication year)	Tested covariates			Covariate selection criteria		Significant covariates			
	Demographic	Laboratory tests	Others	Forward inclusion	Backward elimination	CL	Vc	Q	Vp
Zvada (2014)[47]	Age, Sex, BW, PMA	NR	HIV status	P<0.05	P<0.01	BW, PMA	BW	/	/
Naidoo (2019)[33]	Age, Sex, Race, BW, BMI, FFM	UGT1A, ABCB1, SLCO1B1	HIV status, Concomitant drugs	P<0.05	NR	FFM	FFM	/	/
Hoa (2024)[42]	Age, Sex, BW, Height	ALT, AST, TBIL, BUN, eGFR, SCR, TP, ALB, SLCO1B1	Feeding status	NR	NR	BW, SLCO1B1	BW	/	/
Svensson (2018)[41]	Age, Sex, BW, BMI, FFM, Race	NA	Dose	NA	NA	BW	BW	/	/

Abbreviations: BW, body weight (kg); FFM, fat-free mass (kg); TBIL, total bilirubin (umol/L); BRC, conjugated bilirubin (umol/L); ALT, alanine aminotransferase (U/L); AST, aspartate aminotransferase (U/L); FBS, fasting blood glucose (mg/dL); PP2, 2h post-prandial plasma glucose level (mg/dL); SCR, serum creatinine (mg/dL); CrCL, creatinine clearance (mL/min); DM, diabetes mellitus; ALB, albumin (g/L); CRE, creatinine (umol/L); AADAC, Arylacetamide deacetylase, PMA, postmenstrual age; OGTT2h, 2-hour oral glucose tolerance test; CRP, C-reaction protein; BUN, blood urea nitrogen; UA, uric acid; ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; MAST, aspartate aminotransferase isozyme; GGT, γ-glutamyl transferase; CBC, Whole blood cell count; Hb, Haemoglobin; PLT, Platelet count; TP, total protein; BSA, body surface area; GTP, Glutamyl transpeptidase; CNS, central nervous system; PXR, pregnane-X-receptor; NR: not reported.

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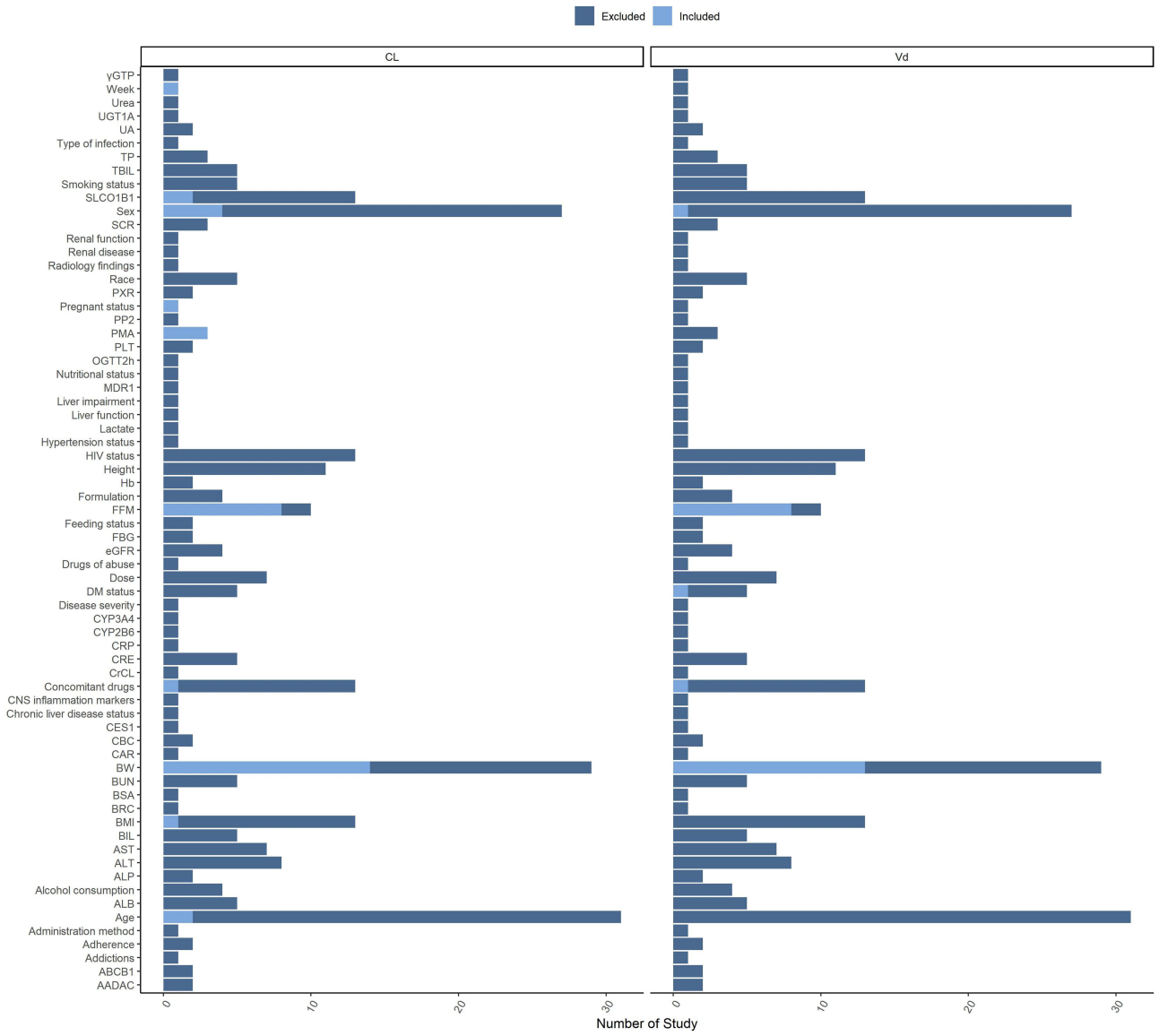

Figure 2 Excluded and Included covariates for clearance and volume of rifampicin.

Abbreviations: BW, body weight (kg); FFM, fat-free mass (kg); TBIL, total bilirubin (umol/L); BRC, conjugated bilirubin (umol/L); ALT, alanine aminotransferase (U/L); AST, aspartate aminotransferase (U/L); FBS, fasting blood glucose (mg/dL); PP2, 2h post-prandial plasma glucose level (mg/dL); SCR, serum creatinine (mg/dL); CrCL, creatinine clearance (mL/min); DM, diabetes mellitus; ALB, albumin (g/L); CRE, creatinine (umol/L); AADAC, Arylacetamide deacetylase, PMA, postmenstrual age; OGTT2h, 2-hour oral glucose tolerance test; CRP, C-reaction protein; BUN, blood urea nitrogen; UA, uric acid; ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; MAST, aspartate aminotransferase isozyme; GGT, γ-glutamyl transferase; CBC, Whole blood cell count; Hb, Haemoglobin; PLT, Platelet count; TP, total protein; BSA, body surface area; GTP, Glutamyl transpeptidase; CNS, central nervous system; PXR,pregnane-X-receptor.

Model Performance

Among the 30 included popPK models, 27 adopted a one-compartment first-order elimination model, and improved fitting performance by incorporating transit compartments or lag time absorption models. Rifampicin exhibits rapid metabolism and minimal accumulation in vivo. Although 28 studies utilized internal validation methods such as GOF, VPC, Bootstrap, or NPDE, only 4 studies incorporated external validation using independent datasets,[23,30,31,42] which raises concerns about their generalizability. For studies involving small sample sizes or sparse sampling points, the informational content of the modeling data may be insufficient to fully elucidate the PK characteristics of RIF in the human body. As such, external validation is crucial for models based on smaller sample sizes and limited sampling

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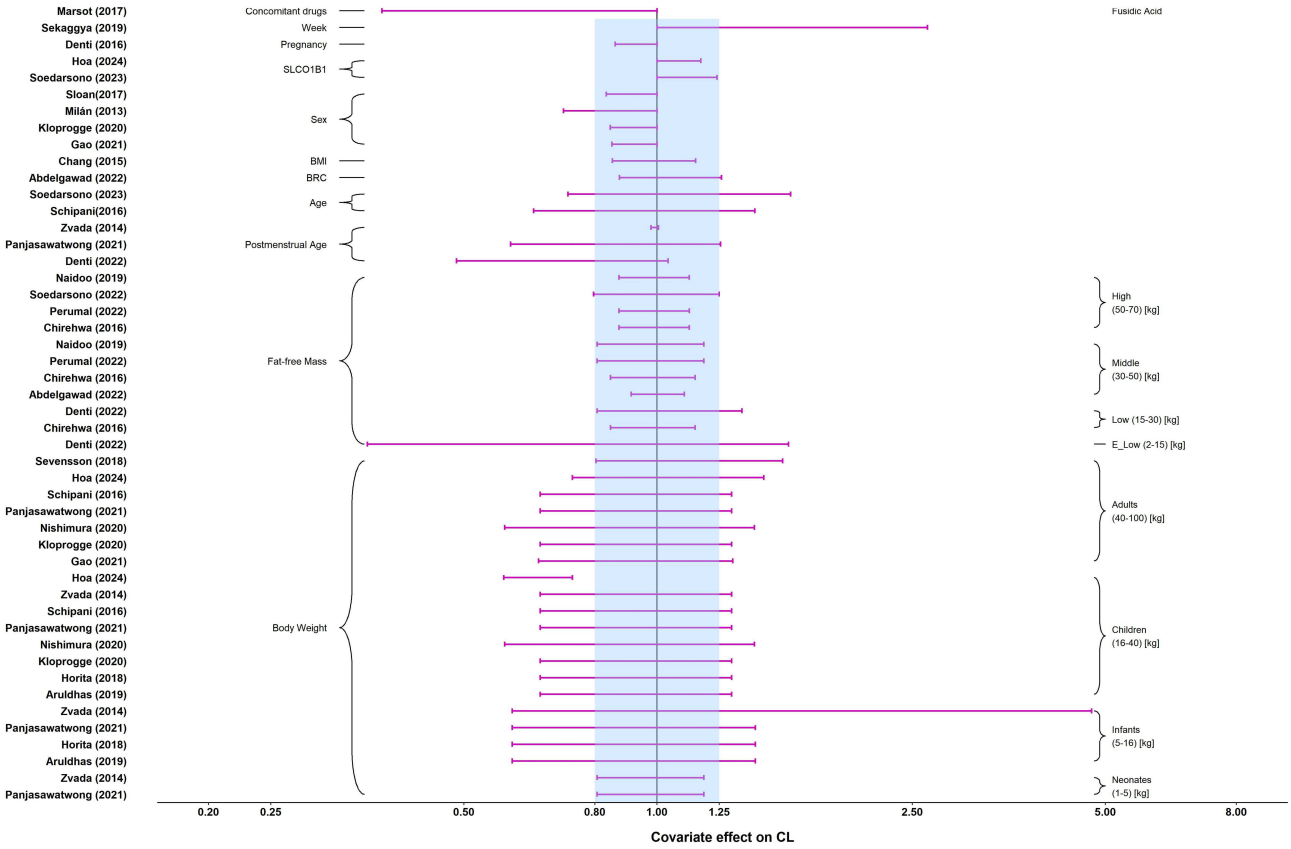

Figure 3 Forest plot of covariates effect on the clearance of rifampicin.
Note: The horizontal bars represent the covariate effect on clearance in each study. The shadow area ranges from 0.8–1.25.

points. All 30 studies reported high-quality models with low bias risks, providing guidance for individualized predictions in clinical practice.

Covariate Effects

Previous research examined numerous demographics, laboratory, comorbidity, concomitant medication, and genomic factors affecting rifampicin PK. Body weight (BW) and fat-free mass (FFM) are considered critical covariates in 21 studies employing allometric growth models, with eight studies comparing BW and FFM separately. Eight studies indicate that FFM provides a better fit and enhanced model performance compared to BW.[5,19,21,24,33,35,39,44] While WHO guidelines recommend body weight-based dosing for rifampicin, considerable variation exists within broad body weight categories.[17] Using FFM results in less fluctuation in rifampicin clearance rates across different intervals, however, caution should be exercised at extremely low FFM levels. While BW was the predominant covariate in most models, studies that included a direct comparison with FFM suggest that FFM may provide a better fit, particularly in patients with muscle wasting, where relying solely on BW could lead to dosage errors. This indicates that while BW remains widely accepted standard, FFM might be more appropriate in certain cases.[5,49] Gender, BMI, and dosing cycles might influence rifampicin clearance, but according to the covariate analyses, their impact may not be clinically significant, thus justifying against dose adjustments based on these factors. Only one study reported the effect of dosing cycle on clearance, indicating the need for further exploration regarding whether rifampicin exposure varies significantly with the dosing regimen.[5]

Laboratory assessments have considered liver function, renal function, nutritional status, and central nervous system inflammation markers, yet only one study incorporated direct bilirubin, finding no clinically significant effect on

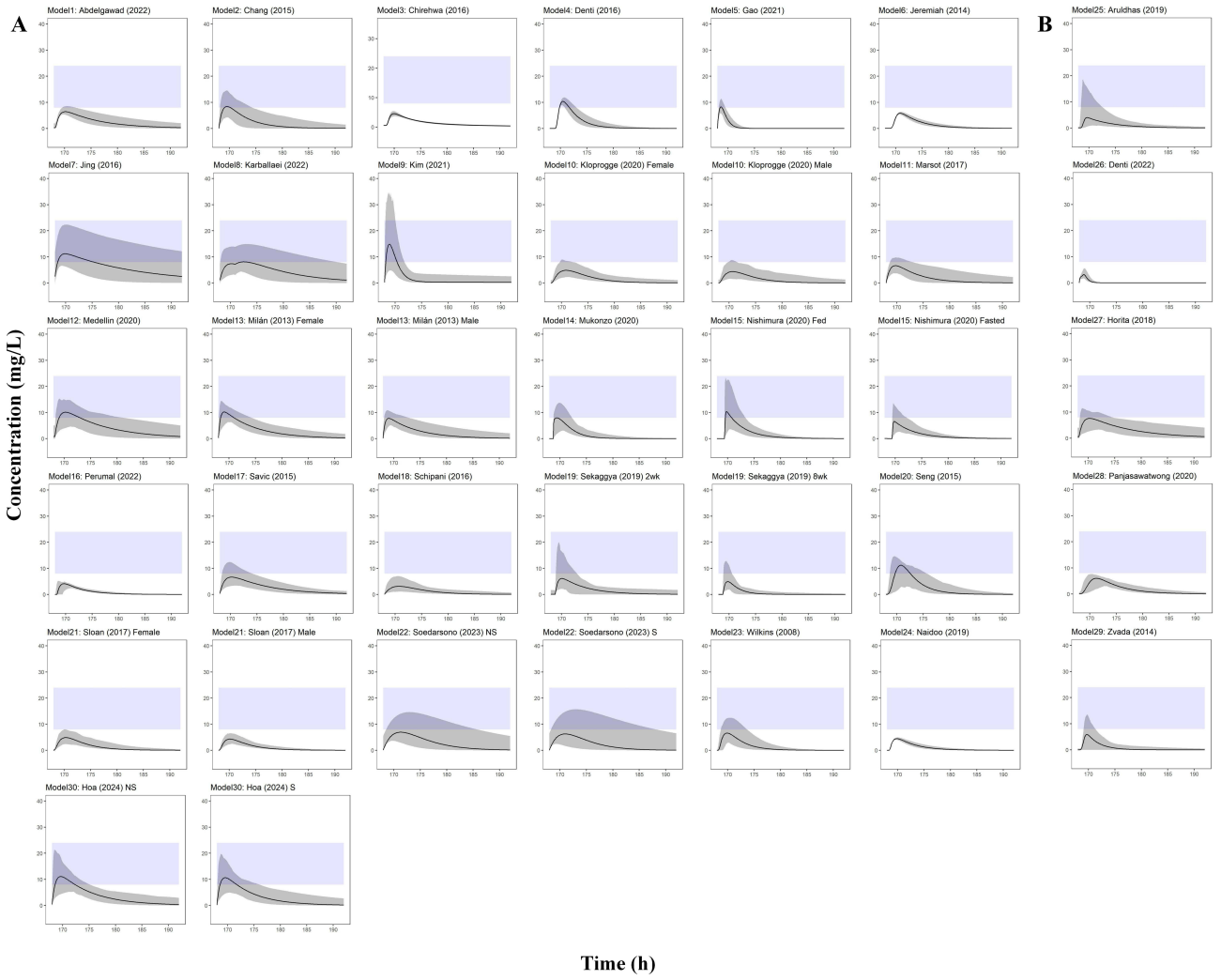

Figure 4 Concentration-time profiles at steady state in retrieved studies.
Note: (**A**) Adult model; (**B**) Pediatric model. The light purple shadow means the population prediction range (90% CI); the light blue shadow means the efficacy range (8–24 mg/L).

clearance. Thirteen studies investigated the impact of SLCO1B1 gene phenotypes on PK parameters, yet only two of them ultimately included this parameter. Furthermore, the examination of covariate effects revealed that the influence of SLCO1B1 gene phenotypes lacks clinical significance. This further supports the notion that SLCO1B1 genetic testing may not be necessary for rifampicin.

Regarding comorbidities, DM and HIV status were frequently analyzed. DM is a known risk factor for TB development, with reports suggesting a threefold increased risk in DM patients.[50] Despite five studies incorporating DM status, only one found an effect on volume of distribution.[20] In African populations, none of the 13 rifampicin studies found HIV status to affect PK parameters. Among concomitant medications, fusidic acid was reported by one study to influence rifampicin clearance and volume of distribution, with covariate analysis revealing substantial changes in CL.[29] However, the mechanism underlying fusidic acid's impact on rifampicin's ADME process remains unclear.

Special Populations

Pregnant women and children are key patient groups requiring tailored drug therapy. Studies have shown that physiological and pathophysiological changes during pregnancy can impact drug ADME processes,[51,52] while infants and preterm/very-low birthweight children often have immature organ systems, necessitating personalized dosing.[53] Our

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model repository includes one study on pregnant women, identifying pregnancy as a significant covariate for rifampicin clearance, although the covariate analysis suggests its impact may not be statistically significant relative to other populations.[22] For pediatric populations, PMA and FFM/BW are more influential on rifampicin exposure.[44,46,47] Further research is needed to substantiate the impact of pregnancy on rifampicin exposure.

Rifampicin Simulations

The rifampicin simulation curves revealed inter-model variability in drug PK. Under WHO-recommended and standard clinical doses, most studies did not achieve the therapeutic range.[9,17] Asians appear more likely to reach this interval relative to other populations,[20,23,25,27,37,39,46] however, considering that TB treatment success rates exceed 90%, the validity of the effective range (8–24 mg/L)[8] based on C_{max} may be questioned along with the consistency of the efficacy window across countries. The long-term follow-up results of 142 tuberculosis patients by Pasipanodya et al indicate that an AUC of rifampin less than 13 mg*h/L is associated with adverse outcomes, demonstrating that a low AUC can predict the clinical prognosis of tuberculosis patients.[54] Three studies built gender-specific covariate models, with simulations showing women generally more easily achieving the therapeutic range.[23,28,38] Two study involving SLCO1B1 gene typing demonstrated similar simulation outcomes.[39,42] Food intake was observed to increase rifampicin exposure in one study,[34] while another study noted that rifampicin exposure decreased between the second and eighth dosing cycles due to auto-induction effects, which led to accelerated elimination and approximately 20% reduction in drug exposure after prolonged administration, consistent with prior reports.[5] The PopPK model analysis results from Svensson et al's ultra-high dose group indicate that the dose level of rifampin significantly influences the drug's bioavailability and clearance rate.[41] Therefore, particular attention should be paid to its PK/PD response when administering high doses.

Utilization of the Model Repository

Our study establishes a rifampicin popPK model repository and a Shiny application, facilitating individualized dosing strategies using mrgsolve for RIF. We have previously developed a parameter-based popPK model repository for isoniazid.[14] By leveraging both rifampicin and isoniazid repositories, users can make precise exposure predictions for individual patients based on their specific characteristics and dosing regimens. These drugs are recommended by WHO for combined therapy,[1] and their models joint application allows for more accurate in vivo exposure analysis.

The Shiny application provides a user-friendly interface that enables clinicians and researchers to simulate RIF dosing regimens based on various patient-specific parameters such as age, sex, BW or FFM. By leveraging Bayesian simulation techniques, the application allows for precise exposure predictions, facilitating the optimization of therapeutic regimens tailored to individual patient needs. The primary advantages of our model application include: (i) Ease of Use: The Shiny application offers an intuitive interface, making it accessible to users with varying levels of technical expertise. (ii) Comprehensive Data Integration: The application integrates demographic, genetic, and physiological data to provide a holistic view of the patient's pharmacokinetic profile. (iii) Real-Time Simulations: Users can perform real-time simulations to explore potential drug exposure scenarios, potentially informing future research and model refinement. (iv) Model Repository: Our extensive repository of popPK models enables users to select models most relevant to specific patient characteristics and clinical scenarios. (v) Research Support: By allowing users to explore exposure predictions, the application can support research and educational efforts, contributing to better understanding of rifampicin pharmacokinetics in specific populations. Moreover, this model repository enables seamless integration with other model-informed optimal experimental design, such as sampling strategy optimization, dosing regimen selection, and missed or delayed dose scenarios.[55]

In managing drugs with a narrow therapeutic window and a high risk of resistance, maintaining drug exposure within the effective therapeutic range is essential to minimize adverse effects and reduce the likelihood of early resistance development. While rifampicin has traditionally been associated with a specific target concentration, recent findings suggest a broader therapeutic range, particularly at higher doses, highlighting the need for flexible, patient-tailored dosing strategies. Given the increasing concern over multi-drug-resistant tuberculosis and the growing emphasis on precision medicine, this comprehensive overview underscores the critical role of popPK models in enhancing our understanding of rifampicin's pharmacokinetics and improving patient care through evidence-based, individualized treatment approaches.

Limitations

This study employed simulated populations to eliminate confounding factors and assess model performance under controlled conditions (eg, typical population and fixed dosing regimen). While this approach provides consistency, it does not account for real-world variability, limiting the direct applicability of our findings to clinical practice.

The Shiny application developed in this study is designed as an investigative and educational tool for exploring population pharmacokinetic models and is not intended for direct application in clinical practice. For clinical use, it is recommended to validate or optimize the models with patient data, ensuring the best model is matched before its application in clinical settings.

Our focus on standard clinical dosing models intentionally excluded the Svensson et al[41] study, which investigates high-dose rifampicin with complex pharmacokinetics, including saturation and autoinduction. These differences precluded its inclusion in our analysis.

In the current PopPK model report, correlations between certain covariates, such as body weight and sex, may exist and require further exploratory analysis during model inclusion. Additionally, we did not perform a non-compartmental analysis to quantify exposure differences between the models. These limitations provide opportunities for improvement in future work. Future research will focus on validating the models included in the Shiny application, conducting external validation, and exploring ways to enhance its clinical applicability.

Conclusion

This study underscores the importance of model-informed precision dosing in optimizing rifampin therapy. By systematically reviewing 31 popPK models, we identified key covariates affecting rifampin pharmacokinetics, including FFM, BW, and PMA in pediatrics, while SLCO1B1 polymorphisms and other covariates showed limited clinical relevance.

Significant inter-model variability was observed in exposure predictions, reflecting differences in model structures and covariate selection. Most models employed a one-compartment approach, while two-compartment models suggested a more complex distribution profile. The lack of external validation in most studies highlights the need for further validation efforts.

To facilitate individualized dosing, we developed a rifampin model repository and Shiny application, enabling real-time exposure simulations. Future research should focus on refining model structures, validating findings across diverse populations, and assessing long-term metabolic changes during therapy to enhance personalized treatment strategies.

Study Highlights

What is the Current Knowledge on the Topic?

Rifampicin is a key first-line drug for tuberculosis treatment, extensively studied through population pharmacokinetic (popPK) models to understand its pharmacokinetics and optimize therapy. Variability in rifampicin exposure due to factors like body weight, genetic polymorphisms, and comorbidities can affect treatment outcomes and contribute to drug resistance. Previous reviews of rifampicin popPK models have limitations, and there is a need for a comprehensive repository to support individualized therapy.

What Question Did This Study Address?

This study aimed to construct a comprehensive rifampicin popPK model repository to support model-informed individualized therapy. It sought to identify significant covariates influencing rifampicin pharmacokinetics, compare pharmacokinetic profiles of different models, and develop a Shiny application for simulation and individualized dosing predictions.

What Does This Study Add to Our Knowledge?

This study provides a comprehensive repository of rifampicin popPK models, incorporating data from 29 studies on various populations, including adults, pediatrics, and pregnant women. It identifies key covariates affecting rifampicin clearance, such as body weight and fat-free mass, and highlights the importance of individualized dosing strategies. The

developed Shiny application allows for real-time simulations and personalized dosing adjustments based on patient-specific parameters.

How Might This Change Drug Discovery, Development, and/or Therapeutics?

The rifampicin popPK model repository and Shiny application enhance clinical decision-making by providing accurate exposure predictions and supporting tailored therapeutic regimens. This approach can improve treatment outcomes, reduce the risk of drug resistance, and pave the way for better patient care through evidence-based, individualized therapy. It also highlights the need for further research on special populations and the impact of covariates on rifampicin pharmacokinetics.

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Disclosure

The authors report no conflicts of interest in this work.

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