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RESEARCH ARTICLE

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Influential predictors of azithromycin pharmacokinetics: a systematic review of population pharmacokinetics

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ABSTRACT

Introduction: Azithromycin exhibits significant pharmacokinetic variability. Thus, dosage optimization is crucial for optimal therapeutic outcomes. This systematic review aims to analyze the population pharmacokinetics (PopPK) of azithromycin and identify key covariates influencing its pharmacokinetics.

Methods: A systematic search was conducted in PubMed, Scopus, and ScienceDirect databases. Azithromycin PopPK studies conducted using a nonlinear mixed-effects approach in humans were included. Studies published in non-English or non-Thai languages were excluded. Moreover, studies with insufficient information, review articles, or registered protocols were also excluded. The reporting quality of the included studies was assessed using adapted guidelines from a previously published framework. Data on study designs, population characteristics, pharmacokinetic parameters, and influential predictors were summarized. Forest plots were used to determine the influence of covariates on azithromycin pharmacokinetics.

Results: Fifteen studies were included. The volume of distribution (V_d) and the clearance in preterm newborns were approximately 68%–94% and 87%–100% lower than those of adults and children. Pregnant women had approximately 85% higher V_d. Patients with alanine aminotransferase >40 U/L had about 24% lower clearance. Azithromycin clearance slightly decreased with advancing age. There is limited data on the relationship between azithromycin exposure and safety outcomes. Finally, most models were not externally evaluated.

Conclusions: Significant predictors for azithromycin pharmacokinetics were identified in this review. However, the limited external validation of most models restricts their clinical utility. Further research is necessary to confirm the models' external validity.

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1. Introduction

Azithromycin, an azalide antibiotic in the macrolide class, has activity against both gram-negative and gram-positive organisms. Its antibiotic efficacy encompasses respiratory, urogenital, cutaneous, ocular, and several other bacterial illnesses. Moreover, it exerts beneficial efficacy in chronic inflammatory conditions including bronchiolitis obliterans and rosacea [1]. Azithromycin exhibits antibacterial activity through its binding to the 50S ribosomal subunit, leading to the inhibition of bacterial protein synthesis [2]. In addition to antibacterial activity, the drug also displays antimalarial action against *Plasmodium falciparum* [3] and *Plasmodium vivax* [4]. As for the safety profile, in contrast to other medications in the macrolide class that carry a risk of cardiac QT prolongation, this occurrence has been documented in a small number of patients after azithromycin treatment [5]. However, there has been evidence of a higher risk of QT prolongation in those who are more vulnerable to negative cardiac consequences [6].

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Azithromycin is incompletely absorbed with oral bioavailability of approximately 37% following a single 500-mg dose, with time to maximum concentration (T_{max}) ranging from 2 to 2.6 h [7]. It has a large volume of distribution with high intracellular concentrations [1]. Azithromycin is bound to alpha- and beta-globulins, but not to albumin, and the binding is concentration dependent, ranging from 12% at concentration 0.5 µg/mL and 50% at concentration 0.02 µg/mL [8]. The drug is rarely metabolized and does not interact with CYP enzymes [9], but is subject to biliary excretion [10], with >50% in an unchanged form [11]. While only 4.5% and 12.2% of the drug are excreted unchanged in the urine after an oral and intravenous 500 mg dosage, respectively. It demonstrates superior pharmacokinetic properties over erythromycin with greater and longer-lasting tissue concentrations, resulting in a longer half-life and a once-daily dosing schedule [12]. In addition, it substantially accumulates in phagocytes, leading to high concentrations at the infection site [13,14]. Depending on the infection type, different dosages of azithromycin are recommended for adults. For mild to moderate respiratory tract infections, 500 mg of azithromycin taken orally on the first day and 250 mg once daily on days 2 through 5 are advised [15]. While for community-acquired pneumonia (CAP), an intravenous dose of 500 mg once daily combined with beta-lactam antibiotics is recommended [15]. In paediatric patients aged >28 days, the recommended dose is 5–12 mg/kg/day and 10 mg/kg/day for oral and intravenous administration, respectively [15]. Due to its time-dependent killing with prolonged persistent effects, AUC_{24}/MIC is used as a pharmacokinetic–pharmacodynamic (PK/PD) target for azithromycin, and the ratio of >25 is associated with successful bacterial eradication for highly susceptible lung pathogens ($MIC_{90} \leq$ 0.125 µg/mL) like erythromycin-susceptible *Streptococcus pneumoniae* [9,16]. This ratio can be easily achieved with the usual recommended dosage. However, for azithromycin-resistant pathogens with higher MIC values, achieving this target ratio can be challenging [16].

Although azithromycin use is widespread, its pharmacokinetic variability among various populations remains a subject of significant interest, with studies highlighting inter-individual differences influenced by factors such as age, weight, ethnicity, disease state, and laboratory values [17–20]. Understanding the pharmacokinetics of azithromycin across populations is essential for optimizing therapy, particularly in vulnerable populations such as children, pregnant women, and those with comorbid conditions. For example, preterm newborns may have lower clearance per bodyweight than children and may require close monitoring than children when receiving treatment with azithromycin. Population pharmacokinetics (PopPK) is a method used to characterize pharmacokinetic behaviour of drugs across diverse populations, identifying patient-specific factors that may influence drug exposure and response. Furthermore, individualization of dosage regimens can be achieved by an integration of Bayesian estimation [21,22]. Given this, the objectives of this systematic review are to (1) provide a thorough overview of the PopPK of azithromycin, (2) pinpoint the important covariates affecting azithromycin's pharmacokinetics, and (3) identify gaps of knowledge for future research areas.

2. Methods

2.1. Study identification

We conducted thorough search of three databases including PubMed, Scopus, and ScienceDirect from the time of their inception until November 2024 using the following search terms: ('azithromycin' OR 'Zithromax' OR 'CP-62993') AND ('population pharmacokinet*' OR 'pharmacokinetic model' OR 'nonlinear mixed effect' OR 'NONMEM' OR 'NLME' OR 'monolix' OR 'WINNONMIX' OR 'P-PHARM' OR 'nlmixed' OR 'Pmetrics' OR 'USC PACK'). The reference list screen was used to find further studies. The obtained articles were kept in a citation manager (EndNote 20, Thomson Reuters, New York, NY, USA). Following the title and abstract screen, which was carried out independently by JM and TJ, the irrelevant articles were eliminated. Then, the same reviewers screened and selected full-text articles using the following inclusion criteria: (1) population pharmacokinetic studies conducted in humans receiving treatment with azithromycin and (2) investigations using a non-linear mixed-effects approach. Exclusion criteria included (1) studies published in languages other than English or Thai, (2) studies with inadequate details on the model development process or those with insufficient pharmacokinetic parameters and their variability, and (3) review articles or registered protocols. Any discordance was settled by consensus among all authors. This review was registered in PROSPERO with the registration number CRD42024609484. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standard version 2020 was adhered to in this review [23].

2.2. Assessment of reporting quality

The reporting quality of the included studies was assessed using a checklist adapted from the guidelines proposed by Kanji et al. [24], Jamsen et al. [25], Abdel

Jalil et al. [26] and Dartoris et al. [27], which was conducted by JM and TJ. The checklist covers 37 items, involving 7 domains. The percentage of compliance with the guidelines and report rate was calculated and presented in Table S1. The non-applicable items were excluded before calculating the compliance rate. The equation used for calculating the compliance rate was as follows:

$$\text{Compliance rate}\,(\%) = \frac{\text{sum of items reported}}{\text{sum of all items}} \times 100\%$$

2.3. Data extraction and study comparison

The data were independently extracted by JM and TJ using the predesigned data abstraction form produced by JM. The following information was extracted: (1) subject's characteristics as well as laboratory values, (2) pharmacokinetic data including dosage regimens, sampling strategy, and bioanalysis, (3) methodology of model development encompassing structural, statistical and covariate model, and (4) model qualification. For the sampling strategy, when there were more than six samples per patient, it was classified as intensive sampling; otherwise, the strategy was classified as sparse sampling. As for the model qualification, it was categorized as basic and advanced internal and external evaluations [28].

The effects of covariates on pharmacokinetic parameters, in particular, clearance was compared across studies and displayed as a forest plot using the approach proposed by Mao et al. [21] and Han et al. [22]. Each study's median covariate values were used to normalize the clearance reference values. The percentage of the estimated clearance range divided by the clearance reference value was used to express the impact of the identified covariates on clearance in each study. A change in clearance was deemed clinically relevant when it departs from the 80% to 125% range, a criterion used in bioequivalence study. A forest plot representing a change in clearance was conducted using Microsoft® Excel (version 16.95).

3. Results

3.1. Study identification

A total of 296 records were identified through the database search. Forty-eight duplicates were removed, leaving 248 records to be screened. Of these, 217 records were excluded as not relevant during the title and abstract screen, and an additional seven studies were removed as non-population pharmacokinetic studies. Ultimately, 24 full-text articles were assessed for eligibility, and 15 of them were included in this systematic review. A PRISMA flow diagram of study identification is presented in Figure 1.

3.2. Quality of reporting

Most studies demonstrated a high compliance rate with the median value of 82.6%. The three most frequently unreported items were storage conditions ($n = 8$), statistical criteria for including covariates to the models ($n = 7$), and methods for covariates inclusion ($n = 6$). Moreover, most studies published prior to 2014 did not disclose conflicts of interest. A detailed assessment of each study's reporting quality is presented in Table S1.

3.3. Study characteristics

Population pharmacokinetics of azithromycin were conducted in various populations including healthy volunteers [20,29–33], pregnant and non-pregnant women with malarial infection [18] and other infections, for example, respiratory tract infection, skin infection [19], African postpartum women [34], Japanese patients with respiratory tract infection [35], mechanically ventilated preterm newborns [36], preterm newborns at risk of *Ureaplasma* respiratory colonization [37] and paediatric patients with various kinds of infection [17,38,39]. In the majority of studies, azithromycin was orally administered, with only four studies utilizing data from intravenous infusion [36–39] and one study using data from subjects receiving azithromycin eye drop [33]. Intensive sampling was employed in most studies [18,20, 29–34], while five studies used sparse sampling [19, 36–39], and two studies utilized both intensive and sparse data [17,35]. Most studies aimed to characterize the pharmacokinetics of azithromycin and identify potential factors affecting its pharmacokinetics. Of these, one study determined the pharmacokinetics of azithromycin transferred into breast milk in breastfeeding mother [34] and the other one examined azithromycin pharmacokinetics in tears, following single-dose topical administration [33]. Five studies extended the developed model to assess the pharmacokinetic–pharmacodynamic relationships [20,33, 35,38,39]. Table 1 provides specific detailed characteristics on each study.

3.4. Population pharmacokinetic analyses

Most studies reported absorption kinetics of azithromycin as a first-order rate, except for two studies in which mixed zero- and first-order absorption was

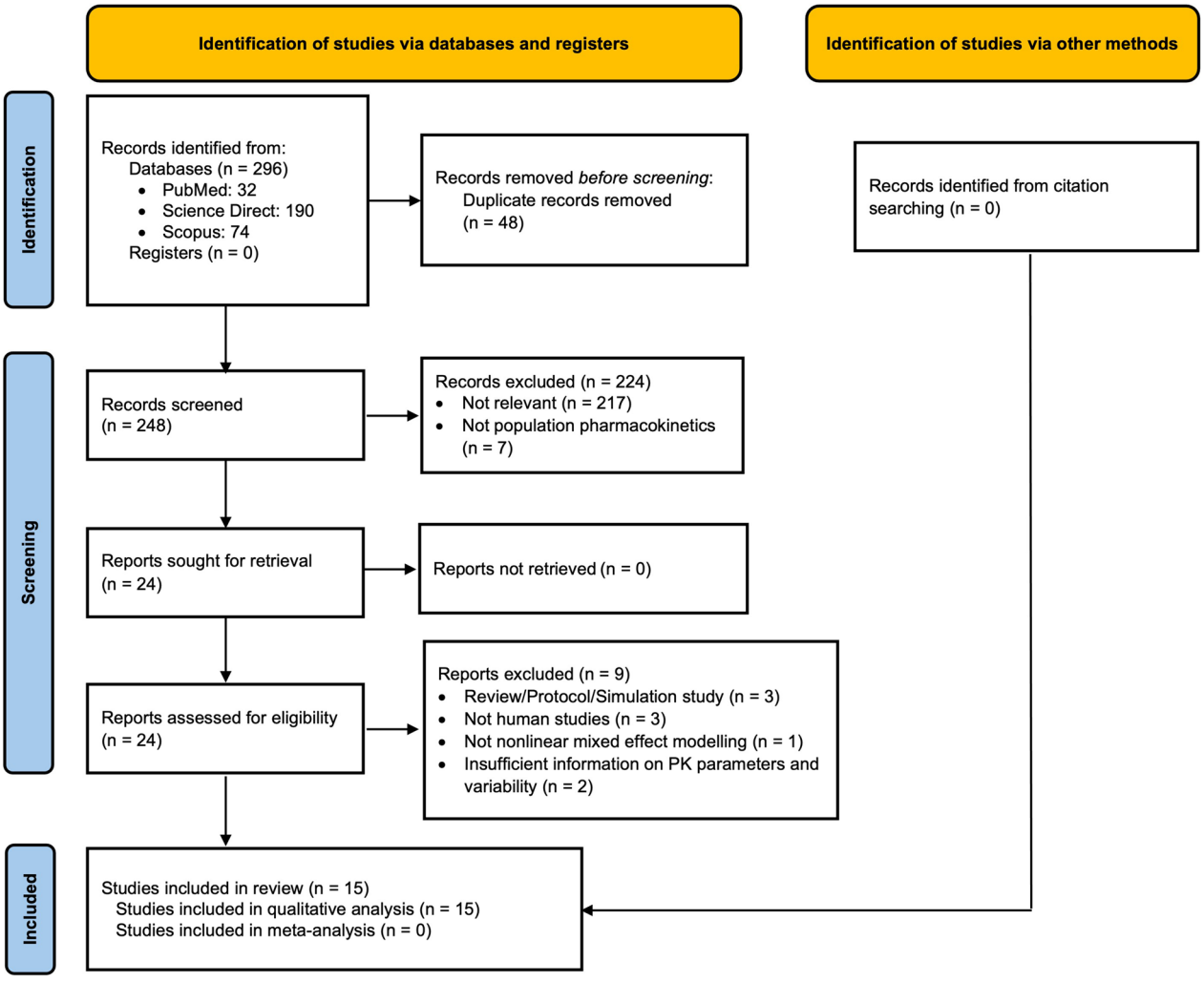

Figure 1. A PRISMA flow diagram of the study identification.

employed, with the duration of zero-order absorption of approximately 1.55 h [18,34]. The estimated absorption rate constant (k_a) ranged from 0.25 to 1.59 h^{-1}, with no significant predictors for this parameter. Moreover, an absorption lag time of approximately 0.457–1.45 h was observed in three studies [30,31,35].

In terms of distribution, azithromycin pharmacokinetics was characterized as a three-compartment model in most studies ($n=7$) [17–20,31, 32,34], followed by a two-compartment model in six studies [29,33, 35–38]. While a one-compartment [39] and a four-compartment model [32] were used to describe azithromycin distribution in each of the study. One study [31] incorporated specific tissue distribution such as intracellular fluid of muscle, subcutaneous adipose tissue, lung, and alveolar into the model. The volumes of distribution of azithromycin in healthy and infected adults and children ranged from 54.1 to 244.5 L/kg. While a substantially lower range of 14.9–17.4 L/kg was observed in preterm newborns.

Four studies [35,36, 38,39] evaluated the influence of body weight on volume of distribution using allometric scaling with an exponent of 1. Salman et al. [18] reported an approximately 86% increase in volume of distribution in pregnant women. Given that azithromycin is lipophilic, a higher volume of distribution in pregnant women, whose lipid content is higher, is expected [40]. The impact of blood cells, i.e. white blood cells, platelets, and haemoglobin on volumes of distribution was also assessed [39], none of which significantly influenced the volumes of distribution.

Elimination kinetics were explained with a first-order rate in all studies. Azithromycin clearance (CL_{AZ}) in preterm newborns, children, and adults ranged from 0.13 to 0.16, 1.16 to 1.27, and 0.96 to 3.69 L/h/kg,

Table 1. Study characteristics.

Study ID	Participant	Study site	Type of study	Sample size (male/female)	Sampling strategy	Mean age (years) ± SD (Median [range])	Mean weight (kg) ± SD (Median [range])	Samples / subjects (total samples)	Daily dose	Bioassay
Salman et al 2010 [18]	Pregnant and non-pregnant women living in a malaria endemic area	Papua New Guinea	Prospective	58 (0/58)29 pregnant 29 non-pregnant	Intensive	Pregnant: 25.45 ± 4.61 Non-pregnant: 26.37 ± 6.17	Pregnant: 54.9 ± 7.5 Non-pregnant: 51.66 ± 5.15	16 (928)	2 g PO	UPLC-LCMS-MS
Zhang et al 2010 [29]	Healthy volunteers	China	Prospective	160 (160/0)	Intensive	26.30 ± 1.53 [22–37]	65.28 ± 5.64 [57–81]	15 (2,400)	0.5 g PO	HPLC-MS
Muto et al 2011 [35]	Healthy westerners and Japanese and Japanese patients with respiratory tract infection	Western countries and Japan	Prospective	559 (203/356)	Intensive and sparse	(36 [16–90])	(60 [30–100])	1–16 (4,310)	2 g PO OD	HPLC
Hassan et al 2011 [36]	Mechanically ventilated preterm newborns	USA	Prospective	12 (6/6)	Sparse	GA (week): 26 ± 1 PNA (week): 47 ± 28	Birth weight: 0.86 ± 0.28	6 (72)	10 mg/kg IV infusion	LC-MS/MS
Fischer et al 2012 [19]	Pregnant and non-pregnant women with infection and healthy women	USA	Prospective	78 (0/78)53 pregnant 13 non-pregnant 12 healthy women	Sparse	Pregnant: (28 [18–41]) Non-pregnant: (33 [24–49]) Healthy: (24 [21–32])	Pregnant: (76 [47–178]) Non-pregnant: (67 [47–112]) Healthy: (61 [45–84])	4 (344)	0.5 g PO on day 1 and 0.25 g PO on days 2-5	HPLC
Dumitrescu et al 2013 [30]	Healthy volunteers	France	Retrospective	25 (25/0)	Intensive	(29 [19–47])	(73 [61.1-87.9])	9 (225)	0.5 g PO OD over 3 days	LC-MS/MS
Sampson et al 2014 [32]	Healthy volunteers	USA	Prospective	20 (12/8)	Intensive	(48.5 [21–63])	BMI: (24.9 [21.4–28.2])	16 (269)	0.25 g or 1 g PO	MS/MS
Zhao et al 2014 [17]	Healthy adults and *P. falciparum* infected children	Sub-Saharan African and USA	Prospective	21940 adults 123 paediatrics aged <5 years 56 paediatrics aged 5–12 years	Intensive and sparse	NR	NR	4–15 (1,198)	• 0.3 g/kg AZ + 10 mg/kg CQ • 0.5 g AZ + 0.3 g CQ	LC-MS/MS
Zheng et al 2014 [31]	Healthy volunteers	Austria	Prospective	6 (6/0)	Intensive	29.0 ± 9.63	77.68 ± 8.56	16 (96)	0.5 g PO OD over 3 days	HPLC
Merchan et al 2015 [37]	Preterm newborns at risk of *Ureaplasma* respiratory colonization	USA	Prospective	15 (8/7)	Sparse	*Ureaplasma* positive GA (week): 26.2 ± 1.2 *Ureaplasma* negative GA (week): 26.3 ± 1.7	*Ureaplasma* positive 0.86 ± 0.2 *Ureaplasma* negative 0.93 ± 0.3	6 (90)	20 mg/kg/day IV inf × 3 days	LC-MS/MS
Salman et al 2016 [34]	African postpartum women	The Gambia	Prospective	20 (0/20)	Sparse	27.7 ± 6.1	68 ± 11	4 (80)	2 g PO	UPLC-MS/MS
Zheng et al 2018 [38]	Paediatric patients	China	Prospective	95 (53/42)	Sparse	6.2 ± 2.6 (5.9 [2.1–11.7])	23.9 ± 9.8 (21.5 [11.0–51.0])	~1–2 (140)	10 mg/kg IV inf OD	LC-MS/MS
Wu et al 2019 [33]	Healthy volunteers	China	Prospective	42 (21/21)	Intensive	28.4 ± 6.8 [18-44]	BMI: 21.8 ± 1.6 [19.1-24]	7 (84)	Single eyedrop (2.5 mg/2.5 mL) into each eye	LC-MS/MS

(*Continued*)

Table 1. Continued.

Study ID	Participant	Study site	Type of study	Sample size (male/female)	Sampling strategy	Mean age (years) ± SD (Median [range])	Mean weight (kg) ± SD (Median [range])	Samples / subjects (total samples)	Daily dose	Bioassay
Chotsiri et al 2022 [20]	Healthy volunteers	Thailand	Prospective	70 (55/15)	Intensive	*CQ 1 g + AZ 0.5 g:* 34.7 ± 12.2 *CQ 1 g + AZ 1 g:* 40.2 ± 12.3 *CQ 1 g + AZ 2 g:* 33.4 ± 13.2	*CQ 1 g + AZ 0.5 g:* 82.9 ± 12.2 *CQ 1 g + AZ 1 g:* 83.9 ± 15.1 *CQ 1 g + AZ 2 g:* 77.6 ± 13.8	19 (1,330)	• 0.5 g PO × 3 days • 1 g PO × 3 days • 1.5 g PO × 3 days	HPLC
Zhang et al 2024 [39]	Children with pneumonia	China	Prospective	148 (74/74)	Sparse	(39 [9–72]) months	(14.4[7.5–24.5])	(254)	10 mg/kg IV inf OD	UPLC-MS/MS

AZ: azithromycin, BMI: body mass index, CQ: chloroquine, GA: gestational age, HPLC-MS: High-Performance Liquid Chromatography-Mass Spectrometry, IV: intravenous, LC-MS/MS: liquid chromatography-tandem mass spectrometry, NR: not reported, OD: once daily, PNA: postnatal age, PO: per oral, UPLC-LCMS-MS: Ultra-Performance Liquid Chromatography Coupled with Tandem Mass Spectrometry, SD: standard deviation.

respectively. Weight was the most incorporated covariate for CL_{AZ} [17,29, 35–39] and volumes of distribution [35,36, 38,39], often utilizing an allometric function in the final models. Age was also a significant predictor for CL_{AZ} [35,39]. The impact of each covariate on CL_{AZ} is illustrated in the forest plot (Figure 2). Investigated covariates on azithromycin pharmacokinetic parameters are summarized in Table 3.

In terms of statistical models, exponential relationships were used to explain inter-individual variability in all studies, while residual variability was mostly described with a proportional relationship [18,19, 30,32, 34–37,39]. The magnitude of inter-individual variability on the absorption rate constant (k_a), azithromycin clearance (CL_{AZ}), and central volume of distribution (V_1) was notably wide, ranging from 26.2% to 110%, 3.04% to 122%, and <0.01% to 189%, respectively. Table 2 summarizes software and estimation methods utilized in model development, covariate–parameter relationships of the final models, along with statistical models as well as model assessment. Figure 3 illustrates the typical values of clearance of each study.

All studies evaluated their models using basic internal (goodness of fit plots) and advanced internal approaches, including bootstrap analysis, visual predictive check and Jackknife method. Notably, one study [38] assessed the model with an external approach utilizing a dataset comprising 28 subjects.

Five studies applied the developed models for dosage recommendations. Muto et al. [35] reported that AUC/MIC > 5 h resulted in substantially high bacteriological (95.8%) and clinical success (100%). Hassan et al. [36] proposed that a dose of 20 mg/kg/day, double the standard dose recommended for children, administered for 3 days, is required to achieve plasma concentrations above the MIC_{50} for *Ureaplasma* spp. in the respiratory tract of preterm newborns. Zheng et al. [38] used Monte Carlo simulations to optimize dosage regimens for CAP treatment. Using a target *f*AUC/MIC value of 3 h obtained from Hassan et al.'s study [36], a loading dose of 15 mg/kg followed by a maintenance dose of 10 mg/kg would result in 50% of paediatric patients achieving the target PK/PD. Using the same target *f*AUC/MIC, Zhang et al. [39] also proposed a dosing scheme based on Monte Carlo simulation, categorized by four age and weight groups. A loading dose ranging from 10 mg/kg/day to 15 mg/kg/day is required to achieve the target. Given that azithromycin has a long elimination half-life [15], a loading dose is of importance to achieve early target attainment. Moreover, Wu et al. [33] proposed that the optimal dosage regimen for azithromycin eyedrops is

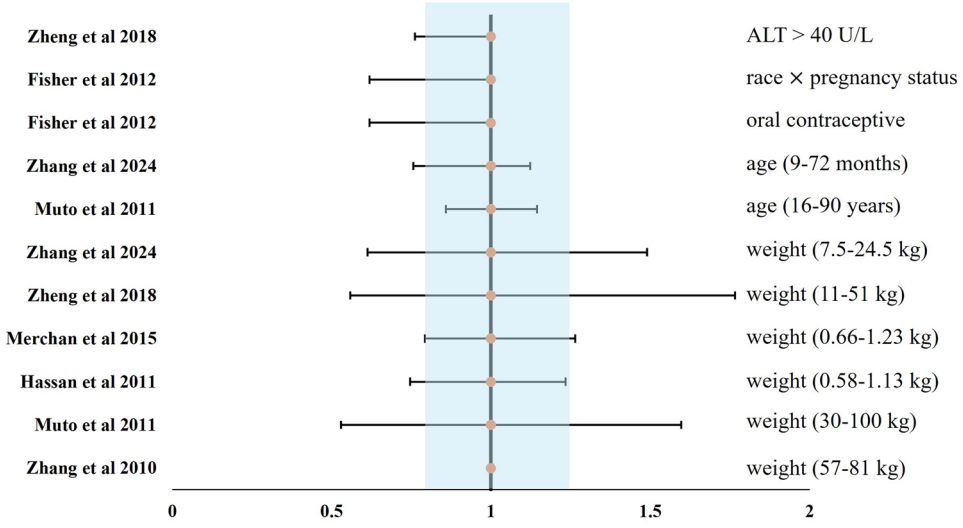

Figure 2. Forest plot of the covariates influencing azithromycin clearance.

twice-daily instillation, based on the MIC thresholds of 2 and 4 mg/L, and the target AUC/MIC ratio of 100.

4. Discussion

Population pharmacokinetics combined with Bayesian estimation has played a crucial role in personalized drug therapy in recent decades. Additionally, it allows researchers to investigate possible factors that affect the pharmacokinetics of drugs. To help individualize drug dosage, several azithromycin PopPK models have been created thus far, each having a unique model structure and important variables. This is the first systematic review of azithromycin specifically aimed at summarizing its key pharmacokinetic properties as well as identifying sources of variability.

From classical pharmacokinetic studies, the absorption kinetics of azithromycin are classified as both zero-order [41] and first-order processes [42]. In agreement with this, most population pharmacokinetic models identified that azithromycin absorption follows a first-order process with a rapid absorption rate, ranging from 0.25 to 1.59 h^{-1}. However, a mixed zero- and first-order absorption model was identified in two studies [18,34]. Azithromycin is a weak base, with a p*Ka* of 8.7 and 9.5 [43], therefore, it is rapidly dissolved in the stomach, resulting in a saturated solution of the drug in the stomach [41]. This zero-order process is hypothesized to represent the gastric emptying time of the drug into the small intestine.

Animal study [44] indicated that azithromycin is a substrate for both Multidrug resistance-associated protein 2 (Mrp2) and P-glycoprotein (P-gp), and these two drug transporters mediate azithromycin's excretion in the intestines and biliary system. Co-administration of azithromycin with drugs that induce or inhibit these transporters may affect azithromycin bioavailability. Nonetheless, this issue has not been investigated, and future studies should be conducted to explore this potential drug interaction. However, according to the label, co-administration of azithromycin with nelfinavir increased the mean area under the concentration-time curve ($AUC_{0-\infty}$) and maximum concentration (C_{max}) by approximately two times and close monitoring for azithromycin side effects is warranted [45]. Moreover, He et al. [46] have indicated that azithromycin may be influenced by polymorphisms of the ABCB1 (ATP-binding cassette B1) gene. However, no studies have investigated such an effect. This aspect should also be determined in a future population pharmacokinetic study.

The reported volumes of distribution of azithromycin in healthy and infected adults and children vary widely, ranging from 54.1 to 244.5 L/kg, which reflects extensive tissue penetration. While preterm newborns showed a much lower range of 14.9–17.4 L/kg, which could be explained by differences in developmental physiology and body composition. Compared to adults and children, newborns have a lower percentage of body fat and a higher percentage of total body water. As a result, lipophilic azithromycin may have less tissue distribution in newborns.

It has been established that azithromycin levels in breast milk are relatively low and are unlikely to cause adverse effects in breastfed infants [47]. Nonetheless, this evidence was based on small numbers of subjects with only a single breast milk sample. Salman et al. [34] have reported that even when a single dose is administered during childbirth, the proportion of infants whose azithromycin dosage via breastfeeding

Table 2. Pharmacokinetic parameter–covariate relationship, variability, estimation methods and software.

Study ID	Software / estimation method	Structural model	PK parameter–covariate relationship	Between-subject variability (%CV)		Residual variability estimate (%CV)	Model qualification
Salman et al 2010 [18]	NONMEM / FOCE-I	3-CMT with zero-order followed by first-order absorption and linear elimination	DUR (h) = 1.55	Expo	76.9%	Prop: (31.2%)	GOF plots, bootstrap, VPC
			k_a (h^{-1}) = 0.525		–		
			V_1/F (L) = 384 + 330 (if pregnant)		99.6%		
			V_2/F (L) = 4,080		35.6%		
			V_3/F (L) = 5,070		–		
			CL/F (L/h) = 158		28.3%		
			Q_2/F (L/h) = 325		–		
			Q_3/F (L/h) = 66.4		–		
Zhang et al 2010 [29]	NONMEM / NR	2-CMT with first-order absorption and elimination	k_a (h^{-1}) = 1.05	Expo	83.2%	Prop: (32.96%) Add: SD < 0.01	GOF, Jackknife (MPE, SPME)
			V_1/F (L) = 1939 − 0.181 × (age − 19.03)		<0.01%		
			V_2/F (L) = 5,650		43.6%		
			CL/F (L/h) = [121–0.0379 × (60.43 − weight)]		14.6%		
			Q_2/F (L/h) = 282		29.7%		
Muto et al 2011 [35]	NONMEM / FOCE-I	2-CMT with first-order absorption and elimination	k_a (h^{-1}) = 0.604	Expo	110%	Prop: (30%)	GOF, Bootstrap
			Lag time (h) 0.457	$COV_{ka-V1/F}$: (r = 0.53)	43%		
			V_1/F (L) = 1,830 × (weight/70)$^{1.03}$ × (age/45)$^{-0.256}$				
			V_2/F (L) = 4,340 × (weight/70)^{1}	$COV_{ka-CL/F}$: (r = 0.65)	34%		
			CL/F (L/h) = 103 × (weight/70)$^{0.917}$ × (age/45)$^{-0.166}$				
			Q_2/F (L/h) = 138 × (weight/70)$^{0.75}$	$COV_{CL-V1/F}$: (r = 0.28)			
Hassan et al 2011 [36]	NONMEM / FOCE-I	2-CMT with first-order elimination	V_1 (L) = 0.93	Expo	–	Prop: (28.7%)	GOF, VPC
			V_2 (L) = 14.2 × weight^{1}		26.2%		
			CL (L/h) = 0.18 × weight$^{0.75}$		23.5%		
			Q_2 (L/h) = 1.0		–		
Fischer et al 2012 [19]	NONMEM / FOCE	3-CMT with first-order absorption (and a lag time) and elimination	k_a (h^{-1}) = 0.8 (fixed)	Expo	–	Prop: (32%)	GOF plots, bootstrap, VPC
			V_1/F (L) = 456		114%		
			V_2/F (L) = 1,560		60%		
			V_3/F (L) = 16,100		NE		
			• CL/F (L/h) = 134 + race × preg × (−51) + OC × (−51) race = 1 for non–African American, 0 otherwise • preg = 1 for pregnant, 0 otherwise • OC = 1 for woman receiving oral contraceptive, 0 otherwise		36%		
			Q_2/F (L/h) = 401		–		
			Q_3/F (L/h) = 120 + race × preg × (−78)		86%		
Dumitrescu et al 2013 [30]	Phoenix NLME / FOCE-I	3-CMT with first-order absorption, lag time, and first-order elimination	k_a (h^{-1}) = 0.604	Expo	26.2%	Prop (plasma): (24.1%) Prop (blood): (23.2%)	GOF plots, bootstrap, VPC
			Lag time (h) 0.95		–		
			V_1/F (L) = 440		107.3%		
			V_{bc}/F (L) = 3,084		–		
			V_t/F (L) = 2,980		–		
			CL/F (L/h) = 118		30.3%		
			Q_{bc}/F (L/h) = 17.8		–		
			Q_t/F (L/h) = 213		8.2%		
Sampson et al 2014 [32]	Phoenix NLME / FOCE-I	4-CMT with first-order absorption and first-order elimination from central compartment	k_a (h^{-1}) = 0.53	Expo	41%	Prop (blood): (47%) Prop (PMBC): (74%)) Prop (PMN): (64%)	GOF plots, bootstrap, VPC
			Lag time (h) = 0.41		–		
			V_1/F (L) = 336		122%		
			V_2/F (L) = 0.62		51%		
			V_3/F (L) = 2.96		53%		
			V_4/F (L) = 4,597		–		
			CL_1/F (L/h) = 67.3		114%		
			CL_2/F (L/h) = 0.0091		–		
			CL_3/F (L/h) = 0.026		–		
			Q_2/F (L/h) = 9.0		75%		
			Q_3/F (L/h) = 26.7		75%		
			Q_4/F (L/h) = 73.2		–		

(*Continued*)

Table 2. Continued.

Study ID	Software / estimation method	Structural model	PK parameter–covariate relationship	Between-subject variability (%CV)		Residual variability estimate (%CV)	Model qualification
Zhao et al 2014 [17]	NONMEM	3-CMT with first-order absorption and elimination	k_a (h^{-1}) = 0.259	NR	–	NR: 0.406	GOF plots, VPC
			Lag time (h): NE		–		
			V_1/F (L) = 186		113%		
			V_2/F (L) = 2,890				
			V_3/F (L) = 2.610		–		
			CL/F (L/h/kg) = $(100/\text{weight})^{0.75}$		31.3%		
			Q_2/F (L/h/kg) = $(180/\text{weight})^{0.75}$		–		
			Q_3/F (L/h) = 10.6		–		
Zheng et al 2014 [31]	NONMEM / FOCE-I	3-CMT with first-order absorption, lag time, and first-order elimination and tissue distribution model in interstitial fluid of muscle and subcutaneous adipose tissue	k_a (h^{-1}) = 0.88 (fixed)	Expo	–	Plasma	GOF plots, bootstrap
			Lag time (h): 1.45 (fixed)		17.6%	Prop: 0.14	
			V_1/F (L) = 160		168.3%	Add: 35.2	
			V_2/F (L) = 1,190		–	Muscle ISF	
			V_3/F (L) = 9,721		–	Prop: 0.14	
			CL/F (L/h) = 258 (fixed)		29.3%	Add: 0.51	
			Q_2/F (L/h) = 207		–	Subcutis ISF	
			Q_3/F (L/h) = 101		–	Prop: 0.34	
			k_{in} (h^{-1}) = 0.16		0.22%	Add: 1×10^{-6}	
			k_{out} (h^{-1}) = 0.15		–	PMLcytosol	
			k_{on} (h^{-1}) = 0.56		–	Prop: 0.23	
			k_{off} (h^{-1}) = 0.05		–	Add: 1×10^{-6}	
			DF_{muscle} = 0.55		26.9%		
			$DF_{subcutaneoustissue}$ = 0.25		31.5%		
			$DF_{PML(cytosol)}$ = 52		0.22%		
Merchan et al 2015 [37]	NONMEM / FOCE-I	2-CMT with first-order elimination	V_1/F (L/kg) = 1.88	Expo	78.2%	Prop: (28%)	GOF plots, VPC
			V_2/F (L/kg) = 13		78.1%		
			CL/F (L/h) = 0.15 × $\text{weight}^{0.75}$		58.1%		
			Q_2/F (L/h) = 1.79× $\text{weight}^{0.75}$		64.3%		
Salman et al 2016 [34]	NONMEM / FOCE-I	3-CMT with mixed zero- and first-order absorption, and first-order elimination	DUR (h) = 1.55 (fixed)	Expo	–	Prop: (32%)	GOF plots, bootstrap, pcVPC
			k_a (h^{-1}) = 0.525 (fixed)		–		
			V_1/F (L/70kg) = 714 (fixed)		–		
			V_2/F (L/70kg) = 4,080 (fixed)		–		
			V_3/F (L/70kg) = 5,070 (fixed)		–		
			CL/F (L/h/70kg) = 104		*F*: 63%		
			Q_2/F (L/h/70kg) = 325 (fixed)		–		
			Q_3/F (L/h/70kg) = 67.2 (fixed)		–		
			MP_{ratio} = 2.49		–		
			SIG_{pos} = 2.49		60%		
			$MAT_{50,pos}$ (h) = 2.49		–		
			$Hill_{pos}$ = 2.49		–		
			SIG_{neg} = 2.49		–		
			$MAT_{50,neg}$ (h) = 2.49		–		
			$Hill_{neg}$ = 2.49		–		
			$MP'_{M,t,Hillpos} = MP_{M,t} \times [1 + SIG_{pos} \times \left(\frac{T_{birth}^{Hillpos}}{T_{birth}^{Hillpos} + MAT_{50,pos}} \right)$		–		
			$MP'_{M,t,Hillneg} = MP_{M,t} \times [1 + SIG_{neg} \times \left(\frac{T_{birth}^{Hillneg}}{T_{birth}^{Hillneg} + MAT_{50,neg}} \right)$		–		

(*Continued*)

Table 2. Continued.

Study ID	Software / estimation method	Structural model	PK parameter–covariate relationship	Between-subject variability (%CV)		Residual variability estimate (%CV)	Model qualification
Zheng et al 2018 [38]	NONMEM / FOCE-I	2-CMT with first-order elimination	V_1/F (L) = 39.5 × (weight/21.5)^1	Expo	84.9%	Expo: (5.7%)	Internal: GOF plots, NPDE, bootstrap External: N = 28, no. of samples = 28
			V_2/F (L) = 377 × (weight/21.5)^1		–		
			CL/F (L/h) = 27.8 × (weight/21.5)$^{0.75}$ ×0.761^{Fliver}		32.1%		
			F_{liver} = 0 for ALT ≤40				
			F_{liver} = 1 for ALT >40				
			Q_2/F (L/h) = 55.7 × (weight/21.5)$^{0.75}$		51.6%		
Wu et al 2019 [33]	Phoenix NLME / FOCE-I	2-CMT with first-order elimination	V_1/F (mL) = 2.86	Expo	189%	Power: 1	GOF plots, bootstrap, VPC
			V_2/F (mL) = 28.7		95.9%		
			CL/F (mL/h) = 0.219		122%		
			Q_2/F (mL/h) = 1.12		85.1%		
Chotsiri et al 2022 [20]	NONMEM	3-CMT with first-order absorption, and first-order elimination	F (%) = 100 (fixed)	Expo	IIV: 21.5% IOV: 14.9%	Add: 0.0194	GOF plots, bootstrap, VPC
			k_a (h^{-1}) = 1.59		IIV: 59.4% IOV: 51.0%		
			V_1/F (L) = 451		IOV: 49.6%		
			V_2/F (L) = 2,510		–		
			V_3/F (L) = 824		–		
			CL/F (L/h) = 101		IIV: 14.8%		
			Q_2/F (L/h) = 80.6		IIV: 30.1%		
			Q_3/F (L/h) = 343				
Zhang et al 2024 [39]	Phoenix NLME / FOCE	1-CMT with first-order elimination	V_1 (L/kg) = 45.65 × (weight/14.4)^1	Expo	6.19%	Prop: (24.31%)	GOF plots, bootstrap, VPC
			CL (L/h/kg) = 1.27 × (weight/14.4)$^{0.75}$ × (age in month/39)$^{0.19}$		CL: 3.04% Age on CL: 35.5%		

Add: additive, CL/F: apparent clearance from the central compartment, CL_2/F: apparent clearance from the second compartment, CL_3/F: apparent clearance from the third compartment, CMT: compartment, COV: covariance, CV: coefficient of variation, DF: distribution factor, DUR: duration for zero-order absorption, Expo: exponential, F: bioavailability, FOCE-I: first-order conditional estimation with interaction, GOF: goodness of fit, k_a, absorption rate constant, $Hill_{pos}$: Hill coefficient for the positive curve, $Hill_{nec}$: Hill coefficient for the negative effect, IIV: inter-individual variability, IOV: inter-occasion variability, k_{in}: rate constant for unbound azithromycin uptake into tissue, k_{out}: rate constant for the reverse process described for k_{in}, k_{on} and k_{off}: on and off rate constants, $MAT_{50,pos}$: time to 50% of the positive curve, $MAT_{50,neg}$: time to 50% of the negative curve, MPE: mean prediction error, MP_{ratio}: milk/plasma ratio, NE: not estimated, PK: pharmacokinetics, PML: polymorphonuclear leukocytes, Prop: proportional, Q_2/F: apparent intercompartmental clearance between the central and the second compartment, Q_3/F: apparent intercompartmental clearance between the central and the third compartment, Q_4/F: apparent intercompartmental clearance between the central and the fourth compartment, r: correlation coefficient, SD; standard deviation, SIG_{neg}: maximum effect on MP_{ratio} of the negative curve, SIG_{pos}: maximum effect on MP_{ratio} of the positive curve, SPME: standard mean prediction error, T_{birth} is the time of birth, Q_{bc}/F: apparent distributional clearance between plasma and blood cell, Q_t/F: apparent distributional clearance between plasma and tissue, V_1/F: apparent central volume of distribution, V_2/F: apparent peripheral volume of distribution of the second compartment, V_3/F: apparent peripheral volume of distribution of the third compartment, V_4/F: apparent peripheral volume of distribution of the fourth compartment, V_{bc}/F: apparent volume of distribution of blood cell, V_t/F: apparent volume of distribution of the fibroblasts in tissues, VPC: visual predictive check.

Table 3. Investigated covariates on azithromycin pharmacokinetic parameters.

Study ID	Age	Body size	Race	Gender	AZ dose	Blood glucose	CBC	Liver function	Renal function	Concurrent medication	Other
Salman et al 2010 [18]	GA	–	–		–	√	Hb	–	–	–	Fundal height, **pregnancy status***, malarial status, treatment type (AZ+CQ, AZ+SP)
Zhang et al 2010 [29]	**GA***	**WT***	–	–	–	–	Hb, platelet, WBC	ALT	BUN, SCr	–	
Muto et al 2011[35]	**√***	**WT***	√	√	–	–	–	–	–	–	–
Hassan et al 2011 [36]	–	**WT***	–	–	–	–	–	–	–	–	–
Fischer et al 2012 [19]	GA, mother age	–	**√***	–	√	–	–	–	CrCl	√	Fasting state, study site, **pregnancy status***, **oral contraceptive***, type of infection, hepatic and renal impairment
Dumitrescu et al 2013 [30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sampson et al 2014 [32]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhao et al 2014 [17]	√	**WT***, HT, BSA, BMI, IDW, LBW	√	√	√	–	–	AST, ALT, bilirubin, albumin	CrCl	–	Study type (1 or 2)
Zheng et al 2014 [31]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Merchan et al 2015 [37]	GA	**WT***, BSA, HT	–	√	–	–	–	–	–	–	–
Salman et al 2016 [34]	GA, maternal age	Infant birth weight	–	–	–	–	–	–	–	–	–
Zheng et al 2018 [38]	√	**WT***, HT	–	√	–	–	–	AST, **ALT***	BUN, SCr	–	–
Wu et al 2019 [33]	√	–	–	√	–	–	–	–	–	–	Intraocular pressure, tear secretion
Chotsiri et al 2022 [20]	√	HT	√	√	–	–	–	–	–	–	Treatment arm
Zhang et al 2024 [39]	**√***	**WT***	–	√	–	–	WBC, platelets, Hb	ALT	SCr	–	

ALT: alanine aminotransferase, AST: aspartate aminotransferase, AZ: azithromycin, BMI: body mass index, BSA: body surface area, BUN: blood urea nitrogen, CBC: complete blood count, CQ: chloroquine, CrCl: creatinine clearance, GA: gestational age, Hb: haemoglobin, HT: height, IDW: ideal body weight, LBW: lean body weight, NR: not reported, SCr: serum creatinine, SP: sulphadoxine-pyrimethamine, WBC: white blood cell, WT: weight.
Covariates marked in bold with asterisks (*) indicate statistically significant effects.

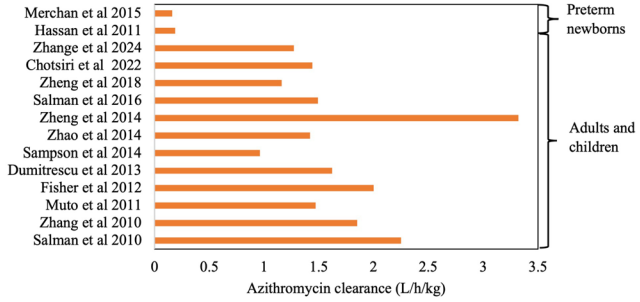

Figure 3. The typical clearance values of each study.

exceeds the recommended 10% safety limit may be rather high. However, the risk of infantile hypertrophic pyloric stenosis remains to be further investigated in a large clinical trial.

Preterm newborns [36,37] had approximately 87.4%–100% lower CL_{AZ} per kilogram body weight than children [38,39], ranging from 0.13 to 0.16 and 1.16 to 1.27 L/h/kg, respectively. This could be due to their immature or inadequate biliary excretion routes, the primary route of azithromycin elimination [10], which may fully mature within the first year of life [48]. According to the lower CL_{AZ} in preterm newborns, close monitoring for signs of toxicity, such as the potential for proarrhythmic or gastrointestinal symptoms, is warranted, especially when administering high doses.

Excluding notably high CL_{AZ} value of 3.69 L/h/kg by Zheng et al.'s study [31], the CL_{AZ} in healthy and infected adults and children ranged from 0.96 to 2.25 L/h/kg. The substantially high CL_{AZ} in Zheng's study was obtained from a fixed literature value, rather than being derived as a population-estimated parameter, which may not capture the true CL_{AZ} value and could introduce bias. Moreover, studies containing pregnant women had slightly higher CL_{AZ} with the values of 1.91 [19] and 2.25 L/h/kg [18]. Pregnant women may experience several physiological changes, such as increased cardiac output [49], resulting in enhanced hepatic perfusion, and in turn higher metabolic and biliary clearance. Nonetheless, the impact of pregnancy on CL_{AZ} is not conclusive from the population pharmacokinetic studies, as Salman et al. [18] did not observe a significant effect of pregnancy on CL_{AZ}. It should be noted that only 29 pregnant women were included in this study; thus, future research with a larger sample size is advised to confirm the results. Fischer et al. [19] found a 38% lower CL_{AZ} in non-African American pregnant women, but no significant effect of pregnancy on CL_{AZ} was observed in African American pregnant women. These ethnic differences may have partly contributed to different P-gp expressions [50], which may affect the biliary excretion of azithromycin. The same magnitude of effect (38% lower CL_{AZ}) was observed in women receiving oral contraceptives. These findings suggested that a lower dosage regimen in non-African American women during pregnancy or those receiving oral contraceptives may be warranted to achieve the same exposure. Even though, based on the forest plot (Figure 2), such an impact is deemed of clinical relevance, an azithromycin pharmacodynamic study during pregnancy is recommended to provide definitive guidance for dosage adjustment.

Body weight was the most commonly identified covariate on CL_{AZ} using allometric scaling with the exponent of 0.75, except for Zhang et al.'s study [29] and Muto et al.'s study [35], in which a linear and a power relationship were utilized, respectively. The impact of weight on CL_{AZ} was consistent across all studies, indicating that higher body weight corresponds to increased CL_{AZ}. This relationship may be explained by the correlation between body weight and the size of elimination organs.

The impacts of age on CL_{AZ} differ between paediatrics and adults. Muto et al. [35] reported a decrease in CL_{AZ} with advancing age. Given that elimination organs deteriorate with age, this effect is to be expected. Nonetheless, such an effect corresponds to only a 4% decrease in CL_{AZ} for a 20-year increase in patient age over the range of 16–90 years, which may not be of clinical importance, and dosage modification may not be warranted. This clinical implication is confirmed by our forest plot (Figure 2), as the impact of age in Muto's study lies within 80%–125% interval. Supporting these findings, the package insert [45] indicated that the pharmacokinetic parameters of azithromycin in elderly men were comparable to those observed in young adults. In elderly women, despite a higher maximum concentration, no significant accumulation of azithromycin was observed. It should be noted that elderly individuals may be more sensitive to QT-prolongation. Zhang et al. [39] observed a rise in CL_{AZ} with age among children <6 years, and this corresponds to approximately a 4% increase in CL_{AZ} for a 1-year increase in patient age, which could be rationalized by developmental alterations in biliary drug excretion observed in children [39,51].

Given that azithromycin is mainly excreted into the bile, it is logical to explore the influence of impaired liver function on CL_{AZ}. Such an impact has been examined in four studies [17,29, 38,39]; however, only one study observed a significant reduction in CL_{AZ} of approximately 24% in patients with alanine aminotransferase (ALT) levels exceeding 40 U/L [38]. The lack of a significant effect of ALT on CL_{AZ} observed in other studies could be attributed to the limited representation of subjects with elevated ALT levels. Even though the forest plot (Figure 2) indicated a clinically significant impact of elevated ALT levels on CL_{AZ}, no dosage adjustments are recommended for patients with Child-Pugh Class A to C [15]. Thus, the decrease in CL_{AZ} in patients with elevated ALT levels may not warrant dosage reduction. Additionally, none of the laboratory values representing renal function had a significant influence on CL_{AZ} [17,19, 29,38,39]. In agreement with this, <15% of the azithromycin is eliminated by the kidneys. Therefore, no dosage adjustment is advised in subjects with renal impairment [45].

Population pharmacokinetic studies did not identify significant impact of sex on azithromycin disposition [17,20, 33,35, 37–39]. Consistent with these findings, dosage modification based on gender is not recommended [45].

It has been recommended that the PK/PD target of azithromycin could be monitored using AUC_{24}/MIC [15], and the target value depends on types of pathogen. Some studies proposed dosage regimens based on simulations for paediatric patients [38,39] and for azithromycin eyedrops [33]. So far, no simulation-based dose recommendations were conducted in adults and infants. This knowledge gap warrants further studies. It is worth mentioning that variability in MIC distributions may significantly influence dosing recommendations. This underscores the importance of regional-specific MIC to be used in Monte Carlo simulations.

Regarding safety, it was discovered that exposure to azithromycin was inversely correlated with treatment-related diarrhoea [35]. Further, Chotsiri et al. [20] demonstrated that azithromycin did not exacerbate the concentration-dependent prolongation of the PR, QRS, corrected J–T (JTc) and corrected Q–T (QTc) intervals induced by chloroquine. However, this study was conducted with 70 healthy volunteers. The risk of developing QT prolongation may be different in high-risk groups such as patients using drugs known to prolong the QT interval, or patients with history of QT prolongation [45]. In these high-risk groups, azithromycin use should be avoided.

This review is subject to certain limitations, notably the inability to perform meta-analyses of pharmacokinetic parameters or meta-modelling, which results from the significant heterogeneity across the populations used to develop models and the lack of access to raw data. Further, relevant information published in other languages was excluded from our study since we solely retrieved English-language literature. Though our finding is not deemed to be affected by the absence of such data, given the English-language studies were high-quality and representative.

5. Conclusion

Significant predictors for azithromycin pharmacokinetics were identified in this review. Moreover, this review emphasizes that newborns have significantly lower CL_{AZ} per bodyweight than children and adults, which may be related to their underdeveloped or inadequate biliary excretion routes. Additionally, children require a loading dose of azithromycin to achieve the ideal target AUC/MIC. Nevertheless, comparable studies evaluating the requirement for a loading dose in adults have not yet been carried out. Finally, most studies did not perform external validation of their models, and this should be undertaken before using these models in clinical practice.

6. Expert opinion

This systematic review is mainly focused on summarizing the factors influencing azithromycin pharmacokinetic variability in various populations. It was identified that age and body weight are significant predictors for CL_{AZ}. This indicates that personalized dosage regimens may be required, particularly in children for whom weight-based dosing is recommended.

Further, though the impact of advancing age on CL_{AZ} is not deemed of clinical importance in the elderly, as only 6.5% reduction in CL_{AZ} is observed in patients aged 90 years compared to 60 years [35], such an impact is important in children aged <6 years. Based on Monte Carlo simulations, it is recommended that in order to accomplish early target achievement, a loading dosage categorized by age and body weight of azithromycin is required [38]. Nonetheless, model-based dosage recommendations have never been reported for adults or infants. Moreover, those reported for preterm newborns were specific for *Ureaplasma* infection [36,37]. Dosage recommendations based on model-based simulations should be further conducted for these populations and for other types of infection.

A difference in CL_{AZ} among African and non-African pregnant women was reported [19]. Nonetheless, the impact of ethnic differences in other populations, such as adult and paediatric patients, remains poorly defined. This issue warrants further investigation.

Impaired liver function (ALT levels >40 U/L) resulted in a decrease in CL_{AZ} of approximately 24% in paediatric patients [38]. However, the results of such an impact are controversial among studies, indicating that dosage adjustments might not be based primarily on this finding. Additionally, the influence of elevated liver enzyme has never been investigated in elderly populations, who are susceptible to experiencing this phenomenon due to underlying diseases or concomitant medications. Thus, it is recommended that future studies should give special attention to the impacts of hepatic impairment in the elderly. Further, animal study [44] showed that azithromycin is a substrate for both Mrp2 and P-gp transporters that mediate excretion of azithromycin in the intestines and biliary system. Therefore, drug interaction may exist when azithromycin is co-administered with compounds that induce or inhibit these two transporters. Nonetheless,

this has never been explored. Future studies should investigate the impacts of drug interactions involving azithromycin.

The clinical applicability of most models is limited by the lack of external validation. Hence, it is advised that these models be evaluated using external datasets derived from the target population prior to implementation in clinical practice. Further, though some simulation-based dosage recommendations are available, little is known about the relationship between exposure and safety outcomes, with only one study identified that diarrhoea associated with azithromycin treatment was shown to be inversely correlated with azithromycin exposure [35]. This underscores the need for further evidence in this area to better characterize the relationships between exposure and safety outcomes of azithromycin.

Author contributions

CRediT: **Janthima Methaneethorn**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Zheng Jiao**: Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing; **Rowan AlEjielat**: Data curation, Validation, Writing – review & editing; **Totsapol Jirasomprasert**: Data curation, Validation, Writing – review & editing.

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