# Title: Population Pharmacokinetics Model Repository for Caspofungin: a Systematic Review

**Running heading: Caspofungin Population Pharmacokinetics Systematic Review**

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# What is already know about this subject

* Numerous studies have demonstrated considerable differences in how caspofungin is processed in the body between individuals. As a result, the importance of customized dosing regimens to improve therapeutic efficacy cannot be overemphasized.
* Despite various population pharmacokinetic studies on caspofungin, there remains a scarcity of research that consolidates and compares existing models.

# What this study adds

* We have developed a model repository of caspofungin parametric population pharmacokinetic models including adults and pediatrics.
* Pediatrics display much higher exposure than adults receiving the recommended dosage regimen but lack pharmacokinetic information in infants under three months.
* Body size was the most identified covariate that affected both clearance and volume of distribution, further studies were needed on the effect of liver function and serum albumin level and dosage adjustments.
* No study has measured the free concentration of caspofungin such that we could have a fuller understanding of its PK behavior in vivo.

# Abstract

## Background

Caspofungin is an echinocandin antifungal commonly used as the first-line therapy for invasive candidiasis, salvage therapy for invasive aspergillosis, and empirical therapy for presumed fungal infections. Pharmacokinetic (PK) variabilities and suboptimal exposure have been reported for caspofungin, increasing the risk of insufficient efficacy.

## Objective

We aimed to consolidate information from population pharmacokinetic (PPK) studies, compare model performance, identify significant covariates affecting caspofungin’s PKs, evaluate probability of target attainment (PTA) in different studies and assemble pharmacokinetic/pharmacodynamic (PK/PD) target information to address existing knowledge gaps that may warrant further investigation in future studies.

## Methods

We performed a systematic search strategy to review the PPK studies of caspofungin. PubMed, Embase, Web of Science, and Scopus databases were searched for papers published by 25 November 2022. We extracted information of all eligible studies for the comparison of models, evaluation of the impact of covariates on clearance and apparent volume and the calculation of probability of target attainment (PTA) under specific minimum inhibitory concentration (MIC).

## Results

Thirteen studies were identified and three focused on pediatric patients only. All studies established a two-compartment model except two studies. The simulation results showed that under labeled dose, children and infants exhibited notably higher AUC and Cmax than adults. Body size was the most identified covariate that affected both clearance and volume of distribution. For *C. albicans* and *C. parapsilosis*, none of the populations achieved a PTA of ≥ 90% at their respective susceptible MIC values. In contrast, for *C. glabrata*, 70% of the adult patients reached a PTA of ≥ 90%, while all pediatric patients achieved the same PTA level.

## Conclusion

At the recommended dosage, adult patients showed notably lower exposure to caspofungin compared to pediatric patients. It is crucial to consider body size, liver function and serum albumin when determining caspofungin dosage regimens. Furthermore, further research is required to comprehensively understand the pharmacokinetics of caspofungin in pediatric patients.

# Keywords

Caspofungin; Individualized drug therapy; Population pharmacokinetics; Model repository

# Introduction

The echinocandins (including caspofungin, micafungin and anidulafungin), which were discovered in the 20th century, are the final milestone of antifungal agent discovery. Caspofungin has a mechanism of action in blocking the synthesis of an essential fungal cell wall component, β-(1,3)-D-glucan, leading to osmotic instability and lysis of the fungal cell. Lacking human targets, caspofungin is usually well tolerated without common significant side effects. Caspofungin exerts potent activity against *Candida* and *Aspergillus spp.* and is the first-line therapy for (invasive fungal infections, IFIs), salvage therapy for invasive aspergillosis, and empirical therapy for presumed fungal infections in children over three months and adults.1, 2

With poor oral bioavailability (<0.2%), caspofungin can only be administered by slow intravenous infusion over approximately one hour. About 97% of caspofungin binds to plasma protein after entering the blood. Following infusion, the plasma concentration of caspofungin declines in a polyphasic manner. The metabolism process is slow, mainly by hydrolysis and N-acetylation.3

Due to the safety profile and relatively low potential for drug-drug interactions, caspofungin has been widely used in the prophylaxis and treatment of invasive fungal infections. However, pharmacokinetic (PK) variabilities and suboptimal exposure with standard dosing have been reported for caspofungin, especially in critically ill patients, leading to the increasing risk of insufficient efficacy.4, 5 Hence, personalized caspofungin dosage recommendations and tailored adjustments for specific patients are imperative to ensure treatment efficacy.

Currently, the clinical efficacy of caspofungin in treating invasive aspergillosis is highly predictable with defined PK/PD indice, peak concentration/minimum effective concentration (Cmax/MEC), and the area under the concentration-time curve/minimum effective concentration (AUC/MEC) ratios.6, 7 According to prior research, the AUC from 0 to 24 hours (AUC0–24) – the most influential PK/PD index for caspofungin – exhibits substantial variability among intensive care unit (ICU) patients.8, 9 Caspofungin exhibits a concentration-dependent decrease in fungal growth.10 Most commonly used PK/PD targets are the ratio of the 24-hour total drug AUC and the minimum inhibitory concentration (AUC0-24h/MIC) and the ratio of the 24-hour free drug AUC and the MIC (*f*AUC0-24h/MIC)11, 12. These targets proposed by preclinical studies have yet to be confirmed and validated in clinical studies.

Population pharmacokinetic (PPK) studies describe the PK profiles of the studied population and evaluate the effect of various covariates on PK variabilities. In combination with Bayesian forecasting, this method has been increasingly utilized for dosing regimen design and adjustments in clinical practice.13 To date, numerous PK/PD studies on caspofungin have been extensively documented in the literature. A comprehensive literature review would prove invaluable in facilitating model-informed precision dosing.

The final aim of this review was to address existing knowledge gaps that may necessitate further investigation in future studies to facilitate optimal caspofungin therapy. This consisted of three specific objectives: 1) to collect data from PPK studies for the assessment of model performance; 2) to pinpoint significant covariates influencing caspofungin's pharmacokinetics; 3) to gauge the probability of target attainment (PTA) across various studies, and compile pharmacokinetic/pharmacodynamic (PK/PD) target information.

# Methods

## Search strategy

Four databases, including PubMed, Embase, Web of Science, and Scopus, were systematically searched for PPK studies of caspofungin published before 25 November 2022, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The relevant PPK researches on caspofungin were unified using the following search terms: 'Caspofungin', 'Cancidas', 'MK 0991', 'MK-0991', 'MK0991', 'L 743,872', 'L-743,872', 'L743872', 'L 743872', 'L-743872' or 'L743872' and 'population pharmacokinetic' or 'nonlinear mixed effect model' or 'NONMEM' or 'Pmetrics' or 'WINNONMIX' or 'ADAPT' or 'P-PHARM' or 'nlmixr' or 'NLME' or 'USC\*PACK' or 'MONOLIX'. On top of these, all reference lists from selected articles were studied to ensure the comprehensiveness of our review. Two independent authors conducted the literature research, and another two senior investigators performed the data validation.14

All studies identified from databases and other sources were screened to evaluate their eligibility based on the consolidated criteria: (1) the subject of studies was human, including healthy volunteers and patients; (2) caspofungin was the study drug; (3) PPK or PK/PD analysis was conducted in the study; (4) the study was published in English. A publication was excluded if (1) it was not an article or only focused on the methodology, algorithm, or software studies; (2) critical PK parameters were insufficient.

## Data extraction

A standardized data extraction method was systematically employed to facilitate data collection from all eligible studies. This process encompassed the following key aspects: (1) demographic characteristics of included population pharmacokinetics studies (e.g., age, sex, and weight range); (2) the study design (e.g., type of study, number of subjects and observations, dosage, administration, and sampling schedule);15 (3) modeling strategies and final pharmacokinetics parameters of included studies (e.g., software/algorithm, fixed effect parameters, inter-individual variation, residual unexplained variability, model evaluation); (4) investigated and identified covariates in the model; (5) PK/PD targets used for simulation; 6) model application and recommended dosage regimens.

## Evaluation of literature quality

The quality of the PPK study was evaluated based on a checklist with 33 items adapted from previous guidelines.15, 16 The literature evaluation was divided into five parts: title and abstract, introduction, methods, results, and discussion and conclusion. A risk of bias assessment was conducted. If the information in a publication were in line with the criteria, it would be marked as having a low risk of bias; otherwise, it would be a high risk of bias. The risk bias plot was conducted using the “ggplot2” package (version 3.3.5; <https://ggplot2.tidyverse.org>) in R software (version 4.1.1; <http://www.r-project.org>).

## Comparison of studies

According to the information extracted from identified studies, virtual populations were divided into three age groups: infants (10 kg, 75 cm, 1-year-old), children (20 kg, 100 cm, 6-year-old), and adults (70 kg, 40-year-old). Infants and children adopted the standard dosage regimen: 70 mg/m2 on the first day, followed by 50 mg/m2 once a day, and adults took a different dosage regimen: 70 mg on the first day, followed by 50 mg once a day. Caspofungin was administered once daily by intravenous infusion over one hour. According to the Mosteller formulation,17 infants’ and children's body surface area (BSA) were set to 0.441 m2 and 0.79 m2, respectively. All patients received multiple doses and reached the steady state. Concentration-time profiles were simulated with the "rxode2" package (version 2.0.12; https://nlmixr2.github.io/rxode2/index.html) in R software (version 4.2.1; www.r-project.org). We employed a similarity comparison method to ensure the accuracy of constructing the model repository.

The effect of covariates was presented through a forest map using "tidyverse" package (version 2.0.0; [Tidyverse packages](https://www.tidyverse.org/packages/)) in R software (version 4.2.1; [www.r-project.org](http://www.r-project.org)). Regarding binary covariates, we calculated the value for each category. As for continuous covariates, the maximum and minimum value from the included study was extracted and used to calculate the range of the effect of different covariates on clearance (CL) or volume of distribution (Vd). For the covariates concerning multiple studies, a uniform range was set up for the comparison based on the demographic information in included studies. Then the value of CL and Vd was further normalized by the reference with the median covariate value (Eq). We regarded covariate effects beyond the 80–125% range as clinically significant, in accordance with the standard employed in bioequivalence studies.18

(Eq)

## Monte Carlo simulation for the probability of target attainment

Currently, dosing regimens were evaluated through PK/PD targets of caspofungin based on trough concentrations and preclinical target value. *In vitro* studies19 showed that the target trough concentration of caspofungin against Candida should be greater than 1 mg/L. Louie found that after a single or multiple administration of the same dose of caspofungin, the number of Candida albicans in kidney tissue decreased to a similar degree. By comparing the relationship of different PK/PD targets with antibacterial effect, Louie put forward that AUC**0-24**/MIC ratio was identified as the most effective PK/PD index for caspofungin in the treatment of Candida infections.**20**

**Based on the *in vivo* PK/PD studies, the PK/PD target in** *C. albicans***,** *C. glabrata*, and *C.parapsilosis* was 865, 450, and 1185 respectively.12, 21 According to CLSI MIC breakpoint *in vitro* broth dilution susceptibility testing of *Candida* spp., each MIC of Candida specie was chosen (C. albicans, susceptible ≤ 0.25 mg/L; C. glabrata, susceptible ≤ 0.12 mg/L; C. parapsilosis, susceptible ≤ 2 mg/L).22 After the PPK model of caspofungin was set up, simulation based on the model was applied to predict the probability of caspofungin reaching the target PK/PD index under labeled dosing regimens and specific MIC. The steps were as follows: (1) Simulate PK profiles of caspofungin; (2) Calculate the steady-state AUC0-24h using the trapezoidal method; (2) Calculate the probability of target attainment (PTA) under specific MIC settings.

# Results

## Identification of studies

The PRISMA diagram of study identification is shown in Figure 1. A total of 26, 150, 185, and 61 studies were identified from the PubMed, Scopus, Web of Science, and Embase database searches, respectively. No additional study was identified from other sources. A total of 315 studies were screened after removing duplicates. Based on the exclusion criteria, 300 studies were removed, and 15 were qualified, among which two studies were excluded due to missing critical PPK parameters. Finally, 13 studies were included in our review for the follow-up analysis.

## Evaluation of literature quality

The risk map concerning the bias of literature has been summarized in Figure 2. Two studies lacked pharmacokinetic data description in the background section and two others did not include the sampling schedule. One study did not mention the formulation, bioanalytical methods, and distribution of individual model parameters. None of the included studies recorded the methods of handling missing data and fewer than 20% of studies reported the specific method of handling the below the quantification limit (BQL). All studies have achieved a compliance rate of 85%, indicating that these studies are of good quality.

## Characteristics of studies

All included studies were published from 2011 to 2022. The characteristics of each study are summarized in Table 1. Eleven of thirteen studies were prospective, and two studies23, 24 were retrospective. The total amount of participants was between 12 and 299 (IQR [19,48]). Wang et al.25 and Wu et al.26 enrolled both patients and healthy subjects, while the other eleven studies were conducted only in patients with invasive candidiasis along with various conditions. Three24, 27, 28 of the included studies enrolled pediatric populations between three months and 18 years old; ten included adults only. Five studies focused on transplant patients including allogeneic hematopoietic stem cell transplant23, 28, heart transplant26, lung transplant25 and liver transplant.29 All three studies focused on pediatrics adopted a sparse sampling strategy. Two out of ten studies concentrated on adults also employed sparse sampling, while the remaining eight studies utilized intensive sampling. Twelve studies collected only plasma samples, while Pressiat et al.29 collected both plasma and peritoneal fluid (PF) samples. All studies examined the total concentration of caspofungin.

The bioassay methods studies employed to determine the concentration of caspofungin were high-performance liquid chromatography (HPLC), liquid chromatography-tandem mass spectroscopy (LC-MS/MS), and ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). The lowest limits of quantitation (LLOQ) in all selected studies ranged from 0.084 mg/L to 0.6 mg/L.

The modeling strategies and final PK parameters of included studies were summarized in Table 2. Ten studies built their models using NONMEM software. Bailly et al.30 and Pressiat et al.29 developed their model using Monolix software, while Niu et al.28 used Phoenix NLIME software. First order conditional estimation with interaction (FOCE-I) was the most commonly used algorithm8, 9, 23, 24, 27, 31-33. All studies effectively elucidated the *in vivo* PKs of caspofungin using the two-compartment model, with two exceptions28, 33 utilized a one-compartment structural model with first-order elimination. These two studies involved acquiring merely two or three plasma samples per patient at peak concentrations and a limited number during the distribution phase, their sampling schedules may be too sparse to reflect the feature of two-compartment PK model.

In all studies, the between-subject variability (BSV) was described using the exponential model. The median and range of BSV are as follows: CL 27.5% (11.8%-42.3%) [n=13]. The residual unexplained variability (RUV) was described by proportional models or addictive models, or both.26 Eleven studies included proportional errors (CV%) ranging from 12.2% to 36%, three9, 25, 26 included addictive errors ranging from 0.0941mg/L to 0.73mg/L. An integration of inter-occasion variability (IOV) on CL was estimated to be 17.2% and 16.0% in Gastine et al.24 and Würthwein et al.31 respectively.

All models conducted internal validation. The predominant method for internal assessment was the goodness-of-fit (GOF) plots, and visual predictive check (VPC) plots/predicted-corrected visual predictive check (pcVPC) plots. Additionally, ten of thirteen studies presented the results of bootstrap. Although normalized prediction distribution errors (NPDEs) are both effective evaluation tools, only three studies26, 27, 32 used NPDEs. Würthwein et al.31 underwent external validation to verify the model.

Ten studies performed Monte Carlo simulation to evaluate or optimize existing dosing regimens. These studies were designed to compare the effect of different dosage regimens or to evaluate the PK and drug interaction of caspofungin in a specific patient population. Nine studies conducted the simulation used AUC**0-24**/MIC as the PK/PD target.

In the eight studies of adults, Pressiat et al.29 concluded that the existing recommended dose of caspofungin was enough and didn’t require higher doses. Five studies8, 9, 26, 32, 33 (62.5%) suggested that a higher maintenance dose ranging from 70 mg to 150 mg should be taken in patients with different disease conditions. Wu et al.26 recommended that the dose of caspofungin should be proportionately increased in patients with decreased ALB levels. Li et al.32 concluded that the currently recommended maintenance dose of 50 mg should be adjusted depending on the the colony, ALB level and liver function.

In the study focused on pediatrics, Niu et al.28 concluded that the existing recommended dose of caspofungin was enough and didn’t require higher doses. Gastine et al.24 reported that a 200mg/m2 twice-weekly extended dosing regimen, with a maximal 200 mg total dose, should result in average weekly exposures matching those achieved with the approved daily-dosing regimen. Despite Yang et al.27 not conducting simulation, their study provided support for a BSA-based dosing regimen

## Comparison of simulated concentration-time profiles

A comprehensive comparison of all the simulated PK parameters for caspofungin was shown in Figure 3. When compared to the adults, children and infants exhibited notably higher AUC and Cmax. The median peak concentration of children (1.178 mg/L/kg) and infants (2.565 mg/L/kg) displayed higher than that of adults (0.125 mg/L/kg), possibly attributed to the apparent Vd in children and infants being smaller than that in adults. Typical value of apparent Vd of central compartment in adult studies ranged from 2.21 L to 9.01 L, while those in children studies ranging from 1.36 L to 2.21 L. Moreover, pediatrics showed a higher CL per kilogram body weight than adults. The median CL in children and infants was 0.0083 L/h/kg (range: 0.005-0.011) and 0.0086 L/h/kg (range: 0.006-0.011), higher than that in adults 0.0061 L/h/kg (range: 0.003-0.014), but it was not clear whether this was significantly different owing to the limited data in pediatrics.

In the pediatric population, three studies24, 27, 28 displayed similar PK characteristics in infants and children. Nevertheless, due to the limited number of studies involving this age group, additional research is required to better understand caspofungin's utilization in the pediatric population and to elucidate the sources of between-subject variability (BSV).

According the studies in adult patients, Wang et al.25 displayed much higher AUC and Cmax than other studies under the same dosage regimen and Bailly et al.30 displayed much lower AUC and Cmax while the remaining eight studies exhibited similar PK characteristics despite patients’ varying disease conditions. The subjects in Wang et al.25 were lung transplantation patients and received follow-up treatment in ICU. These patients shared lower CL and Vd due to the lower body weight, situation of hypoalbuminemia, and the critically ill condition. The patients enrolled in Bailly et al.30 received a maintenance dose of 140 mg, while our simulation used the recommended maintenance dose of 50 mg, which may have contributed to the low exposure.

## Investigated and identified covariates

The histogram of the amount of investigated and identified covariates was shown in Figure 4. All tested covariates identified significant covariates were summarized in Table 3. In addition to essential demographic data and laboratory test results, liver and kidney function, as well as specific clinical scenarios, such as continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) had also been investigated in included studies. Würthwein et al.31 also investigated the effect of liposomal amphotericin B (LAMB) in caspofungin and concluded that the PK of caspofungin was not altered by coadministration of LAMB. Three studies8, 25, 26 investigating the difference of PK characteristics in grouped patients who had received CRRT or ECMO indicated that these factors had no significant effect.

Four studies didn’t include any covariate, which may attribute to the high degree of consistency of the included patients. The most influential covariate was body size such as body weight and BSA. Three studies15,19,33 (23.1%) concluded that body wight was closely related to CL, and five (38.5%) indicated that weight greatly impacted Vd. Yang et al.27 and Niu et al.28 identified BSA as a crucial covariate that affects both CL and Vd. Three studies26, 32, 33 confirmed ALB level as a significant covariate affecting CL. Niu et al.28 and Li et al.32 included the liver function index as the covariate in their final model. Interestingly, among three studies including pediatrics, two identified BSA as a significant covariate both on CL and Vd, which corroborated the rationale for dosing children based on their BSA.

## Covariate effect on CL and Vd

All studies investigated the potential covariates, and their identified covariates on CL and Vd were visualized using the forest map in Figure 5 and Figure 6. Compared to the reference value, all five studies including body size as significant covariates demonstrated the impact on CL with greater than 20% change under the normal range of body size. Li et al.32 and Niu et al.28 demonstrated the influence of liver function greater than 20% change under a wide range of different liver functions. Hepatic function affects liver clearance of caspofungin, which is the primary eliminate pathway of caspofungin. Three out of nine studies included ALB as significant covariate, which showcased an impact on CL, with changes exceeding 20% within the normal range of ALB level.

Body size, including body weight and BSA, were evaluated and included as significant covariates in 7 (77.8%) studies. Compared to the reference value, six out of seven demonstrated significant impact of body size on Vd with greater than 20% change under the normal range of body size. Two studies demonstrated the influence of ALB greater than 20% change on Vd under the normal range of ALB level. Wang et al. found that male gender was associated with increased caspofungin Vd.

## Probability of target attainment

PK/PD cut-off is key indicator for determing the PK/PD folding point. Ten of thirteen studies conducted simulation based on the PPK model. Seven of the ten studies used AUC24/MIC as the PK/PD target while three used fAUC24/MIC. AUC/MIC and fAUC/MIC were assessed as pharmacodynamic targets for the simulated regimen simultaneously in Gastine et al.24 In addition to the PK/PD targets mentioned above, indices like Cmax/MIC, Cmax/MEC and Cmin were also assessed in several studies.

The simulated Probability of Target Attainment (PTA) for each published PPK model was assessed with three different *Candida strains* and was presented in Figure 7. For *C. albicans* (MIC=0.25 mg/L) and *C. parapsilosis* (MIC=2 mg/L), none of the population achieved a PTA of ≥ 90%. However, for *C. glabrata* (MIC=0.12 mg/L), 70% of the adult patients in the studies reached a PTA of ≥ 90%, while all pediatric patients achieved a PTA of ≥ 90%. The PTA results suggested that caspofungin was underexposed in adult patients and that the dosage of the drug must be based on the results of *Candida strains* and the value of MIC.

# Discussion

Caspofungin is an echinocandin antifungal agent used as first-line therapy for the treatment of invasive candidiasis (IC) and invasive aspergillosis (IA).34 Numerous studies have been conducted on PKs of caspofungin in recent years, and several PPK studies have been reported to investigate the causes of PK variability. To our knowledge, this is the first comprehensive review to systematically summarize the data related to the PPK modeling of caspofungin.

Caspofungin displayed varying PK behavior in both pediatrics and adults. To ensure the highest standard of patient care, we need to consider a spectrum of factors beyond body size. In this review, we have proposed other promising covariates such as liver function and hypoproteinemia as well as stratifying these important clinical parameters according to the use cases and the population of the intended patient groups.

## Pediatric patients

The PKs of caspofungin exhibited substantial differences among infants and children. Two of three studies focusing on children identified BSA as a significant covariate affecting both CL and Vd. This indicated that while using caspofungin in pediatric patients, it might be more reasonable to adjust the administered dose based on BSA, which was consistent with the rational dosage regimen. However, pediatrics shared lower clearance compared to adults, this difference might be affected by the differential rate of distribution from plasma into hepatic tissue in pediatrics. In vitro data suggested that caspofungin tissue distribution may be mediated by uptake transporters and that the OATP1B1 transporter may be involved in the hepatic uptake of caspofungin.35 The caspofungin concentrations attained in neonates and infants fell within the clinical concentration range, as observed in the BSA study published by Sáez-Llorens et al., in adult patients who had received multiple doses of caspofungin up to 100 mg per day.36 Furthermore, Sáez-Llorens et al.36 suggested that caspofungin clearance increases from infancy to childhood and then decreases from childhood to adolescence, continuing to decline into adulthood. Infants and children demonstrate lower CL levels and Vd than adults when following the standard dosage regimen. This could be attributed to several factors such as reduced blood flow, an altered body fat-to-lean mass ratio, and decreased total body water associated with the aging process. Comparing to adults, pediatric patients exhibit distinct physiological and pathological characteristics as mentioned, as well as differences in drug-handling processes, resulting in substantial PK disparities. This divergence is particularly pronounced in infants under one year old, whose renal excretion and hepatic metabolism have not yet fully matured. Consequently, these factors can markedly influence the absorption, distribution, metabolism, and excretion of caspofungin within the body. Li et al.32 observed that as body weight increased, the average Cmax value decreased by 7%, and there was greater PK variability in pediatric patients with lower body weight. The critically pharmacokinetic parameter for efficacy of caspofungin and other echinocandins were concentration dependent, rather than time dependent. In a word, BSA-based dosage regimen may not fully satisfy the clinical need, more blood biochemical parameters and physiologic conditions such as serum albumin level, hepatic function and blood flow needed to be taken into consideration.

Although rare, caspofungin had clinical applications in very low-birth-weight infants. Among the antifungal treatments for preterm infants, 0.5% of very low birth weight infants and 1% of extremely low birth weight infants have received caspofungin.37 However, there was a lack of relevant PK information in this particular group.37 Therefore, it is worth noting that the number of studies involving caspofungin in pediatrics remains insufficient, especially scientific evidence regarding medication use in infants under three months. Few studies that had been conducted were retrospective studies. More large-scale, prospective controlled trials are needed to clearly define the efficacy, safety, and role of caspofungin in neonatal candidiasis and the optimal dose to use in this population.

## Adult patients

Despite population variations, most PPK studies and simulations exhibit similar PK characteristics, body weight is a significant covariate affecting CL and Vd. Insufficient drug exposure is a common issue with the recommended dosing regimen in adult patients. Half studies proposed increasing the dosage of caspofungin to achieve target exposure. In patients with normal liver and kidney function, hypoalbuminemia can result in elevated levels of unbound drugs, potentially leading to an increased CL, especially in highly protein-bound antibiotics like caspofungin. Additionally, being a hydrophilic drug, the apparent volume of distribution of caspofungin might be significantly augmented due to fluid shifts and extensive fluid resuscitation.38, 39 In critical care settings, these scenarios are frequently encountered. Except for fungal infection, patients in the included studies mostly shared different disease states, such as obesity, hepatic insufficiency, and specific infusion protocols. Caspofungin concentrations measured in ICU patients exhibited significant variability, which could be attributed to their compromised physical conditions, time-varying serum albumin, and other contributing factors. This suggested that dosing solely based on body weight or BSA should not be the standard practice. Borsuk-De Moor et al.8 noted a time-varying CL in ICU patients: 0.563 L/h on day 1, 0.737 L/h on day 2, and 1.01 L/h on day 3, respectively. Given the connection between caspofungin exposure and CL values, an escalating CL could result in reduced exposure, consequently impacting its efficacy. Nonetheless, there was a limited number of models that factored in time-dependent variables. To enhance the customization of patient medications, long-term monitoring of caspofungin administration is advisable.

Critically ill patients tend to present with various underlying diseases, comorbidities, and constitutions, which could contribute to the high inter-individual variability of caspofungin pharmacokinetics in vivo.40 Caspofungin exposure was confirmed lower in critically ill patients, with a median area under the curve over 24 hours (AUC24) of 78 (interquartile range [IQR] 69–97) mg\*h/L, compared to an AUC24 of 98 mg.h/L in healthy subjects.5 Betts et al. demonstrated a large safety margin for caspofungin, thereby allowing physicians the option of using higher-dose therapy up to 150 mg per day if a proven need arises.41 Their study could not support the standard dose of caspofungin for the treatment of fungal wound infections. Kurland et al. argued against a reduction of the caspofungin dose in critically ill patients with hypoalbuminemia and abnormal liver function.42 But the consensus was on the importance of therapeutic drug monitoring (TDM) for critically ill patients with hypoalbuminemia, with or without abnormal liver function, or strains with elevated minimum inhibitory concentrations that needs to be explored. Critically ill patients are usually accompanied by some treatment options. ECMO and CRRT are frequently employed in ICU patients, one study30 suggested that ECMO might increase CL of caspofungin, while another study31 concluded that ECMO had no discernible impact on PKs of caspofungin, likely due to its high solubility in both water and methanol. Nevertheless, a consensus on this matter remains elusive, necessitating further investigations.

In the literature we reviewed, none of the studies encompassed both adults and children. Consequently, conducting an objective comparison between these two populations within the same study was not feasible.

## PK/PD target of caspofungin

Due to substantial disparities in the PK profiles of pediatrics and adults, and the notable observation that children exhibit exposure significantly higher than those of adults, often by a factor of 1 to 1.5 with recommended dosage regimens, it is advisable not to apply a unified PK/PD target simultaneously to both adults and children.

For caspofungin, preclinical PK/PD target values had not been confirmed in clinical studies. Among the studies included, a recurring observation is the absence of established clinical PK/PD targets, prompting reliance on preclinical PK/PD targets. It is widely acknowledged that only the free form of a drug can exert its therapeutic effects, making the assessment of free drug concentration more relevant for research. Furthermore, reduced plasma protein levels in vitro increased the antifungal activity of caspofungin and lowered the pharmacodynamic target AUCtotal/MIC, most likely by increasing the free concentration.43 However, none included study detected the concentrations of free caspofungin. In cases where fAUC24/MIC was employed as the PK/PD target, it was calculated based on the total AUC/MIC target and caspofungin's plasma protein binding rate (97%).

In studies involving adults for *C. albicans*, *C. glabrata,* and *C. parapsilosis*, the PK/PD cut-off values were found to be 0.074 ± 0.05 (67.5%, CV%), 0.149 ± 0.11 (72.3%, CV%), and 0.044 ± 0.02 (46.9%, CV%), respectively. These findings indicated that establishing caspofungin cut-off values in various populations involves considerable variability and poses a challenge.

## 4.4. Limitations

Our research has certain limitations. Firstly, due to the limited number of studies involving pediatric patients, we were unable to comprehensively investigate and compare the pharmacokinetics of both children and infants. Furthermore, as the focus of this review was to summarize significant covariates influencing caspofungin PKs and compare PPK modeling across different age groups, we replicated the published models to align with our study objectives and the characteristics of the medications under investigation. Additionally, the PTA results were derived from in vitro data provided by CLSI. However, it's essential to note that the absence of in vivo studies in humans may lead to discrepancies in the accurate calculation of PTA. Finally, we restricted our review to literature published in English, potentially missing relevant studies published in other languages.

# Conclusion

In this study, a systematic review of published PPK studies involving caspofungin was conducted. Notably, the PKs of caspofungin exhibited variations between pediatrics and adults, with children displaying a lower CL and Vd when administered the recommended dosing guidelines. Furthermore, children had a larger variability in PK than adults. This review has demonstrated that optimizing the dosing regimen of caspofungin requires more than just considering body size. To meet clinical needs effectively, various factors, including liver function and hypoproteinemia, must be taken into consideration. Additionally, prospective PK/PD studies of caspofungin on pediatrics are warranted to elucidate the exposure-response relationship associated with this medication.

# Declarations

**Conflicts of Interest:** The authors declare they have no conflicts of interest.

**Availability of data and material:** Not applicable.

**Ethics approval:** Not applicable.

**Consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Code availability:** Applicable.

# Author contributions

Conceptualization and methodology, N.X., Y.S., and X.Z.; software and validation, W.Y., Q.H., and Y.W.; formal analysis and investigation, N.X., Y.S., and W.Y.; resources, Z.T., Y.W., X.X., Q.H., and G.Y.; writing—original draft preparation, N.X. and Y.S.; writing—review and editing, W.Y., Z.T., Y.W., Q.H., G.Y., X.Z. and X.X.; visualization, N.X., Y.W. and W.Y.; supervision, Q.H., G.Y., X.X., and X.Z.; funding acquisition, X.Z. All authors have read and agreed to the published version of the manuscript.

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