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ORIGINAL RESEARCH

Advancing Daptomycin Precision Dosing Through Evaluation of Published Population Pharmacokinetic Models and Development of a Dosing Tool

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Background: Daptomycin is an important antibiotic against multidrug-resistant Gram-positive infections, but its wide interindividual variability and narrow therapeutic window pose challenges for optimal dosing. Population pharmacokinetic (PopPK) models provide a quantitative framework for precision dosing, yet a systematic evaluation of existing models and their clinical application method remains lacking.

Methods: Model structures, demographic characteristics, and covariate effects were systematically summarized from previously published papers. Predictive performance was compared through simulations in virtual populations with varying renal function. Monte Carlo simulations were performed to evaluate the probability of target attainment (PTA; AUC24*h*/MIC ≥ 666) and the probability of toxicity (Cmin ≥ 24.3 mg/L). Furthermore, an open-access precision dosing tool was developed based on maximum a posteriori Bayesian estimation using representative model structure and parameters.

Results: Eighteen PopPK studies were included in this analysis. Renal function was the most frequently identified covariate influencing clearance. Model comparisons revealed variability in predicting exposure and PTA. Simulations indicated that patients with impaired renal function face a higher risk of exceeding the toxicity threshold, even at moderate doses. The developed Shiny-based tool enables real-time estimation of AUC and Cmin, integration of therapeutic drug monitoring data, and individualized dose adjustment.

Conclusion: This study provides a comprehensive evaluation of daptomycin PopPK models and translates these findings into a practical precision dosing tool. This work enhances understanding of interindividual variability of daptomycin and offers clinicians a scientifically grounded resource to optimize daptomycin therapy in diverse patient populations.

Keywords: population pharmacokinetic, precision dosing, daptomycin, renal impairment

Introduction

Gram-positive bacteria remain major pathogens responsible for severe infections,[1] and the escalating prevalence of antimicrobial resistance has emerged as a critical global health concern, driving both morbidity and healthcare costs.

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Daptomycin, a cyclic lipopeptide antibiotic, exhibits potent activity against multidrug-resistant Gram-positive organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[2,3] Pharmacokinetically, daptomycin shows extensive plasma protein binding (90–93%), a small volume of distribution (about 0.1 L/kg), and predominant renal elimination, with nearly 50% of the dose excreted unchanged in urine.[4] Owing to these properties and its rapid and potent concentration-dependent bactericidal activity, daptomycin has been approved for indications such as bacteriaemia, complicated soft tissue infections,[5] with commonly recommended doses ranging from 4 to 12 mg/kg. However, this broad dosing range creates clinical uncertainty.[6] It may compromise both efficacy and safety, especially in vulnerable patients such as those with renal impairment.[7] Thus, the need for precision dosing has become increasingly urgent.

Optimizing daptomycin therapy requires quantitative approaches rather than empirical decision-making. Daptomycin is a concentration-dependent bactericidal agent, with efficacy best correlated to an exposure target of AUC_{24h}/MIC ≥666.[8,9] In contrast, toxicity is linked to elevated trough concentrations (C_{min}>24.3 mg/L),[10] which predispose patients to dose-limiting myopathy. Although therapeutic drug monitoring (TDM) has been recommended for improving the treatment outcomes,[11] its practical use is somehow restricted, as it requires multiple steady-state samples, delays timely adjustment, and relies heavily on expert interpretation.[12] These limitations hinder real-time dose optimization in daily practice. Previous studies have proposed several strategies to optimize precision dosing of daptomycin, as target exposure attainment has not been consistently achieved. These include TDM-guided dose adjustment, Bayesian forecasting tools such as BestDose[13] and Tucuxi[14] for individual PK parameter estimation, and nomogram-based dosing strategies have been proposed for specific clinical settings, such as vancomycin-resistant enterococcal infections.[15] However, to date, no dedicated pharmacometric platform has been established to comprehensively support model-informed precision dosing of daptomycin.

Model-informed precision dosing (MIPD) has therefore emerged as a promising strategy for individualized pharmacotherapy.[12,16] By combining drug concentration data with patient-specific covariates, MIPD allows proactive and adaptive dose optimization, even before treatment initiation.[17,18] Population pharmacokinetics (PopPK), as the foundation of MIPD, serve as the key strategy for individualized dosing through informing remedial dosing strategies,[19] optimal sampling design,[20] and clinical decision-support tools.[21] Although several PopPK models of daptomycin have been published, systematic evaluation of their predictive performance and clinical utility remains limited.

The present study was designed to address this gap. Specifically, we (i) systematically reviewed published PopPK models of daptomycin, (ii) compared their predictive performance, and (iii) identified covariates contributing to interindividual variability. Furthermore, we developed an open-access maximum a posteriori (MAP) Bayesian estimator based on the PopPK repository. Together, these efforts aim to advance the clinical application of MIPD and facilitate precision dosing of daptomycin.

Methods

Search Strategy and Data Extraction

A systematic literature search was conducted in PubMed, Web of Science, and Embase to identify daptomycin PopPK models published up to 6 May 2025, following the PRISMA reporting guidelines. The search was restricted to parametric PopPK models to ensure consistency with the study objectives, including structural model comparison, interindividual variability assessment, covariate extraction, and evaluation of model-informed precision dosing trends. The nonlinear mixed-effects framework provides standardized reporting of fixed and random effects, enabling direct cross-study comparison.[22] The search terms and selection criteria were presented in the Supplemental Materials 1.

Two authors independently extracted the following information from eligible articles: (1) baseline data: first author, year of publication, population Characteristics (including number of subjects, participant characteristics country, age, sex, weight, etc).; (2) study characteristics: sampling schedule, administration protocol, sample number, analysis method, etc.; (3) PopPK characteristics: model parameters, modeling software/algorithm, covariates, covariate selection criteria, inter-individual variability (IIV), and residual unexplained variability (RUV). (4) model application.

PopPK Models Predictive Performance Comparison

A total of 1000 virtual subjects were generated and stratified by renal function into four groups using rxode2 (version 4.0.3) package in R (version 4.5.1): normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment. Each virtual subject was assigned a standard age of 70 years and a body weight of 70 kg, reflecting the typical characteristics reported in most identified PopPK studies. Published PopPK models were then applied to simulate concentration–time profiles in these populations. A daily intravenous infusion of 6 mg/kg (infusion duration 1 h) was administered for 5 consecutive days to ensure steady state. Following the final dose, concentrations were sampled over a 24-hour period, and a non-compartment analysis was conducted to calculate the AUC and Cmin of different model prediction. All simulations were conducted using the rxode2 package in R.

Effect of Covariates on Clearance Variation

Clearance (CL) is a key determinant of individualized daptomycin dosing. To assess the influence of different covariates, we constructed a forest plot comparing their effects on CL. A covariate was considered clinically significant if the resulting change in CL exceeded 80–125%. For comparability, all continuous covariates were standardized to the same range. For renal function, different indicators such as CLcr and eGFRcys were used across studies. To ensure consistency, renal function was categorized into four groups: normal, mild, moderate, and severe. Body weight was classified according to previous studies[21,23–25]into three groups: low (30–59 kg), medium (60–100 kg), and high (>100 kg). Age was divided into three categories based on World Health Organization standards. Binary covariates, such as methadone[23] co-administration, which was reported as a significant covariate that influence daptomycin CL, were coded such that the control group without methadone co-administartion was assigned as (COVi = 0), and the test group with methadone co-administration was assigned as (COVi = 1):

$$CL_i = CL_{common} + CL_{diff} \times COV_i \quad (1)$$

Accordingly, the range of individual clearance (CL_i) is [CL_{common}, CL_{common} + CL_{diff}] when $CL_{diff} > 0$, and [CL_{common} + CL_{diff}, CL_{common}] when $CL_{diff} < 0$. The final impact of each covariate on CL was quantified using equation 2.

$$\text{Covariate effect} = \frac{\text{The minimum CL or the maximum CL}}{\text{Reference CL}} \times 100\% \quad (2)$$

Monte Carlo Simulation for the Probability of Target Attainment

After the PopPK model repository of daptomycin was established, Monte Carlo simulations (n = 1000) were conducted for populations with different level of renal function (normal, mild, moderate, severe). Daptomycin was assumed to be administered via a 30-minute intravenous infusion under five common dosage regimens: 4, 6, 8, 10, and 12 mg/kg/d. For each regimen, the total area under the concentration-time curve at the steady state ($AUC_{24h,ss}$) was calculated. Eight MIC values were considered: 0.25, 0.5, 1, 2, 4, and 8 mg/L, with MIC = 1 mg/L established as the threshold for daptomycin to cover most target strains under the current dosage regimens. The pharmacodynamic target was defined as $AUC_{24h}/MIC \geq 666$.[9,26] The probability of target attainment (PTA) was then computed to evaluate the likelihood of achieving this target across renal function groups, dosing regimens, and MIC values. Toxicity risk was also assessed. Since a trough concentration (C_{min}) ≥ 24.3 mg/L has been associated with a 50% probability of creatine phosphokinase elevation,[10] we simulated the probability of $C_{min} \geq 24.3$ mg/L at 24 hours for each scenario. Optimal dosing was defined as regimens achieving PTA ≥ 90% for the PK/PD target, while maintaining the probability of $C_{min} \geq 24.3$ mg/L at ≤ 20%.[27]

Precision Dosing Tool Development

In clinical practice, clinicians often need to assess both AUC and C_{min} to determine whether patients achieve adequate exposure and to evaluate the risk of toxicity. To support this process, we developed an AUC calculation tool based on maximum a posteriori Bayesian estimation (MAP-BE). The tool could integrate TDM data with population pharmacokinetic models and was implemented using R Shiny (version 1.11.1) and the mapbayr package (version 0.10.0).

Results

Overview of Included PopPK Studies for Daptomycin

Study Identification and Characteristic

A total of 592 records were retrieved through a comprehensive search strategy: 274 from PubMed, 93 from Embase, and 225 from Web of Science. After applying the eligibility criteria, 33 full-text articles were reviewed in detail. Among these, two studies were excluded because they used a nonparametric modeling approach. Four study was based solely on in vitro data and adopted model structures from previous work. Seven studies did not report PopPK parameters, and five studies only performed simulations without parameter estimation. Ultimately, 15 studies met the inclusion criteria and were incorporated into the present analysis. The study selection workflow is summarized in Figure 1.

Study Characteristics

The demographic characteristics of all included studies are summarized in Table 1. The studies were published between 2013 and 2024 and involved populations from China, the United States of America (USA), Japan, Spain, Italy, and France. Of the 15 included studies, 14 were conducted in adult patients.[3,4,23–28,30–35] Only one study involved pediatric participants receiving dialysis.[29] Most adult studies focused on elderly patients with renal impairment, notably, one study extended its investigation to individuals with normal renal function.[26] Regarding modeling software, the majority of studies used NONMEM.[3,4,24–27,30–35] Two studies adopted Phoenix NLME,[28,29] and one used Monolix.[23] In terms of structural models, 10 studies employed a two-compartment model to describe daptomycin pharmacokinetics,[3,4,24–30,32] while 5 studies applied a one-compartment model.[23,31,33–35] Internal validation was commonly performed using goodness-of-fit (GOF) plots, visual predictive checks (VPC), and bootstrap. Two studies also incorporated normalized prediction distribution errors (NPDE). However, none of the included models underwent external validation. The detailed model characteristics and pharmacokinetic parameters are summarized in Table 2.

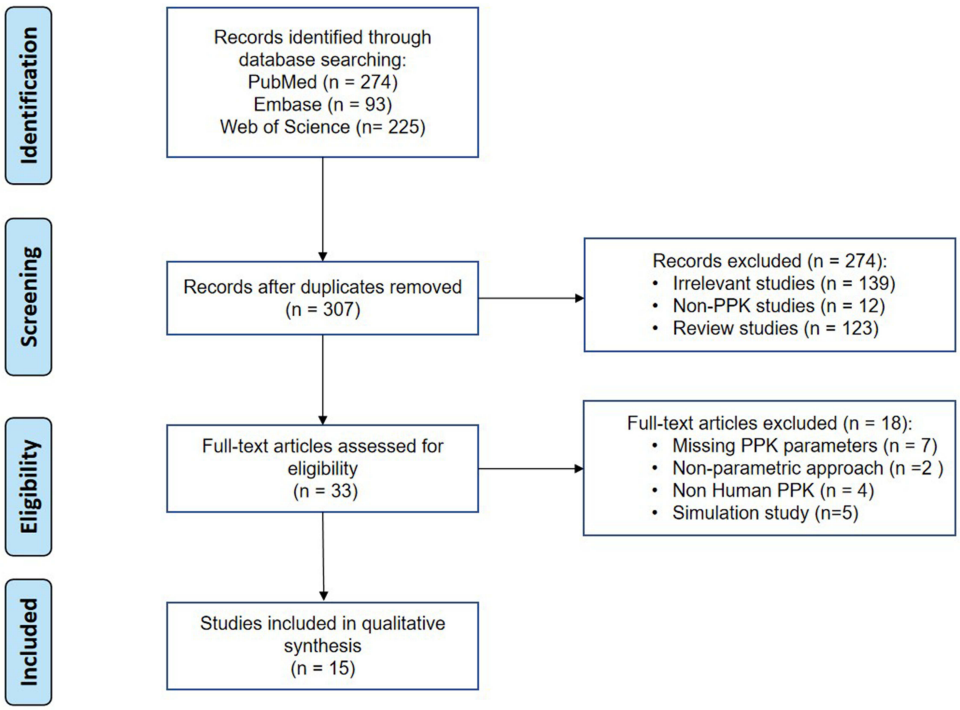

Figure 1 PRISMA flow diagram illustrating the study selection process for parametric population pharmacokinetic models of daptomycin.

Table 1 Characteristics of Included Population Pharmacokinetic Studies

Study (Publication Year)	Country	Number of Subjects (Male/ Female)	Characteristics of Subjects	Number of Observations	Sampling Schedule	Age (Years) a. Mean±SD b. Median[Range] c. Median [Q1-Q3]	Weight (kg) a. Mean±SD b. Median[Range] c. Median [Q1-Q3]	CLcr (mL/min) a. Mean±SD b. Median[Range] c. Median [Q1-Q3]	Daily Dose a. Mean±SD b. Median[Range]	Bioassay [LOQ]
Olney (2024)[23]	USA	31 (15/16)	S.aureus infection	122	0, 1, 12, 24 h following the start of infusion	50[30–62][c]	74 [54–156][c]	113[43–183][c]	750 mg infusion 30min	-
Zhang (2024)[24]	China	1.ECMO group: 24 (16/8) 2.Non-ECMO group: 12 (8/4)	Critically ill patients receiving extracorporeal membrane oxygenation	293	0, 1 h, 2–4 h, 4–6 h, 6–8 h, 8–12 h, 12–16 h and 16–24 h after the completion of the infusion	1. ECMO group: 53.5 [34–78][b] 2. Non-ECMO group: 53.0 [44–84][b]	1.ECMO group: 70.0 [55–92][b] 2.Non-ECMO group: 67.5 [40–95][b]	1.ECMO group: 52.2 [16.8–131.5][b] 2.Non-ECMO group: 42.9 [16–157.2][b]	500 mg infusion 30 min (4–12 mg/kg/dose)	UPLC-MS/MS [0.25μg/mL]
Wu (2024)[25]	China	64 (43/21)	Gram-positive infection patients in ICU	737	Day 1: 0, 0.5, 1, 2, 4, 8, 12, and 24 h after infusion; Day 3: 0, 0.5, 1, 2, 4, 8, 12, and 24 h after infusion Day 5.7: 0, 0.5, 4 h after infusion	57.5 ± 16.5[a]	64.5[45–170][c]	54.25[8.3–200.2][c]	500 mg infusion 30 min every 24h	UPLC [0.05μg/mL]
Takahashi (2023)[3]	Japan	58 (33/25)	Methicillin-resistant Staphylococcus aureus infection	Total Concentration: 339; Unbound Concentration: 329	4–24 h after dose	71 [18–86][c]	51 [32–99][c]	1.Patient underwent hemodialysis:9.03 [5–25.5][c] 2. Patient not underwent hemodialysis:64 [11–206][c]	4–10 mg/ kg every 24–48 h	HPLC [0.25mg/L]
García-Martínez (2022)[26]	Spain	46 (43/3)	Normal and impaired renal function	157	Pre-dose, 0.5, 1–2, 4–10 h after the infusion ended and before the next dose at steady state	68 [59–81][c]	75 [65–85][c]	93 [50–136][c]	4–12 mg/kg infusion 30min every 24h	UPLC-MS/MS [0.027mg/L]
Yamada (2022)[27]	Japan	47 (28/19)	Gram-positive infections	110	1.At trough: ①q24h treatment: at least 18 h after injection; ②q48h treatment: at least 42 h after injection; 2.At the peak:2 ± 1 h after injection	52.7 ± 17.7[a] [21–85][b]	57.6 ± 13.5[a] [33.2–105.0][b]	87.8 ± 58.4[a] [8.1–294.2][b]	6 ± 1[a] mg/kg [4–9.4][b] mg/kg infusion 30min q24h or q48h	HPLC [6.25mg/L]
Samura (2021)[28]	Japan	25 (14/11)	Nonobese elderly patients with hypoalbuminemia and chronic kidney disease	137 for unbound	1.>Day3: immediately before and after administration and 2–4 h after administration 2.Other time: at any given time > 2h after administration	86 [67–97][b]	42.9 [30–63][b]	31.9 [14.3–100.2][b]	4–10 mg/kg q24h or q48h	HPLC [1μg/mL for total concentration; 0.1 μg/mL for unbound]
Lim (2021)[29]	USA	6(5/1)	Children with hemodialysis and peritoneal dialysis	Plasma: 48; urine:12; dialysis fluid: 29	1.Patients received HD:at 0, 0.5, 2, 3, 4.5, 6, 24, and 48 h relative to administration 2.Patients received CCPD:at 0, 0.5, 2, 3, 4, 8, 9, 24, and 48 hours relative to infusion	Hemodialysis: 15.3 [14–17][b] Peritoneal Dialysis: 13.7[12–15][b]	Hemodialysis: 32.2 [29–34.3][b] Peritoneal Dialysis: 51.3[38.8–64][b]	-	5 mg/kg infusion 30min	HPLC [3.0mg/L]

(*Continued*)

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Table 1 (Continued).

Study (Publication Year)	Country	Number of Subjects (Male/ Female)	Characteristics of Subjects	Number of Observations	Sampling Schedule	Age (Years)	Weight (kg)	CLcr (mL/min)	Daily Dose	Bioassay [LOQ]
						a. Mean±SD	a. Mean±SD	a. Mean±SD	a. Mean±SD	
						b. Median[Range]	b. Median[Range]	b. Median[Range]	b. Median[Range]	
						c. Median [Q1-Q3]	c. Median [Q1-Q3]	c. Median [Q1-Q3]		
Lou (2021)[30]	China	49 (16/33)	Kidney transplant patients	537	0.5 h before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after drug infusion or 30 min before administration	48 [18–65][b]	60 [42–90][b]	-	500 mg infusion 30 min every 24h	HPLC [5mg/L]
Yamada (2019)[31]	Japan	20 (12/8)	Gram-positive bacterial infections	28	①during the trough period and within 60 min after the infusion(Cpeak) on day 3 ②later after initial DAP administration at a steady-state concentration.	67.8[42–88][b]	57.35[32.0–81][b]	69.7[16.2–173.4][b]	4-12 mg/kg/day infusion 30 min every 24 h	HPLC [1.0μg/mL]
Xie (2020)[32]	USA	32 (22/10)	CRRT patients with Staphylococcus aureus infections	-	Pooled data from other publications	66.0 [61.5–72.3][c]	81.5 [69.3–91.1][c]	-	4, 6 and 8 mg/kg infusion 30 min every 24 or 48h,	-
Piva (2019)[33]	Italy	9(4/5)	Patients with an implanted external ventricular drainage and a diagnosis of a healthcare-associated meningitis	87 CSF and 99 plasma samples	0 and 1 h after the end of the infusion(tmax)	44.22±20.23[a]	56.89±14.17[a]	110.88±55.85[a]	10 mg/kg/24h infusion 40min	LC-MS [1.56mg/L]
Gre´goire (2018)[4]	French	24 (16/8) CLcr<30 mL/min: 6(3/3) CLcr≥30 to<50 mL/min: 5 (3/2) CLcr≥50 to<80 mL/min: 7 (6/1) CLcr≥80 mL/min: 6(4/2)	Infected ICU patients with various degrees of renal impairment	-	1.Administered every 24 h: 0, 0.5, 2–3, 4–8, 8–12, 12–16 and 16–24 h 2.Administered every 48 h: 0, 0.5, 2–6, 8–12, 16–24, 28–36 and 40–48 h	58[50–82][b] 78[63–82][b] 69[56–82][b] 63[56–72][b]	79[55–90][b] 76[56–103][b] 74[55–103][b] 93[74–106][b]	22[7–34][b] 49[36–77][b] 64[42–115][b] 121[80–135][b]	1.Patients with CLCR ≥ 30mL/min: 10 mg/kg every 24 h infusion 30 min; 2. Patients with CLCR < 30mL/min: 10 mg/kg every 48 h infusion 30 min	LC-MS/MS [1 mg/L for plasma and urine; 0.05 mg/L for ultrafiltrate]
Soraluce (2018)[34]	Spain	16 (7/9)	Intensive care unit patients	-	At pre-dose and the end of the infusion:one sample was taken within the interval of 4 to 8 h, a second at 10 to 14 h, and another at 24 h and 48 h (when dosed every 48 h)	67 [48–83][b]	84 [52–100][b]	1.NO CRRT:66 [20–121][b] 2.CRRT: 8[0–54][b]	350-850 mg infusion 20–60 min every 24 or 48 hours	HPLC [0.1μg/mL]
Di Paolo (2013)[35]	Italy	58 (38/20)	Patients with severe Gram_x005f positive infections.	158	0.5, 1.0 and 23.5 h	65.8 ± 14.5[a]	70.6 ± 17.2[a]	-	4-12mg/kg/every 24h infusion 30 min	HPLC [0.78mg/L]

Notes: [a] Mean±SD; [b] Median[Range]; [c] Median[Q1-Q3].

Abbreviations: -, not provided; CLcr, creatinine clearance; CRRT, continuous renal replacement therapy; DAP, Daptomycin; ECMO, extracorporeal membrane oxygenation; HPLC, high-performance liquid; ICU, intensive care unit; LC-MS, liquid chromatograph mass spectrometer or mass spectrometer; LOQ, lower of quantity; SD, standard deviation; UPLC-MS/MS, ultra performance liquid chromatography/tandem mass spectrometry.

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Table 2 Model Strategies and Final Pharmacokinetic Parameters of Included Studies

Study (Publication Year)	Software/ Algorithm	Fixed Effect Parameters	Between-Subject Variability (CV%)	Residual Unexplained Variability	Internal Validation	External Validation (N=Number of Subjects)	Model Application
Olney (2024)[23]	Monolix/-	CL = 0.62×(CLcr/120)$^{\circ 59}$×0.52$^{(METHADONE)}$×0.4^{SEX} L/h	41.18	Prop = 20%	GOF, VPC	-	Compare the weight-based dosing and fixed dosing, the fixed dosing is better
		V = 12.55 L	65.45				
			ω_{V_CL}=0.8				
Zhang (2024)[24]	NONMEM/FOCE	CL = 0.736×(CLcr/50)$^{\circ 464}$ L/h	28.7	Prop = 10.1%	GOF, bootstrap, NPDEs, pc-VPCs	-	Assess different dosage regimens over a range of MIC in different renal function patients
		Vc = 8.78 L	28.4	Add = 1.24 μg/mL			
		Vp = 5.59 L	46.9				
		Q=3.24 L/h	-				
Wu (2024)[25]	NONMEM/FOCE-I	In CRRT patients: CL = 0.386 L/h in others: CL = 0.229+0.148×(CLcr/54) L/h	30.17	Prop = 1.8%	GOF, VPC, bootstrap	-	Assess different dosage regimens over a range of MIC in different renal function patients
		Vc = 4.14 L	33.76	Add = 38.095			
		Vp = 3.52 L	44.94				
		Q = 2.09 L/h	-				
Takahashi (2023)[3]	NONMEM/FOCE-I	**Ubound:**	-	Prop.total = 13.6%	Bootstrap, GOF, pcVPC	-	Simulate the effect of renal function on unbound daptomycin concentration
		CL = [2.38+6.49×(CLcr/6)] × [(WT/70)$^{\circ 75}$] h	29.8	Add.total = 1.27 mg/L			
		Vc = 151×(FFM/5.127487) L	34.8	Prop.unbound = 15.9%			
		Q = 0.799×(FFM/5.127487) L/h	118	Add.unbound = 0.217 mg/L			
		Vp = 53.7×[(WT/70)^{75}] L	270				
		fu = 1-(1-0.0659) × (1+0.00148×(ALB-45)) ×(1+0.0187×(RF-1))	16				
		Total:	-				
		Y = ($Y_{PRED,\ unbound}$/fu)×(1+prop.total)+ add.total	-				
García-Martínez (2022)[26]	NONMEM/SAEM-IS	CL = 6.98×(CLcr/92.8)$^{\circ 19}$ L/h	32	Add = 22%(On log scale)	GOF, pc-VPC, bootstrap, NPDE	-	Establish the optimal dose recommendation of daptomycin in different renal function patients
		Vc = 0.95 L	-				
		Q = 1.96 L/h	-				
		Vp = 21 L	47				
		Bmax = 160 mg/L	-				
		KD = 3.56 mg/L	-				
Yamada (2022)[27]	NONMEM/FOCE-I	CL = 0.59×(CLcr/90)$^{\circ 43}$ L/h	17.7	Prop = 2.4%	GOF, pc-VPC, bootstrap	-	Explore the optimal dosing regimens stratified by renal function and MIC values
		Vc = 6.46 L	14.9				
		Q = 3.64×(WT/70)$^{\circ 855}$ L/h	-				
		Vp = 5.58×(WT/70)$^{\circ 775}$ L	-				
Samura (2021)[28]	Phoenix NLME/ FOCE-ELS	CL = 4.01×(eGFRcys/2.08)$^{\circ 33}$×(Age/86)$^{(-1.25)}$ L/h	22.36	-	GOF, VPC, bootstrap	-	Optimize the dosing regimens based on free daptomycin concentration and cystatin C in specific populations (elderly, hypoalbuminemia,CKD)
		Vc = 44.96 L	54.77				
		Vp = 62.12 L	-				
		Q = 10.91 L/h	-				

(*Continued*)

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Table 2 (Continued).

Study (Publication Year)	Software/ Algorithm	Fixed Effect Parameters	Between-Subject Variability (CV%)	Residual Unexplained Variability	Internal Validation	External Validation (N=Number of Subjects)	Model Application
Lim (2021)[29]	Phoenix NLME/ FOCE-ELS	Vc = 3.67 L Ke = 0.00574 h^{-1} K_{12} = 0.222 h^{-1} K_{21} = 0.370 h^{-1} Knr = 0.0428 h^{-1} Kd_{HD} = 0.171 h^{-1} K1p = 0.0130 h^{-1} Kp1= 0.00126 h^{-1} CL = 0.174 L/h CL_{HD} = 0.619 L/h CL_{1P} = 0.0508 L/h CL_{renal} = 0.226 L/h CL_{nr} = 0.158 L/h Vss = 5.9 L	11.2 40.5 - - 8.78 - 23.6 90.8 - - - - - -	Plasma: prop = 8.5% HD/urine: prop = 11% PD: add = 0.78 mg	GOF	-	Examine the pharmacodynamic outcome in patients receiving HD and CCPD
Lou (2021)[30]	NONMEM /FOCE-I	CL = 0.316 × $(WT/60)^{722}$ ×$(GFR/39.4)^{238}$L/h Vc = 6.04×$(WT/60)^{1.18}$ L Vp = 2.46L Q = 2.31L/h	29.4 21.06 - -	Prop = 36.2% Add = 0.09	GOF, bootstrap, NPDE	-	Provide a strategy for adjusting the dose according to renal function and weight.
Yamada (2019)[31]	NONMEM/FOCE-I	CL = 0.469×(WT/50) L/h V = 6.720×(WT/50) L	32.4 -	Prop = 5.8%	GOF bootstrap	-	Optimize the doses of daptomycin
Xie (2020)[32]	NONMEM/FOCE-I	CL= 0.365×$(WT/88.6)^{647}$ L/h Vc = 6.33 L Vp = 7.26 L Q = 3.90 L/h	73.1 26 50 $\omega_{CL,\ Vc}$ = 0.112	Prop = 14.0% Add = 0.254 mg/L	pcVPCGOF	-	Evaluate daptomycin's effifficacy and toxicity in CRRT patients receiving different dosing regimens
Piva (2019)[33]	NONMEM/ -	CLp = 0.57×[$(CLcr/80)^{24}$] L/h V = 0.19×WT L	46.9 -	Prop=32% Add=2.65	GOFVPCBootstrap	-	1.Characterize the pharmacokinetics of daptomycin in humans during a 7-day intravenous (IV) therapy course; 2.Study the penetration of daptomycin in the CSF after IV infusion at the dose of 10 mg/kg.
Gre´goire (2018)[4]	NONMEM/IMP	CL_{renal} = 2.70×[1 +0.0199×(CLcr-50)] L/h CL_{nr} = 4.12 L/h $C_b = N \times C_u^{1.14}$ N = 8.62×[1 + 0.0283×(ALB-20)] Vc = 83.6 L Vp = 70.1 L Q = 33.3 L/h N_{TV} = 8.62	37 36 - - 36 49 63 55	Prop.Cu = 26% Prop.Ct = 13% Prop.Curine = 42%	GOF	-	Assess the probability of attaining antimicrobial efficacy and the risks of toxicity in infected ICU patients with various degrees of renal impairment

Soraluce (2018)[34]	NONMEM/FOCE-I	CL = 0.16+0.367×(CLcr/49) + CL_{EC} L/h V = 12.5 L	36.7 27.8	Add = 0.123 μg/mL(log-scale)	GOFpvcVPCbootstrap	-	Study CL_{EC}=Sc×Qef=0.2×1.5 L/h or 0.2×2.5 L/h
Di Paolo (2013)[35]	NONMEM/FO	CL = 0.8016×$(CLcr/80)^{2026}$ L/h V = 12.29 L	20.74 -	Prop = 36.28% Add = 1.422 mg/L	GOFpcVPCbootstrap	-	Evaluate the population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections

Abbreviations: -, not provided; ALB, albumin; Bmax, maximal binding cap; C_b, the bound concentration; CL, total clearance; CLp, plasma clearance; CL_{EC}, extra-corporeal clearance; CLcr, creatinine clearance; CL_{HD}, hemodialysis clearance; CL_{nr}, non-renal clearance; CL_{renal}, renal clearance; CRRT, continuous renal replacement therapy; CSF, colony stimulating factor; C_u, the unbound concentration; CKD, chronic kidney disease; CCPD, continuous cycling peritoneal dialysis; eGFR-cys, eGFR-based on Cystatin C; FFM, the fat-free mass predicted from weight(kg) and height (m): FFM(kg) =WHS_{max}×HT^2×[weight/(WHS_{50}×$height^2$+weight)] (male: WHS_{max} = 42.92kg/m^2, WHS_{50} = 30.93kg/m^2; female: WHS_{max} = 37.99kg/m^2, WHS_{50} = 35.98kg/m^2);FO, first-order elimination; FOCE, first order conditional estimation; FOCE-ELS, FOCE-extended least squares; FOCE-I, FOCE with the interaction; fu, fraction unbound; GOF, goodness-of-fit plot; HD, hemodialysis; IMP, importance sampling algorithm; ICU, intensive care unit; K_{12}, distributional rate from central to peripheral compartment; K_{21}, distributional rate from peripheral to central compartment; K_{1p}, distributional rate from central to peritoneal compartment; Kd_{HD}, hemodialytic elimination rate; Ke, renal elimination rate; KD, equilibrium dissociation constant; Knr, non-renal elimination rate; K_{p1}, distributional rate from peritoneal to central compartment; MIC, minimum inhibitory concentration; N, a proportionality constant; N_{TV}, typical value for the coefficient of the power model for Cb; NPDE, normalized prediction distribution errors; PD, peritoneal dialysis; pcVPC, prediction corrected visual predictive check; pvcVPC, percentile visual predictive check; Q, intercompartmental clearance; RF, renal function; SAEM-ELS, stochastic approximation of the expectation maximization and the importance sampling; V, apparent volume of distribution; Vc, central volume of distribution; Vp, peripheral volume of distribution; VPC, visual predictive check; Vss, volume of distribution at steady state; WT, weight; $\omega_{CL,Vc}$, covariance between the variances of CL and Vc × Multiplication.

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Application of the PopPK Model Repository

Daptomycin PK Profiles

The steady state concentration–time profiles (assumed steady state is reached by the fifth dose) of daptomycin in populations with different levels of renal function are presented in Figure 2. Across all models, reduced renal function was associated with a marked increase in drug exposure, reflected by higher AUC values. This finding highlights the elevated risk of drug accumulation in patients with impaired renal function and underscores the need for careful dose adjustment to minimize toxicity.

In addition to total daptomycin concentrations, four studies[3,4,26,28] in the repository developed models describing unbound daptomycin concentrations. Their predictions were also compared (Figure S1). Furthermore, two studies[25,34] specifically modeled patients undergoing continuous renal replacement therapy (CRRT). In this subgroup, Soraluce's[34] model predicted exposures that were nearly half of those from Wu's[25] model (Figure S2).

Covariate Screening and Covariate Effect

The covariates tested and identified in the PopPK model repository are summarized in Table 3. Renal function and body weight were the most frequently reported covariates influencing daptomycin pharmacokinetics. Renal function (CLcr or eGFRcys) was evaluated in 12 studies (80%),[3,4,23–28,30,33–35] and 12 (100%) of these[3,4,23–28,30,33–35] identified it as a significant covariate. This confirms that renal function has clinically meaningful effects on clearance, supporting the need for dose adjustments according to renal status. Body weight was identified as a significant covariate in four studies.[27,30,32,33] Among these, three studies[30,33] reported its impact on the volume of distribution, and two studies[23,30] identified an effect on clearance. To further assess the clinical relevance of covariates, a forest plot was generated (Figure 3). The results demonstrated that patients with severe renal impairment differed significantly from those with moderate impairment (reference group). Moreover, even patients with normal or mildly impaired renal function exhibited significant differences in CL compared with the reference group, highlighting the need for dose optimization across renal function categories, rather than only adjusting the dosage for patients with severe renal impairment as indicated on the label.[36] The effect of body weight on clearance was more modest. Higher body weight had little influence on clearance, whereas low body weight was associated with reduced clearance. Age showed minimal impact on clearance overall. In addition, Olney's[23] study identified lower clearance in females compared with males, and methadone co-administration significantly reduced daptomycin clearance.

The Probability of Target Attainment

Although PK parameters varied among subpopulations, it was essential to determine whether these differences translated into altered pharmacodynamic outcomes. The results of all PTA simulations are summarized in Figure S3. Using an efficacy target of $AUC_{24h}/MIC \geq 666$, the simulations showed that PTA increased as renal function declined, and higher daily doses consistently produced higher PTA values across all populations. At the lowest dose (4 mg/kg), only three studies,[25,27,30] predicted that patients with severe renal impairment could achieve the target, whereas patients with better renal function generally failed to reach it. Due to most of the predicted AUC was below the 666 mg*h/L (Figure 4). When the dose was increased to 10 mg/kg, most models predicted that patients with CLcr values between 15 and 60 mL/min achieved the efficacy target (Figures S4–S7).

For toxicity assessment, with the toxicity threshold defined as $C_{min} \geq 24.3$ mg/L, the results are summarized in Figure 5. The probability of exceeding this threshold increased both with worsening renal function and with higher doses. Across most models, patients with severe renal impairment had a three- to fourfold higher risk of exceeding the toxicity threshold compared with those with normal renal function. Even at 4 mg/kg, six studies[3,23,25,27,30,34] predicted that more than 20% of patients with severe renal impairment would exceed the safety limit. At 6 mg/kg, 9 out of 11 models[3,4,23–25,27,30,33,34] predicted excessive toxicity, indicating that patients with moderate to severe renal impairment should be treated with caution at doses ≥ 6 mg/kg.

Calculator Based on MAP-BE

With the purpose of transferring the model to clinical bedside, we developed a precision dosing calculator based on the model established by Grégoire[4] as an example. The tool estimates $AUC_{interveal}$ and C_{min} following daptomycin

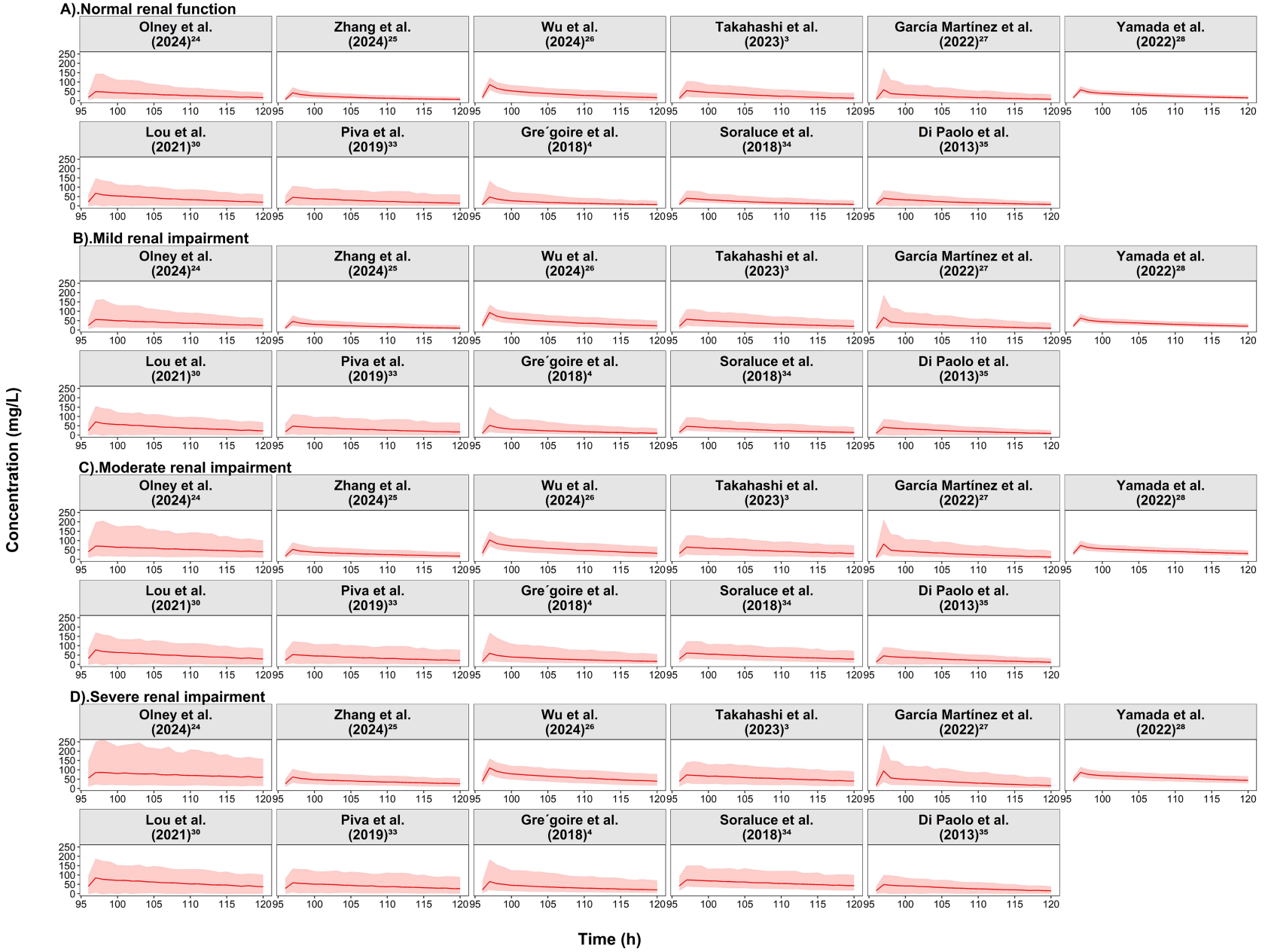

Figure 2 Simulated steady-state daptomycin total concentration-time profiles across different renal function subpopulations following intravenous infusion of 6 mg/kg every 24 hours based on retrieved population pharmacokinetic models.

Notes: (**A**) Normal renal function; (**B**) Mild renal impairment; (**C**) Moderate renal impairment; (**D**) Severe renal impairment (renal categories defined according to each original model). The solid line represents the median predicted concentration–time profile, and the shaded area represents the 5th-95th percentile range derived from Monte Carlo simulations. All simulations assumed adult male patients receiving daptomycin monotherapy. Concentrations represent total plasma concentrations.

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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	Co-Administration	Forward Inclusion	Backward Elimination	CL	Vc	Vp	Q
Olney (2024)[23]	Age, Height, Weight, Sex, BMI Self-identified race, Pittsburgh acteremia Score, Body surface area using Mosteller's adaptation	Scr, CPK ALB, CLcr using the Cockcroft-Gault equation and weight,	Statin, Methadone	p<0.05	-	Methadone, CLcr, sex	-	-	-
Zhang (2024)[24]	Age, Sex, Weight, BMI, APACHE II, SOFA score, Use of CRRT	TBIL, DBIL, ALT, AST, ALP, GGT, DH, TP, ALB, SCr, CLcr, BUN	-	-	-	CLcr	-	-	-
Wu (2024)[25]	Age, Sex, Weight, BMI, APACHE II score, SOFA score	CLcr, ALB	-	p<0.05	p<0.01	CLcr	-	-	-
Takahashi (2023)[3]	Sex, Age, Total body mass, BMI, Type of infection	CRP, CPK, ALT, Scr, CLcr, ALB	-	P<0.05	-	CLcr	-	-	
García-Martínez (2022)[26]	Sex, Age, Weight, Height	ALB, Scr, CLcr	statin	p<0.05	-	CLcr	-	-	-
Yamada (2022)[27]	Sex, Age, Weight, Body temperature	CLcr, ALB	-	p<0.05	p<0.01	CLcr	-	Weight	Weight
Samura (2021)[28]	Sex, Age, Height, Weight, BMI, Diabetic complications	CLcr, eGFRcre, eGFRcys, ALB, Glomerular filtration rate from eGFRcre, Glomerular filtration rate from eGFRcys	-	p<0.05	p<0.05	eGFRcys, Age	-	-	-
Lim (2021)[29]	-	-	-	-	-	-	-		-
Lou (2021)[30]	Sex, Age, Height, Weight, BMI,	GFR, Scr, GLU, BUN, ALT, AST, TP, ALB, TCHO, LDL, HDL, WBC, N, L, HB, HCT, PLT	p<0.05	p<0.01	GFR, Weight	Weight	-		-
Yamada (2019)[31]	Sex, Age	ALB, Glomerular filtration rate	p<0.05	p<0.01	-	-	-		-
Xie (2020)[32]	Sex, Age, Weight, BMI, CRRT modality	-	p<0.05	p<0.01	Weight	-	-		-
Piva (2019)[33]	Sex, Age, Weight, Diagnosis	CLcr	-	-	CLcr	Weight	-		-
Gre´goire (2018)[4]	Sex, Age, Weight, SOFA score,	Temperature, CLcr MDRD estimate at inclusion, CLcr measured on PK occasions, ALB, TP	-	-	-	CL_{Cr}	-	-	-
Soraluce (2018)[34]	Sex, Age, Weight, BMI, APACHE II	CLcr, Glucose, Haemoglobin, Haematocrit, ALB, TP, Bilirubin, Leukocytes, AST, ALT, CPK	-	p<0.05	p<0.01	CLcr	-	-	-
Di Paolo (2013)[35]	Sex, Age, Weight, Site of infection, Bacterial strain, Bacteraemia,	Scr, Reciprocal scr, CLcr	-	p<0.05	p<0.01	CLcr	-	-	-

Abbreviations: -, not provided; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APACHE II, acute physiology and chronic health evaluation II; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CL, total clearance; CLcr, creatinine clearance; CPK, creatine phosphokinase; CRP, c-reactive protein; CRRT, continuous renal replacement therapy; DAP, daptomycin; DBIL, direct bilirubin; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; eGFR-cre, eGFR based on creatinine; eGFR-cys, eGFR based on Cystatin C; GGT, gamma-glutamyl-transferase; GLU, blood glucose; HB, hemoglobin; HCT, red blood cell specific volume; HDL, high-density lipoprotein; L, lymphocyte; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; N, neutrophil; PLT, platelet; Scr, serum creatinine; SOFA, sequential organ failure assessment; TBIL, total bilirubin; TCHO, total cholesterol; TP, total protein; WBC, white blood cell.

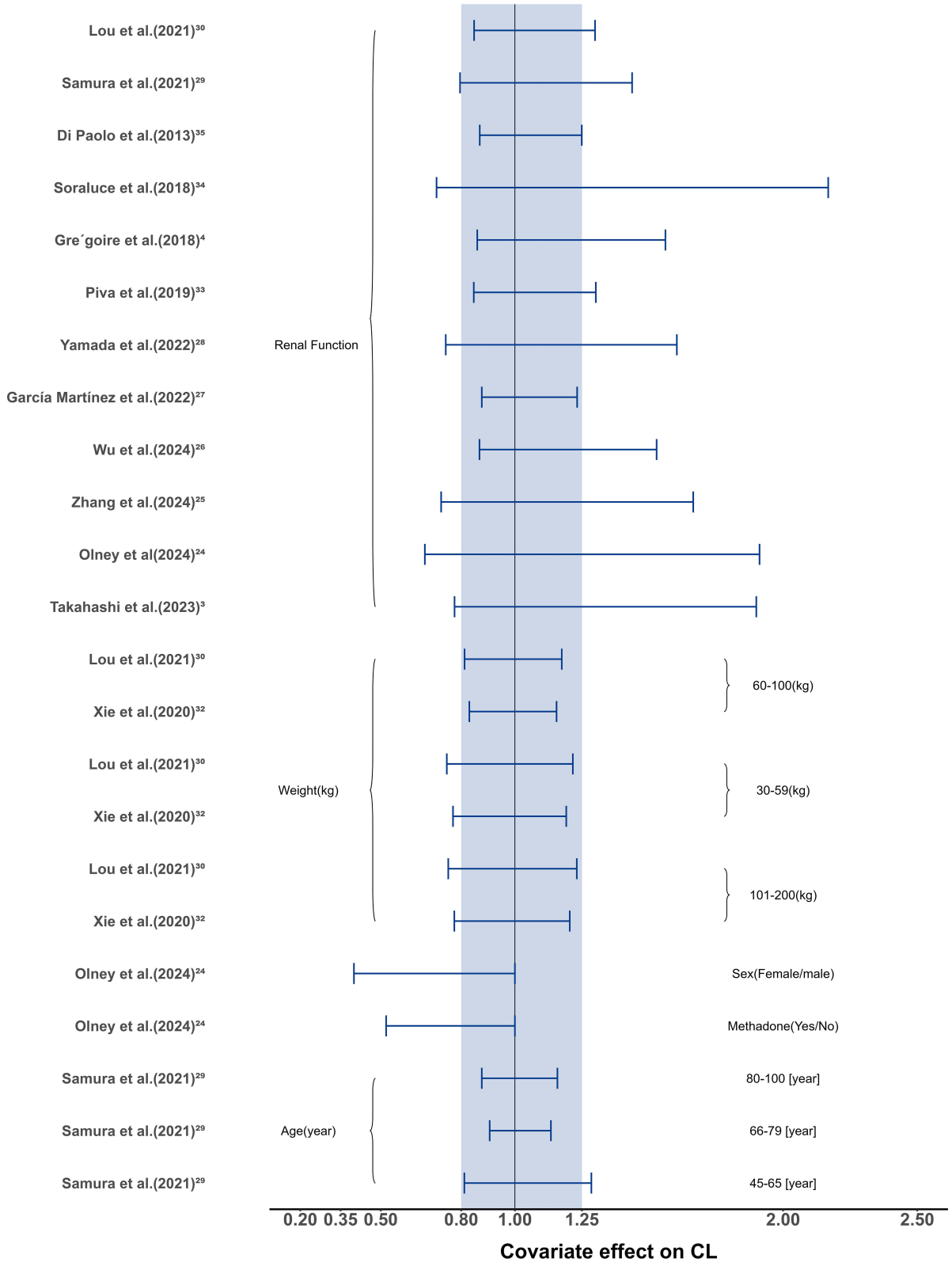

Figure 3 Forest plot summarizing the reported covariate effects on daptomycin clearance across included population pharmacokinetic models.
Notes: Each horizontal bar represents the fold-change in clearance associated with a specific covariate relative to the reference value reported in the original study. The shaded region (0.8–1.25-fold) indicates the range considered clinically non-significant according to bioequivalence criteria.

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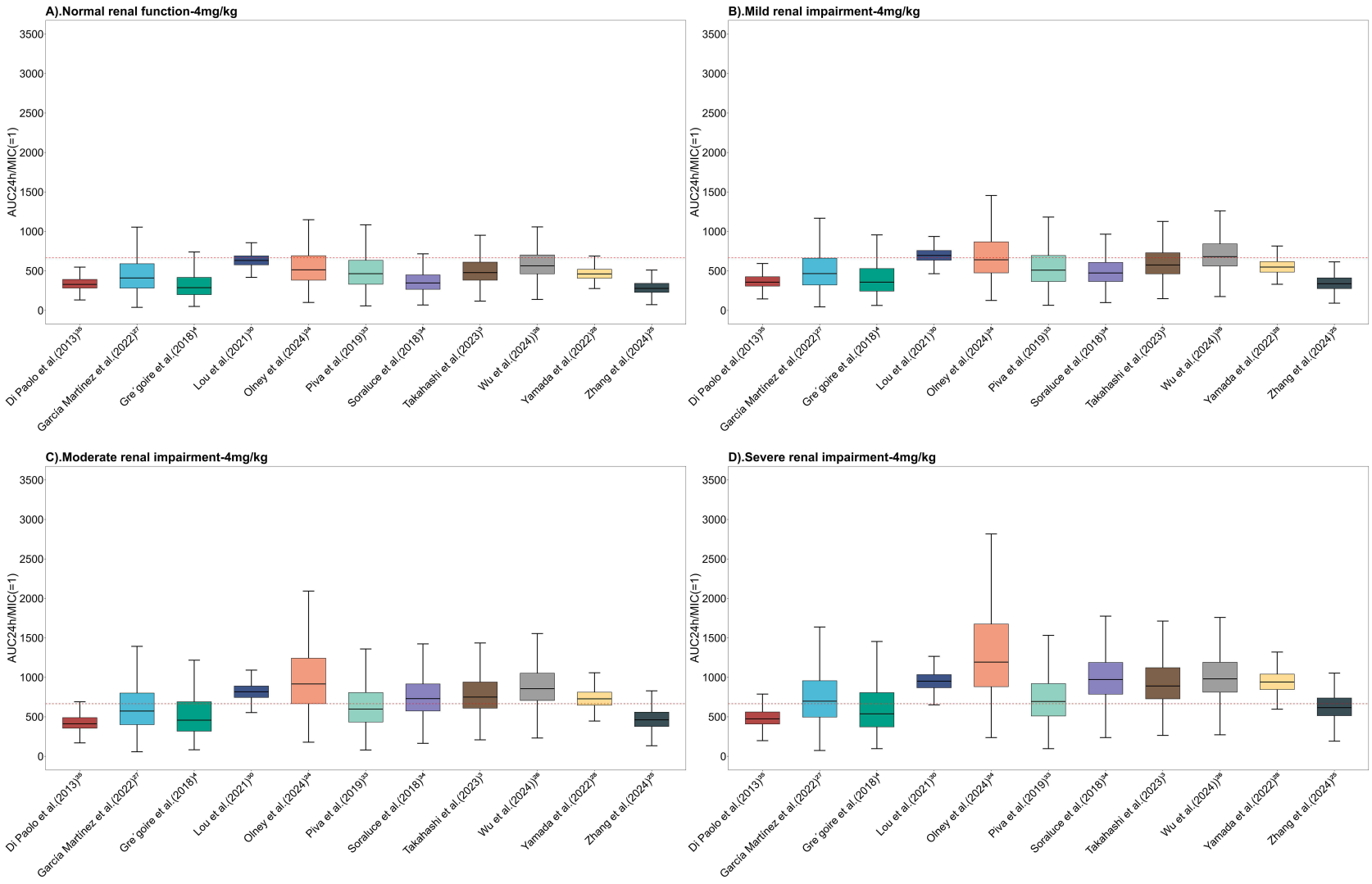

Figure 4 Predicted area under the concentration-time curve over 24 hours ($AUC_{0\text{-}24h}$) following a 4 mg/kg intravenous infusion of daptomycin across renal function subpopulations based on retrieved population pharmacokinetic models.

Notes: (**A**) Normal renal function, (**B**) Mild renal impairment, (**C**) Moderate renal impairment, (**D**) Severe renal impairment. The red dashed line represents AUC_{24h}/MIC = 666/1.

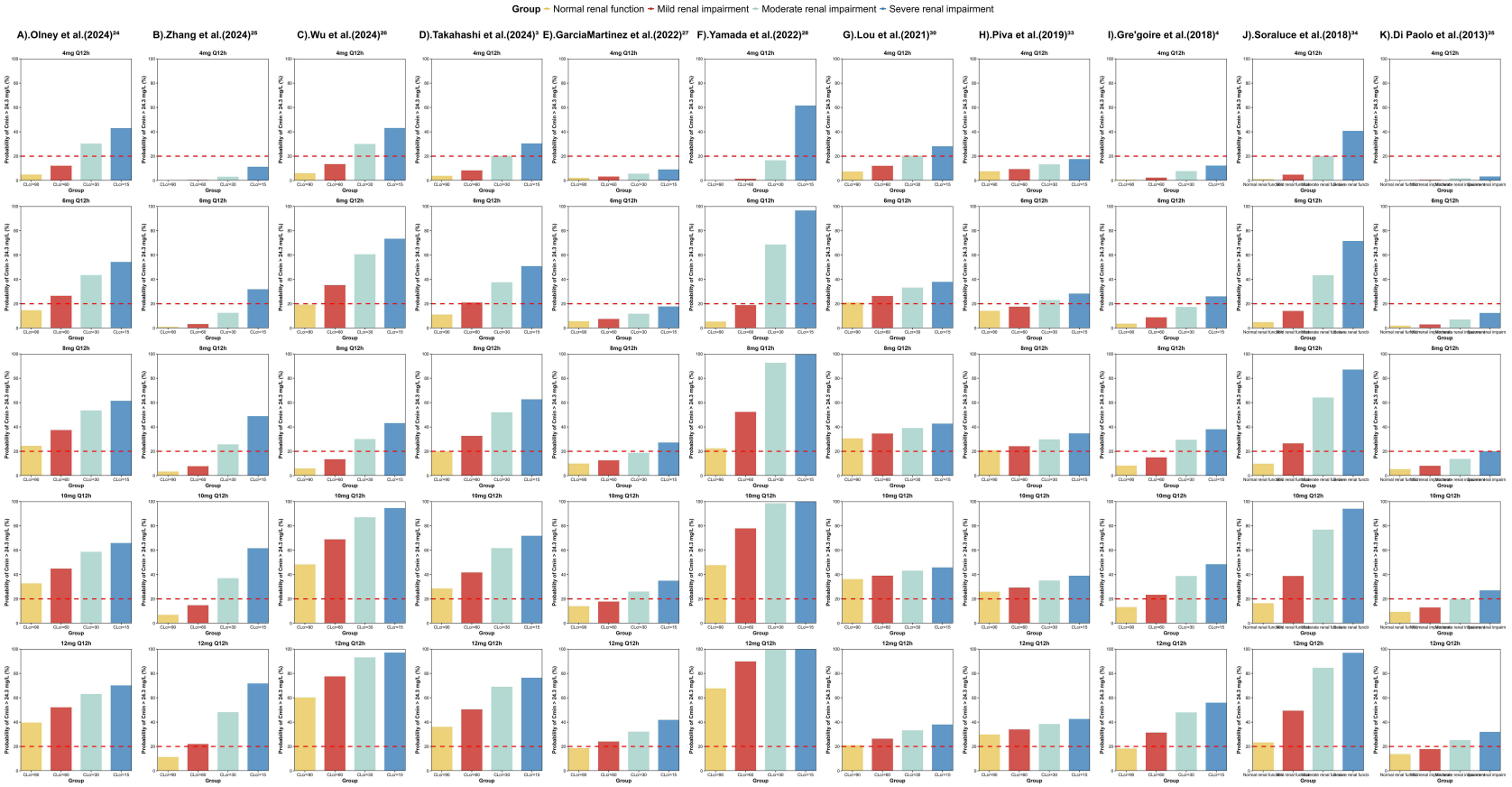

Figure 5 Predicted probability of trough concentration exceeding 24.3 mg/L at steady state across different renal function subpopulations for each retrieved population pharmacokinetic model.

Notes: (**A**)–(**K**) represent different population pharmacokinetic models from different studies used in the simulations. The red dashed line represents the 20% threshold. The yellow column represents the normal renal function, the red column represents the mild renal impairment, the light blue column represents the moderate renal impairment, the blue column represents the severe renal impairment.

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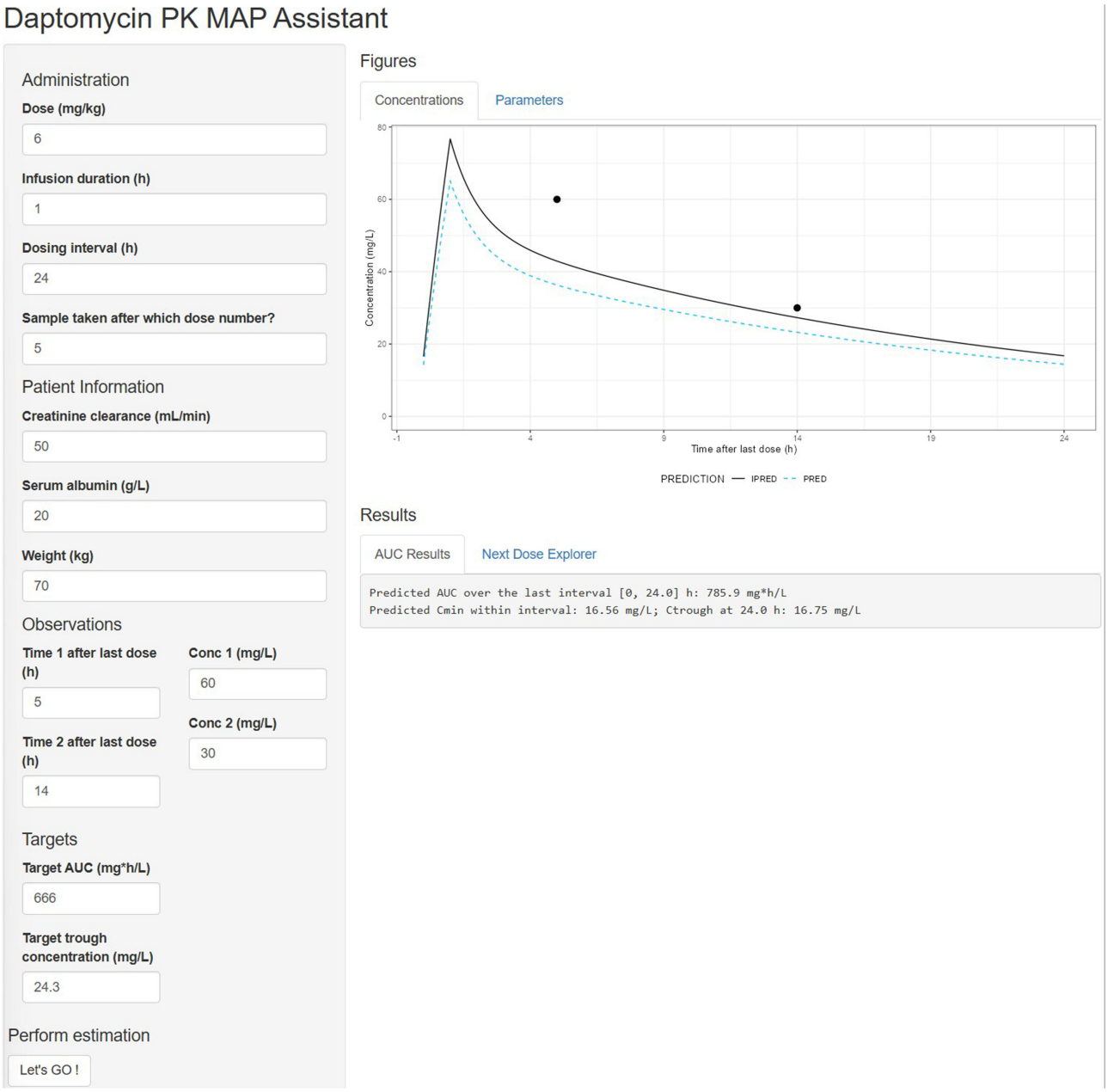

Figure 6 Schematic workflow of the Maximum A Posteriori Bayesian estimator assistant developed for individualized daptomycin pharmacokinetic prediction.

administration. Briefly, as it illustrated in Figure 6, to perform these calculations, the calculator requires input of dosing information (eg., dose amount, infusion duration, dosing interval), sampling data (eg., sampling time, observed concentrations), and patient demographics (eg., body weight, serum albumin, creatinine clearance). By entering these parameters, a simulated concentration–time profile is generated for the individual patient, from which AUC and C_{min} are calculated for the dosing interval. If the target exposure is not achieved, the "Next Dose Explorer" module provides recommendations for dose adjustment. A demonstration version of this calculator is available online (https://mipdshinyapp.shinyapps.io/Daptomycin/), and a detailed user guide is provided in the Supplementary Materials 2.

Discussion

To the best of our knowledge, this is the first study to establish a parametric PopPK model repository for daptomycin. By systematically evaluating existing models and integrating their structures, we provide a unified platform to simulate

concentration–time profiles, explore covariate effects, and predict probability of target attainment. In addition, we developed a precision dosing tool based on this repository, demonstrating a practical pathway to translate pharmacometrics models into clinical use.

Renal clearance is the main elimination pathway of daptomycin, with approximately 50% of the administered dose excreted unchanged in urine. Accordingly, the drug label recommends dose adjustment based on creatinine clearance, such as extending the dosing interval when CLcr < 30 mL/min. Consistent with this, our analysis found that 12 of 15 PopPK models identified renal function as a significant covariate for clearance. Among them, Soraluce's[34] model showed the largest variability of CL in different renal function patients, likely because it was developed in a cohort covering a broad range of renal function, and less patients (only 16) involved in the model development. However, Di Paolo[35] and García-Martínez's[26] models suggested smaller renal effects on clearance, with the upper and lower bounds fall in the 0.8–1.25 range. This may be attributable to the limited variability in renal function among the patients included in their studies. Using moderate impairment as the reference, we observed clinically significant differences not only between severe and moderate impairment, but also between normal/mild renal impairment function and moderate impairment (Figure 3).

Model performance differed in predicting efficacy. For example, Wu,[25] and Yamada's[27] and Lou's models[30] predicted that patients with severe renal impairment could still achieve the efficacy target with 4 mg/kg dosing, whereas other studies did not. This suggests that the standard 4 mg/kg regimen may be inadequate for patients with renal impairment, the higher doses might be required. With respect to safety, the probability of exceeding the C_{min} threshold was substantially higher in patients with reduced renal function, indicating an increased risk of toxicity in this group. Previous reports have also suggested that halving the dosing rate in renally impaired patients can lower the incidence of adverse events.[4,37] Besides, higher doses were associated with a significantly increased risk of creatine phosphokinase elevation.[38] Moreover, genetic polymorphisms may influence daptomycin pharmacokinetics. Romain et al[39] reported that the volume of distribution was approximately 25% lower in patients with the homozygous CGC *ABCB1* haplotype compared with other genotypes, which may affect target attainment in patients infected with high-MIC pathogens. In addition, Lorena et al[40] found that the *ABCB1* 3435C>T polymorphism influenced daptomycin exposure, with the 3435TT genotype associated with higher $AUC_{0\text{-}24h}$ values. Protein binding is another key determinant of daptomycin pharmacokinetics and pharmacodynamics, as only the unbound fraction mediates antibacterial activity. Daptomycin is highly protein bound (90–93%), only four studies[3,4,26,28] developed models accounting for bound and unbound drug. Grégoire et al[4] measured both plasma and urine samples, finding that the unbound fraction increased as renal function declined. Based on these data, they recommended 10 mg/kg q24h for ICU patients with CLcr ≥ 30 mL/min and q48h for those with CLcr < 30 mL/min. Martínez et al[26] also developed a bound/unbound model, but they did not use free concentrations directly, leading to potential structural identifiability issues. For instance, their estimated central compartment volume (0.95 L) was substantially lower than reported in other studies. Special consideration is required for patients receiving CRRT. Xie et al[32] developed a PopPK model in this population with *Staphylococcus aureus* infections. Their simulations indicated that q48h dosing was inadequate, whereas a regimen of 6 mg/kg q24h combined with CRRT doses of 30–35 mL/h/kg provided the best balance of efficacy and safety. These findings align with the drug label, which recommends 6 mg/kg for *S. aureus* infections and 4 mg/kg for cSSTI.

Body weight and age were less frequently identified as covariates. Only three studies reported significant effects, despite the label recommending weight-based dosing in pediatric and adult populations. This likely reflect the fact that most included studies predominantly enrolled elderly patients (>60 years). The lack of pediatric data highlights an important knowledge gap, particularly regarding precision dosing in children with renal impairment. Further studies are warranted to establish safe and effective regimens in this population.

Moreover, in this study, we further developed a user-friendly interface based on Grégoire's[4] model to support individualized dosing in patients with varying renal function as an example. The tool allows clinicians to integrate TDM data, estimate AUC and C_{min}, and explore alternative regimens using MAP Bayesian estimation. It enables real-time PopPK simulations and "what-if" decision-making scenarios. Compared with traditional PopPK model applications, this platform lowers the technical barrier, offering clinicians and pharmacists a practical option to optimize daptomycin therapy at the bedside.

This study has several limitations. First, only English-language publications were included, which may have led to omission of relevant PopPK models published in other languages. Second, due to limited available data, external validation of the published models was not feasible. As a result, only one model was selected as a demonstration for tool development. Future work should conduct external evaluations of existing models and validate the Shiny-based dosing tool in prospective clinical settings.

Conclusion

This study provides a comprehensive evaluation of published PopPK models of daptomycin. By comparing demographic characteristics, structural assumptions, and covariate effects across models, we obtained a clearer understanding of the sources of interindividual variability. In addition, we developed a precision dosing tool based on this model repository. This tool represents a step forward in translating pharmacometric research into clinical practice, providing clinicians with a practical and scientifically grounded resource to support individualized daptomycin therapy.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (Xin Liu) upon reasonable request.

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Disclosure

The authors declare that they have no conflict of interest.

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