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REVIEW

Population Pharmacokinetics of Tigecycline and Implications for Individualized Therapy Optimization: A Systematic Review

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Background: Tigecycline, owing to its broad-spectrum antimicrobial activity, has emerged as an important option in the treatment of infections. However, its optimal dosing strategy remains controversial in clinical practice. Recent studies have provided valuable insights into the population pharmacokinetics (PopPK) of tigecycline. This review aims to synthesize the current literature to offer theoretical guidance for individualized clinical management.

Methods: A systematic search of PopPK studies on tigecycline published from inception to April 2025 was conducted in the PubMed and Web of Science databases. The pharmacokinetics of tigecycline in different populations were systematically reviewed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results: 16 studies were included, of which 11 focused on critically ill populations (such as those with severe infections, sepsis, renal replacement therapy, multi-drug resistant Gram-negative infections, and impaired liver function, etc). The majority of studies (12/16) adopted a two-compartment model, with the typical parameter ranges as follows: clearance (CL) 3.09–25.2 L/h, intercompartmental clearance (Q) 31.9–85.1 L/h, central volume of distribution (V1) 30.9–162 L, and peripheral volume of distribution (V2) 87.9–1030 L. This systematic analysis suggested that covariates influencing tigecycline pharmacokinetics were primarily classified into three categories: hepatic function indicators, renal function markers, and body weight-related parameters. All included models underwent internal validation.

Conclusion: Based on the existing evidence, it is recommended to use high-dose tigecycline (100mg, q12h) for drug-resistant bacterial infections, cSSI and VAP, and consider combination therapy. Individualized dose adjustment should be based on liver function and the degree of drug resistance of the pathogen, without considering renal function. The application of other covariates and the model needs to be further verified.

Keywords: tigecycline, population pharmacokinetics, model, covariate, NONMEM

Introduction

With the global rise in antimicrobial resistance, infections caused by drug-resistant bacteria have emerged as a major threat to public health.[1,2] Tigecycline, a representative agent of the glycylcycline class, has gained a pivotal role in clinical practice because of its broad-spectrum antibacterial activity. The US Food and Drug Administration (FDA) approved tigecycline in 2005 for the treatment of complicated intra-abdominal infections (cIAI) and complicated skin and skin structure infections (cSSSI) and subsequently expanded its indications in 2009 to include community-acquired pneumonia (CAP).[3] In cases of infections caused by multidrug-resistant (MDR) organisms where conventional antibiotics fail, tigecycline monotherapy or combination regimens are frequently regarded as important therapeutic options.[4–6]

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The recommended standard intravenous dosing regimen for tigecycline is a 100 mg loading dose followed by 50 mg every 12 hours. However, multiple studies have indicated that this standard dosage may be suboptimal for achieving the desired antimicrobial effect in certain patient populations.[7,8] Clinical data have shown that in patients with hospital-acquired pneumonia (HAP), increasing the dose of tigecycline to 100 mg twice daily significantly improves clinical outcomes.[9] Similarly, patients in the intensive care unit (ICU) frequently exhibit suboptimal drug exposure with standard antibiotic dosing, potentially leading to treatment failure and poor prognosis.[10,11] These findings underscore the necessity of optimizing tigecycline dosing strategies, particularly in specific patient subgroups.

Population pharmacokinetics (PopPK) offers a valuable framework for guiding individualized therapy. It can analyze plasma drug concentration data, even in sparsely sampled samples, to analyze the interindividual and intraindividual variations in pharmacokinetics and quantify the influence of covariates such as age, weight, and liver and kidney functions on pharmacokinetic parameters, thereby optimizing individualized dosing regimens. It is particularly suitable for special populations, such as elderly individuals and those with severe conditions.

To maximize the rigor and transparency of the method and enhance the reliability of the results, this study strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria, aiming to conduct the most comprehensive systematic review of tigecycline population pharmacokinetics (PopPK) models to date. By systematically comparing existing models, it focuses on analyzing key covariates influencing tigecycline pharmacokinetics and evaluating the potential need for individualized dose adjustments, thereby providing a robust evidence base for optimizing clinical dosing strategies.

Methods

Search Strategy

A systematic literature search was conducted in the PubMed and Web of Science databases to identify PopPK studies of tigecycline published from its inception to April 17, 2025. The search adhered to the PRISMA criteria. The following keywords were used for searching: (“tigecycline”) AND (“population pharmacokinetics” OR “pharmacokinetics” OR “NONMEM” OR “nonlinear mixed-effects model”).

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met the following criteria: (1) studies performed in humans (either healthy volunteers or patients); (2) Tigecycline was administered via intravenous infusion; (3) population pharmacokinetic analysis was performed and reported in studies; and (4) the language of the published article was English.

Studies were excluded based on the following criteria: (1) those were reviews, letters, books or conference abstracts; (2) those focused primarily on methodological, algorithmic, or software-related aspects; (3) those lacked sufficient methodological or pharmacokinetic information; and (4) those only conducted external validation on the published PopPK model.

Literature Quality Assessment

The quality of each selected study was assessed according to the combined checklist adopted by previous studies,[12–14] which was based on clinical pharmacokinetics[15] and population pharmacokinetic-pharmacodynamic guidelines,[16] to facilitate an appropriate reporting process. The checklist consisted of 35 criteria categorized into five domains: title/abstract, background, methods, results, and discussion/conclusion. A score of 1 was assigned for each criterion if the relevant data could be identified in the study; otherwise, a score of 0 was given. Descriptions of the operational standards for each item are provided in Supplementary Table S1. The compliance rate of each study was calculated using the formula below and expressed as a percentage.

$$\text{Compliance rate}(\%) = \frac{\text{Total number of criteria satisfied}}{\text{Total number of criteria}} \times 100$$

Data Extraction

Two authors independently extracted data from the full texts of eligible articles via a standardized data extraction form, followed by cross-checking. A third person resolved any discrepancies in the data. The following information was collected: (1) study design: publication year, country, study type (prospective or retrospective), study population, sample size, dosing regimen, sampling time points, analytical methods, etc.; (2) demographic characteristics: age, sex, body weight, ethnicity, causative pathogens, etc.; and (3) PopPK model details: compartmental model, model evaluation methods, software, estimated pharmacokinetic parameters, and identified covariates, etc.

Results

Literature Search

Details of the literature search process are presented in Figure 1. A total of 1119 articles were initially identified, including 373 from PubMed and 746 from Web of Science. Following title and abstract screening, 754 articles were excluded, including 20 full-text articles. Among these, 4 articles were excluded for the following reasons: (1) review article (n = 1), (2) letter article (n = 1) and (3) insufficient methodological or pharmacokinetic information (n = 2). The specific titles of the excluded articles can be found in Supplementary Materials Table S2. Ultimately, 16 studies were included in this review.

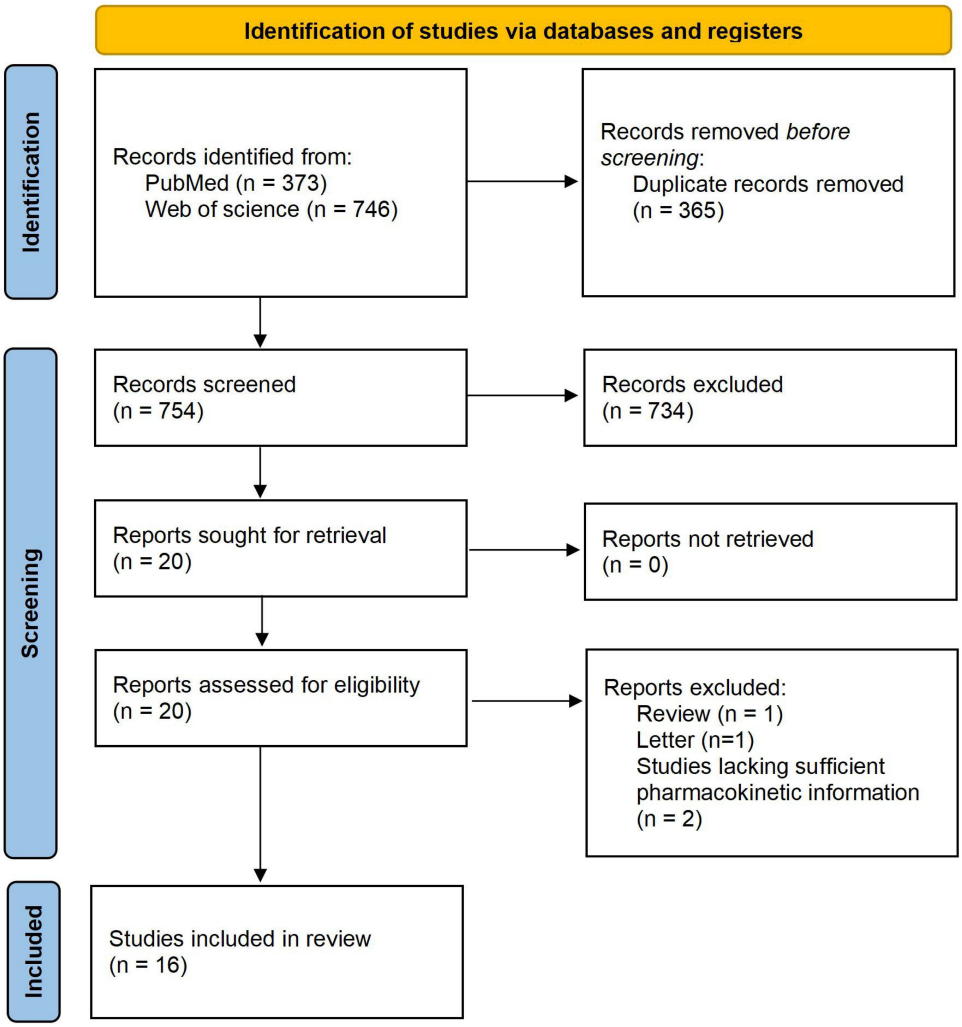

Figure 1 PRISMA flowchart for tigecycline population pharmacokinetic studies. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

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Evaluation of Literature Quality

All studies performed well in terms of quality standard compliance, with compliance rates exceeding 70% (Range: 74.29–94.29%), among which 10 studies had compliance rates exceeding 80%. Notably, 16 items achieved 100% compliance. In the title/abstract sections, the majority of studies (11, 69%) did not clearly state the route of administration, which might be related to the fact that tigecycline is only administered intravenously. In the background section, only one study did not propose specific research objectives or hypotheses. In terms of methodological reports, only one study mentioned "Methods for handling missing data". Information regarding "Co-administration or food" was provided in the first 4 studies, as its data originated from clinical trials where this record was set. Since then, neither prospective nor retrospective studies have reported such information again. In terms of results, a few studies (4, 25%) only reported the number of subjects but not the number of samples. In terms of discussion/conclusion, all studies have reported their main findings. For details, please refer to Supplementary Materials Table S3.

Study Population Characteristics

Table 1 systematically reviews the characteristics of the target population and samples in 16 population pharmacokinetic studies. The most crucial information lies in that these studies extensively covered patients ranging from healthy volunteers to those with various complex infections and special physiological and pathological conditions (such as critical illness, obesity, liver and kidney dysfunction).

There are clear emphases and trends in the characteristics of the target population. Most studies focused on critically ill patients (11 studies),[21–25,27–32] including those with severe infections,[21,28] sepsis or septic shock,[22] continuous renal replacement therapy (CRRT),[23,32] MDR gram-negative infections,[24] HAP,[25] severe hepatic impairment,[27] decompensated cirrhosis,[28] and ventilator-associated pneumonia (VAP).[29] This reflects the urgent need in clinical practice to optimize the dosing regimens for such high-risk groups. From a pathogen perspective, most patients are infected with Gram-negative pathogens such as CRAB (carbapenem-resistant Acinetobacter baumannii) and CRKP (carbapenem-resistant Klebsiella pneumoniae).

Regarding study characteristics, these studies included patients from 6 countries: China (6/16), the United States (4/16), Germany (2/16), Spain (2/16), Finland (1/16), and Greece (1/16). Patient enrollment varied significantly across studies, ranging from 9 to 410 participants, with total plasma sample volumes ranging from 72 to 2,233 samples. Demographically, the study populations were predominantly middle-aged and elderly patients with a wide range of body weights.

Study Designs

Table 2 systematically summarizes the design details of the clinical protocols included in the study. The key information indicates that these studies are mainly prospective; dosing regimens are diverse, with approximately half of the studies including high-dose or multiple-dose strategies. Blood sampling schedules varied considerably in frequency, ranging from intensive to sparse sampling.

Among the 16 studies, 11 were prospective, and 5 were retrospective. The recommended standard dosing regimen of tigecycline is a 100 mg loading dose followed by 50 mg twice daily, and 5 studies employed this standard dosage. 2 studies (by Borsuk-De Moor et al[22] and Dimopoulos et al[29]) employed high-dose regimens (200 mg loading dose followed by 100 mg twice daily). The study by Pai et al[20] evaluated the pharmacokinetics of a single 100 mg intravenous dose in obese and healthy individuals. 6 studies included multiple dosing regimens, such as both standard and high-dose regimens. 2 studies (Su et al[31] and Song et al[32]) did not report specific dosing regimens.

The number of blood sampling points varied across the studies. The most intensive sampling involved 11 time points (Pai et al[20]), while some sparse sampling studies only use 4 time points (eg, Van Wart et al,[17] Zhou et al,[25] Luo et al[30]). Regarding analytical methods, liquid chromatography-tandem mass spectrometry (LC-MS/MS) was the predominant technique, employed in 8 studies. Additionally, 3 studies used high-performance liquid chromatography (HPLC). The remaining studies employed the following methods respectively: high-performance liquid chromatography–ultraviolet (HPLC-UV, n = 1), high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS, n = 1), two-dimensional liquid chromatography (2D-LC, n = 1), ultrahigh-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS, n = 1), and a combination of HPLC-UV and LC–MS/MS (n = 1). In addition, Broeker et al.[23] And Ruiz et al[24] also measured the concentration of free tigecycline.

Table 1 Characteristics of the Population Pharmacokinetic Studies Included in the Systematic Review

ID	Author	Publication Year	Country	Patient Group	Number of Patients	Sample Size	Gender (Male/ Female)	Age (year)	Weight (kg)	Pathogen
1	Van Wart et al[17]	2006	USA	Patients with complicated intra-abdominal (cIAI) or skin and skin structure infections (cSSSI)	146	631	103/43	45.7 ± 15.6 (18–82)	84.3 ± 25.8 (47–227)	NR
2	Van Wart et al[18]	2007	USA	Healthy volunteer	174	2233	149/25	35 (18–84)	76 (50–112)	NR
3	Rubino et al[19]	2010	USA	Patients with community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP)	410	1581	250/160	55.2 ± 17.5 (18–92)	74.7 ± 17.8 (33.8–140)	NR
4	Pai et al[20]	2014	USA	Obese class III (obese-C_3) and normal weight (NW) adults	12	NR	4/8	37.5 ± 10.5 (20–50)	Obese-C_3 group: 135 ± 14.7 (121–160) NW group: 65.± 4.98 (61–70)	NR
5	Xie et al[21]	2017	China	Critically ill patients with severe infections	10	NR	6/4	64 (36.5–73)	69.1 (59.7–70.8)	NR
6	Borsuk-De Moor et al[22]	2018	Poland	Patients with sepsis or septic shock	37	940	26/11	61 (25–79)	80 (50–129)	Suspected nosocomial infection with MDR or XDR strains
7	Broeker et al[23]	2018	Germany	Critically ill patients on continuous renal replacement therapy (CRRT)	11 (CVVHD, n = 8; CVVHDF, n = 3)	Blood samples: 107 Effluent samples: 108	10/1	69 (37–81)	80 (68–104)	Complex abdominal infection (10) AB infection (1)
8	Ruiz et al[24]	2020	Spain	Critically ill patients with multidrug-resistant gram-negative infections	25	NR	18/7	47.7 ± 12.8	NR	CRKP (16, 64.0%) ESBL Enterobacter (5, 20.0%)
9	Zhou et al[25]	2021	China	Patients with HAP	89	328	55/34	61 (18–89)	60 (35–80)	MDRAB (55) CRKP (36) PA (24) *Stenotrophomonas maltophilia* (6)
10	Yang et al[26]	2021	China	Patients with HAP, cSSSI, or cIAI	67	186	50/17	65.5 ± 23	64.83 ± 14.96	AB (15, 25.86%) AB+ KP/E. coli (9, 15.52%) KP (4, 6.9%) Others (30, 51.72%)
11	Amann et al[27]	2022	Germany	Critically ill liver-impaired patients	39	283	13/27	62 (34–85)	80.0 (44.5–119)	*Enterococcus orniformis* (1) *Enterococcus faecalis* (4) *Enterococcus faecalis* (10) *Escherichia coli* (4) KP (1) MRSA (2) *Staphylococcus epidermidis* (6) VRE (12)
12	Bastida et al[28]	2022	Spain	Critically ill patients with decompensated cirrhosis and severe infections	20	99	16/4	59 ± 11 (51–67)	75 ± 18	Culture positive (7, 35%) MDR bacteria (6, 30%)
13	Dimopoulos et al[29]	2022	Greece	Critically ill patients	9	72	5/4	69 ± 11.86	78 ± 15.46	KP (5, 56%) AB (3, 33%) PA (1, 11%) *Escherichia coli* (1, 11%) Acromobacter xylosidans (1, 11%)
14	Luo et al[30]	2023	China	Critically ill patients	54	143	30/24	72.0 (57.5–80.3)	68.0 (58.3–70.0)	NR

(*Continued*)

Table 1 (Continued).

ID	Author	Publication Year	Country	Patient Group	Number of Patients	Sample Size	Gender (Male/ Female)	Age (year)	Weight (kg)	Pathogen
15	Su et al[31]	2024	China	Critically ill patients	98	751	65/33	63.4 ± 18.0 (20–92)	62.3 ± 12.4 (38–92.5)	CRAB (46, 46.9%) CRKP (24, 24.5%) CRPA (2, 2.04%) CRE (1, 1.02%) MRSA (1, 1.02%) ESBL+ (2, 2.04%) Other (25, 25.5%) Undefined (7, 7.14%)
16	Song et al[32]	2024	China	Critically ill patients undergoing CRRT	21 (CVVH, n = 20 CVVHDF, n = 1)	167	15/6	66 (22–87)	70.0 (47.4–100)	NR

Notes: The age and weight values are presented as the means ± SDs (ranges) or medians (ranges).

Abbreviations: USA, United States of America; MDR, multidrug-resistant; XDR, extensively drug-resistant; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBL, extended-spectrum β-lactam; MDRAB, multidrug-resistant *Acinetobacter baumannii*; PA, *Pseudomonas aeruginosa*; AB, *Acinetobacter baumannii*; KP, *Klebsiella pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended spectrum beta-lactamase; CVVH, continuous venous hemofiltration; CVVHD, continuous venous hemodialysis; CVVHDF, continuous venous hemodiafiltration; cIAI, complicated intra-abdominal; cSSSI, skin and skin structure infections; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; NW, normal weight; CRRT, continuous renal replacement therapy; NR, no record.

Table 2 Clinical Protocol Design of the Studies Included in the Systematic Review

ID	Author	Study Type	Dosage	Sampling Time Point	Assay
1	Van Wart et al[17]	Retrospective	100 mg (50 mg, q12h) 50 mg (25 mg, q12h)	Prior to dosing, at the end of infusion (either 0.5 h or 1 h), and at 3 h and 6 h after the start of infusion on the day before or the day of discharge from the study unit.	LC-MS/MS
2	Van Wart et al[18]	Retrospective	Single dose: (12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg) Multiple doses: (25 mg, 50 mg, 75 mg, 100 mg, q12h)	Single-dose study: Before infusion, 0.5, 1, 1.5, 2, 3, 4, 4.5*, 5*, 6, 7*, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours. Multidose study: After a Single dose: before infusion, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours.Sampling points on Day 10: before infusion, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120 hours. Note: The sampling points marked with * are only applicable to the subjects who received a 4-hour infusion.	HPLC-UV; LC-MS/MS
3	Rubino et al[19]	Retrospective	100 mg (50 mg, q12h)	1. 0 h (before the first dose). 2. On any day on or after day 3 (after a minimum of 6 tigecycline doses): 0 h, within 10 min before the end of the infusion, within 1 min after the end of the infusion. 3. On any day on or after day 3 (after a minimum of 6 tigecycline doses), 3 and 6 h from the start of the infusion (±30 minute window allowed).	LC-MS/MS
4	Pai et al[20]	Prospective	Single dose: 100 mg	Blood samples: 0 (just prior to the dose), 0.5 (end of infusion), 1.5, 3, 6, 9, 12, 24, 48, 72 and 96 h after the dose. Urine samples: (i) predose and (ii) 0–6 h, (iii) 6–12 h, (iv) 12–24 h, and (v) 24–48 h after the dose.	LC-MS/MS
5	Xie et al[21]	Prospective	100 mg (50 mg, q12h)	Before the seventh dose of tigecycline (time point 0; presumed pharmacokinetic steady state) and at 0.5, 1, 2, 3, 4, 6, 8, and 12 h after that dose.	LC-MS/MS
6	Borsuk-De Moor et al[22]	Retrospective	200 mg (100 mg, q12h)	0.5, 2, 4, 8, and 12 h after each tigecycline administration.	HPLC
7	Broeker et al[23]	Prospective	100 mg (50 mg, q12h)	Before the start of infusion (time 0), after 1 h (ie, the end of infusion), and then at 1.25, 1.5, 1.75, 2, 4, 6, 8, and 12 h on day 4 of treatment with tigecycline after at least 24 h on CRRT.	HPLC-UV
8	Ruiz et al[24]	Prospective	100 mg, q12h50 mg, q12h	Over one dosing interval in each patient between day 3 and 5 of treatment at 0 (predose), 1 h (postdose), 2, 6 and 12 h after the start of infusion.	LC-MS/MS
9	Zhou et al[25]	Prospective	100 mg (50 mg, q12h)	Before the ninth dose of tigecycline and at 0, 3, and 8 h after the end of infusion.	2D-LC
10	Yang et al[26]	Prospective	100 mg (50 mg, q12h) 100 mg, q12h 50 mg, q12h	0, 0.5, 1.5, 3, 6, 9, and 12 h after administration.	HPLC-MS /MS
11	Amann et al[27]	Prospective	100 mg (50 mg, q12h) 100 mg, q12h 50 mg, q12h 12 mg, q12h	0.3, 2, 5, 8, and 11.5 h after infusion at least 36 h after the start of therapy.	HPLC
12	Bastida et al[28]	Prospective	100 mg (50 mg, q12h) 100 mg, q12h	0.5 h before drug administration (predose), and 1, 2, 5 and 8–12 h after drug administration.	UPLC-MS /MS
13	Dimopoulos et al[29]	Prospective	200 mg (100 mg, q12h)	0 h (immediately before the start of infusion), 0.5 h (during the infusion), 1, 2, 4, 6 and 12 h after the start of drug administration.	HPLC
14	Luo et al[30]	Retrospective	100 mg (50 mg, q12h)	0 h (before administration) and 1, 2, and 4 h after administration.	LC-MS/MS
15	Su et al[31]	Prospective	NR	Before the seventh drug administration and at 0.5, 1, 2, 3, 4, 6, and 12 h postdose.	LC-MS/MS
16	Song et al[32]	Prospective	NR	Before the seventh drug administration and at 0.5, 1, 2, 3, 4, 6, and 12 h postdose.	LC-MS/MS

Abbreviations: LC–MS/MS, liquid chromatography–tandem mass spectrometry; HPLC–UV, high-performance liquid chromatography–ultraviolet detection; HPLC, high-performance liquid chromatography; 2D–LC, two-dimensional liquid chromatography; HPLC–MS/MS, high-performance liquid chromatography–tandem mass spectrometry; UPLC–MS/MS, ultraperformance liquid chromatography–tandem mass spectrometry; NR, no record.

Population Pharmacokinetic Analyses

Table 3 summarizes the final population pharmacokinetic model structures and parameter estimates of all included studies. The most crucial information lies in that the pharmacokinetic behavior of tigecycline is generally described using a two-compartment model, with significant inter-individual variability (IIV) observed in clearance (CL) and volume of distribution. Moreover, even among similar patient groups (eg, those receiving CRRT), there are significant differences in the typical parameter values reported across studies.

Regarding model structure, the majority of studies (12/16) adopted a two-compartment model. A three-compartment model was selected by Van Wart et al[18] based on rich sampling data from healthy volunteers. Pai et al[20] compared one-, two-, and three-compartment models and ultimately chose a three-compartment model incorporating both plasma and urine data because of its superior fit. Given that sparse sampling data are limited in supporting more complex structural models, simpler one-compartment models were adopted in studies by Yang et al[26] and Luo et al.[30]

For typical pharmacokinetic parameters, CL exhibits a wide range from 3.09 to 25.2 L/h. Systematic variations in parameters were observed in special populations. For instance, in patients with hepatic impairment, CL significantly decreased with increasing Child-Pugh scores. For patients undergoing CRRT, the model additionally quantified the contribution of the dialysis process itself to drug CL. Regarding model validation, the most commonly used model evaluation methods included goodness-of-fit (GOF) plots, bootstrap resampling, and visual predictive checks (VPC). To develop the PopPK models, NONMEM was the most frequently used software (11 studies), whereas others employed S-ADAPT, ADAPT 5, Pmetrics, Phoenix NLME, and Monolix.

Covariates

Table S4 summarizes the covariates included in the final models of each study. The most critical insight is that the in vivo disposition of tigecycline is significantly influenced by patient-specific factors such as hepatic and renal function and body weight, etc. Researchers quantified these factors into mathematical models using standardized statistical methods, providing the core basis for individualized dosing.

During model development, covariate selection mostly combines forward inclusion and backward elimination strategies. Demographic and physiological factors have been universally considered across studies. For specific patient populations, researchers employed corresponding assessment methods: for hepatic impairment, liver function was evaluated by the Child–Pugh score (CPS),[27] Model for End-Stage Liver Disease (MELD),[27,28] LiMAX test,[27] or acute–on–chronic liver failure (ACLF) grading;[28] for critically ill patients, the severity of illness was assessed via the Acute Physiology And Chronic Health Evaluation II (APACHE II)[19,21,28,30] and Sequential Organ Failure Assessment (SOFA) scores;[22,28] and for dialysis patients, treatment-related variables such as dialysis volume,[22] ultrafiltration rate,[22] and CRRT mode[32] were included.

Among the covariates, body weight was most frequently identified as a significant factor: it was significantly associated with CL in 4 studies, influenced central volume of distribution (V1) in 3 studies, and was linked to the peripheral volume of distribution (V2) in 1 study. In addition, several studies have consistently reported that hepatic function indicators (eg, bilirubin levels, CPS) and renal function indicators (eg, serum creatinine, creatinine clearance (CrCl)) significantly influence the tigecycline CL and Vd. These key covariates that were screened out were ultimately integrated into the final pharmacokinetic model through power functions or linear relationships, thereby precisely quantifying the extent to which individual patient characteristics affect drug metabolism.

Discussion

As a key therapeutic agent for MDR bacterial infections, tigecycline often faces the challenge of suboptimal drug exposure when standard dosing regimens are applied in special patient populations. PopPK models have identified critical covariates influencing tigecycline exposure and quantified interindividual variability, thereby providing a robust basis for clinical dose optimization. This review systematically evaluated all available PopPK studies of tigecycline published from the establishment of the library to April 2025, and to our knowledge, represents the most comprehensive review of tigecycline PopPK modeling to date.

Table 3 Population Pharmacokinetic Models of the Studies Included in the Systematic Review

ID	Author	Compartments	Population Typical Value	Inter-individual variability (IIV)	Residual variability (RV)	Model Evaluation Method	Software
1	Van Wart et al[17]	2-CMT	CL: 15.7 L/h Q: 70.9 L/h V1: 155 L V2: 644 L	CL: 35.1% Q: 49.3% V1: 43.2%	Residual variability: 21%	GOF	NONMEM
2	Van Wart et al[18]	Dense sampling: 3-CMT Sparse sampling: 2-CMT	(3-CMT model of multi-dose administration) CL: 16.8 L/h Q2: 3.02 L/h Q3: 100 L/h V1: 27.8 L V2: 388 L V3: 439 L (2-CMT model of multi-dose administration) CL: 16.3 L/h Q: 74.7 L/h V1: 57.7 L V2: 1030 L	(Three-compartment model of multi-dose administration) CL: 14.9% Q2: 36.2% V2: 40.5% (Two-compartment model of multi-dose administration) CL: 13.1% V1: 56.8%	(Three-compartment model of multi-dose administration) Residual variability: 15% (Two-compartment model of multi-dose administration) Residual variability: 11%	GOF	NONMEM
3	Rubino et al[19]	2-CMT	CL: 19.2 L/h Q: 85.1 L/h V1: 65.2 L Vss: 398 L	CL: 40.4% Q: 110% V1: 82.1% Vss: 40.2%	Additive: 0.025 μg/mL Proportional:14.5%	GOF, Bootstrap	S-ADAPT
4	Pai et al[20]	3-CMT	CL: 10.2 L/h Q2: 33.6 L/h Q3: 27.8 L/h V1: 27.1 L V2: 257 L V3: 164 L	NE	NE	GOF, Bootstrap, VPC, NPDE	ADAPT 5
5	Xie et al[21]	2-CMT	CL: 7.50 L/h V1: 72.49 L Kcp: 0.31 h^{-1} Kpc: 0.29 h^{-1}	CL: 14.8% V1: 29.22% Kcp: 51.85% Kpc: 104.41%	NE	GOF, GOF, Bootstrap, VPC	Pmetrics
6	Borsuk-De Moor et al[22]	2-CMT	CL: 22.1 L/h Q: 69.4 L/h V1: 162 L V2: 87.9 L	CL: 17.3% V1: 19.2% V2: 38.7%	Additive: 0.021 μg/mL Proportional: 13%	GOF, Bootstrap, VPC	NONMEM

(*Continued*)

Table 3 (Continued).

ID	Author	Compartments	Population Typical Value	Inter-individual variability (IIV)	Residual variability (RV)	Model Evaluation Method	Software
7	Broeker et al[23]	2-CMT	CL: 18.3 L/h Q: 56.4 L/h V1: 58.7 L V2: 154 L Dialysis CL CVVHD: 1.69 L/h Dialysis CL CVVHDF: 2.71 L/h	CL: 43.6% Q: 41.8% V1: 110.9% CL CVVHD: 43.5%	Proportional (prefilter plasma): 16.9% Proportional (effluent): 40.6%	GOF, Bootstrap, VPC	NONMEM
8	Ruiz et al[24]	2-CMT	CL: 0.18 L/h/kg Vss: 3.16 L/kg	CL: 72.2% Vss: 23.3%	NR	GOF	NONMEM
9	Zhou et al[25]	2-CMT	CL: 23.1 L/h Q: 31.9 L/h V1: 105.9 L V2: 124.9 L	CL: 39.1% V1: 58.7%	Proportional: 27.8%	GOF, Bootstrap, VPC	Phoenix NLME
10	Yang et al[26]	1-CMT	CL: 25.2 L/h V: 417 L	CL: 58.7%	Proportional: 57.6%	GOF, Bootstrap	NONMEM
11	Amann et al[27]	2-CMT	Model A: CL CPS-A: 11.3 L/h CL CPS-B: 7.69 L/h CL CPS-C: 4.81 L/h V1: 64.7 L Q: 48.4 L/h V2: 119 L Model B: CL: 8.57 L/h V1: 64.2 L Q: 48.7 L/h V2: 119 L Model C: CL: 7.52 L/h V1: 63.4 L Q: 48 L/h V2: 120 L	Model A: CL: 41.8% V1: 70% V2: 30.5% Model B: CL: 37.9% V1: 69.1% V2: 29.1% Model C: CL: 38.3% V1: 72.4% V2: 29.9%	Model A: Proportional: 13.5% Model B: Proportional: 13.9% Model C: Proportional: 12.4%	GOF, Bootstrap, VPC	NONMEM
12	Bastida et al[28]	2-CMT	CL: 14.8 L/h Q: 38.4 L/h V1: 63.7 L V2: 233 L	CL: 46.6% V1: 50.2%	Proportional: 21.7%	GOF, Bootstrap, VPC	NONMEM

13	Dimopoulos et al[29]	2-CMT	CL: 11.64 L/h Q: 62.81 L/h V1: 79.01 L V2: 92.95 L	CL: 158% V1: 97%	Additive: 0.092 μg/mL Proportional: 14%	GOF	Monolix
14	Luo et al[30]	1-CMT	CL: 11.30 L/h Vd: 105.00 L	CL: 6.5% Vd: 16%	Residual variability: 0.0316	GOF, Bootstrap, VPC, NPDE	NONMEM
15	Su et al[31]	2-CMT	CL: 3.09 L/h Q: 39.7 L/h V1: 32.1 L V2: 113 L	CL: 27.0% Q: 18.8% V1: 72.5%	Proportional: 2.02%	GOF, Bootstrap, VPC	NONMEM, PDx-Pop
16	Song et al[32]	2-CMT	CL: 4.22 L/h Q: 34.8 L/h V1: 30.9 L V2: 98.7 L	CL: 22.4% V1: 55.2%	Proportional: 1.58%	GOF, Bootstrap, VPC, NPC	NONMEM, PDx-Pop

Abbreviations: CMT, Compartment; CL, Clearance; Q, Intercompartmental Clearance; Q2, Intercompartmental Clearance (Peripheral Compartment 1); Q3, Intercompartmental Clearance (Peripheral Compartment 2); V1, Volume of Central Compartment; V2, Volume of Peripheral Compartment/Peripheral Compartment 1; V3, Volume of Peripheral Compartment 2; Vss, Volume of Distribution at Steady State; Vd, Volume of Distribution; Kcp, Rate Constant from Central to Peripheral Compartment; Kpc, Rate Constant from Peripheral to Central Compartment; CPS-A/B/C, Child–Pugh Score Class A/B/C; CVVHD, Continuous Veno-Venous Hemodialysis; CVVHDF, Continuous Veno-Venous Hemodiafiltration; GOF, Goodness–of-fit Plots; VPC, Visual Predictive Checks; NPDE, Normalized Prediction Distribution Errors; NPC, Numerical Predictive Check; NONMEM, Nonlinear Mixed Effects Modeling; S-ADAPT, Simulation and Adaptive Population Analysis Tool; NLME, Nonlinear Mixed Effects; PDx-Pop, Population Dynamics Explorer for Pharmacometrics; NE, not evaluated; NR, no record.

Currently, the pharmacokinetics of tigecycline are described primarily via a two-compartment model (12/16 studies). The reported ranges of pharmacokinetic parameters in these models were as follows: CL, 3.09–25.2 L/h; intercompartmental clearance (Q), 31.9–85.1 L/h; V1, 30.9–162 L; and V2, 87.9–1030 L. The significant variations in pharmacokinetic parameters across different studies are likely attributable to the substantial interindividual variability of tigecycline, as well as potential differences in tigecycline assay methodologies. Further comparative analysis revealed that critically ill patients generally had lower volumes of distribution at steady state (Vss) than noncritically ill individuals did, for example, 229.9 L (Zhou et al[25]) and 145.1 L (Su et al[31]) vs 398 L (Rubino et al[19]) and 759 L (Van Wart et al[17]). This discrepancy may reflect the underlying pathophysiological changes in critical illness. Notably, substantial variation in CL was observed even within critically ill populations. For example, typical CL values reported by Borsuk-De Moor et al[22] and Broeker et al[23] were relatively high (22.1 and 18.3 L/h, respectively), whereas values reported by Su et al[31] and Song et al[32] were significantly lower (3.09 and 4.22 L/h, respectively). Such variations in CL may be attributed to the heterogeneous and complex physiological conditions of critically ill patients, as well as differences in CRRT modalities. In addition, in patients with severe hepatic impairment, CL was further reduced (7.52 L/h), with considerable interindividual variability (CV = 38.3%). Similarly, patients with liver cirrhosis presented a lower CL (14.8 L/h) and greater variability (CV = 46.6%), highlighting the significant impact of hepatic function on tigecycline metabolism.

Given that tigecycline is primarily eliminated via biliary excretion (59%), most studies have evaluated liver function markers as potential covariates. As early as 2006, Van Wart et al[17] identified total bilirubin as a significant covariate, although it was not included in their final model. Subsequent studies by Broeker et al,[23] Ruiz et al,[24] Amann et al,[27] and Su et al.[31] These findings consistently confirmed a significant negative correlation between total bilirubin levels and CL. The MELD score and CPS score are established clinical tools for objectively quantifying hepatic function impairment, with the former primarily assessing end-stage liver disease severity and the latter incorporating clinical symptom evaluation to reflect the functional hepatic reserve. The tigecycline drug label states that no dose adjustment is required for patients with mild or moderate hepatic impairment (Child–Pugh class A or B). However, for patients with severe impairment (Child–Pugh class C), the maintenance dose should be reduced to 25 mg every 12 hours.[33] Amann et al[27] developed three PopPK models for patients with severe hepatic impairment: Model A incorporated the CPS score, Model B used the MELD score, and Model C included the estimated glomerular filtration rate (eGFR) and total bilirubin, suggesting that the bilirubin or MELD score may serve as alternative dose-adjustment indicators when the CPS is unavailable. Similarly, Bastida et al[28] found that the MELD score was a key covariate of CL in patients with decompensated cirrhosis, indicating that higher scores may require a reduction in the tigecycline dose. The LiMAX (liver maximum capacity) test is a quantitative liver function assessment method used to evaluate the maximal functional capacity of the liver. Research by Alraish et al[34] demonstrated a significant correlation between the LiMAX test results (indicating the degree of liver dysfunction) and the maximum plasma concentration (Cmax) of tigecycline. These findings suggest that the LiMAX test could serve as a valuable tool for optimizing antibiotic dosages in critically ill patients on the basis of hepatic metabolic capacity. Zhou et al[25] identified aspartate aminotransferase (AST), rather than bilirubin, as a significant covariate for CL, although the mechanism remains unclear. In addition, Su et al[31] were the first to report a significant association between albumin (ALB) and V2, which may be attributed to its influence on the protein binding rate of tigecycline in vivo. Therefore, we need to reduce the dosage of patients with liver injury, but in the future, a larger sample size study is needed to clarify the quantitative guidance value of different liver injury indicators and select the most effective covariates for dose adjustment.

Renal excretion accounts for approximately 15–22% of tigecycline elimination. Accordingly, renal function markers, such as serum creatinine, CrCl, blood urea nitrogen (BUN), and eGFR, were identified in several studies as significant covariates for CL or Vd. Amann et al.[27] Specifically, in patients with severe hepatic impairment, progressive liver disease may lead to secondary renal dysfunction, possibly explaining the observed correlation between the eGFR and CL.[35] Pharmacokinetic analysis by Van Wart et al[17] showed that the AUC_{0-12} in patients with moderate renal impairment was approximately 19% greater than that in those with normal function, although this difference was not considered clinically significant for dose adjustment. Su et al[31] further confirmed via probability of target attainment (PTA) analysis that adjusting the tigecycline dose based on CrCl was not necessary. The impact of continuous renal replacement therapy (CRRT) on tigecycline metabolism is a clinically significant issue. The research results of Broeker et al[23] and Song et al[32]

consistently demonstrate that CRRT contributes minimally to tigecycline CL, as its metabolism remains predominantly dependent on the liver. Finally, combined with the results of the two prospective observational studies,[36,37] there is a consensus that tigecycline dose adjustment is not needed for CRRT patients.

Existing evidence suggests that body weight (body surface area (BSA) or body mass index (BMI)) is an important covariate affecting tigecycline CL and Vd. Weight gain can increase CrCl, as indicated by its inclusion in CrCl formulas. Moreover, weight may influence nonrenal elimination pathways by increasing liver volume, altering biliary transport, or enhancing irreversible tissue binding or changing the release rates of tigecycline. Rubino et al[19] reported a correlation between BSA and tigecycline CL, and Xie et al[21] suggested that BMI may also affect drug metabolism, although data in obese populations are lacking. This gap was addressed by Pai et al,[20] who demonstrated similar pharmacokinetic profiles in obese and normal-weight healthy subjects and concluded that the recommended dosing regimen (100 mg loading dose, followed by 50 mg q12h maintenance) was equally applicable in obese individuals. Therefore, although body weight has been incorporated as a covariate in PopPK models, a uniform dosing regimen remains in clinical practice. However, special attention should be given to populations such as obese individuals or those with markedly increased renal CL (CrCl > 130 mL/min), as they may be at risk of subtherapeutic exposure. This conclusion aligns with existing clinical guidelines, underscoring the need for individualized monitoring in specific patient groups.[38] To further confirm the applicability of the standard dose in a wider range of obese populations (especially those with different degrees of obesity and comorbidities), larger sample size studies are still needed for verification in the future.

In addition to the major covariates discussed above, some studies have identified other influencing factors. Zhou et al[25] and Luo et al[30] observed associations between age and both CL and Vd, potentially reflecting age-related physiological changes in drug distribution or organ function. Van Wart et al[17] suggested that sex may influence the CL, possibly because the greater bone mass in males influences the slow redistribution of the drug into the systemic circulation. Nevertheless, this finding was not confirmed by subsequent studies. Muralidharan et al[39] explored the effects of age and sex on the pharmacokinetics of tigecycline in healthy subjects receiving a single dose of tigecycline, and the results were negative. Bastida et al[28] reported that V1 in patients with hypoproteinaemia was twice as high as that in those with normal protein levels. However, pharmacokinetic simulations have indicated that adjusting the loading dose on the basis of the serum protein concentration provides limited clinical benefit. While these findings offer valuable insights into tigecycline pharmacokinetics, their generalizability requires further validation.

The application of PopPK models represents a paradigm shift from empirical dosing to data-driven precision medicine. On the basis of these models, researchers have employed Monte Carlo simulations and dose stratification analyses to estimate target attainment probabilities under different dosing regimens, guiding individualized dosing strategies. The applicable conditions of high-dose regimens have drawn significant attention, and in the studies included in this review, researchers have shared their insights. For example, Song et al[32] recommended a regimen of 100 mg q12h for treating CAP or cSSSI caused by *Acinetobacter baumannii* or *Klebsiella pneumoniae*. Su et al[31] suggested that 100 mg q12h regimens were appropriate for treating CAP, cSSSI, and infections caused by less susceptible pathogens. Xie et al[21] also advocated for higher doses (eg, 200 mg q12h) in cases such as skin infections or *A. baumannii* infections, especially in obese patients. Yang et al[26] exhibited a 100 mg q12h regimen for treating *A. baumannii* infections. Pai et al[20] proposed the use of higher doses or alternative therapies for infections caused by *A. baumannii, Enterobacter cloacae*, or *K. pneumoniae*. Dimopoulos et al[29] supported the use of 100 mg q12h for VAP, and Luo et al[30] found that high-dose regimens were more effective for HAP and cIAI, although not for cSSSI. Based on the existing research evidence, we recommend that for infections caused by low-sensitivity bacteria (such as *A. baumannii* and *K. pneumoniae*), cSSI, and VAP, a higher maintenance dose (100mg, q12h) should be routinely recommended, and a combination therapy strategy can be considered. For cIAI, the standard dose (50mg, q12h) is usually sufficient to be effective. When making individualized dose adjustments, particular attention should be paid to the patient's liver function and the degree of drug resistance of pathogenic bacteria, while renal function usually does not need to be considered. The clinical significance of other covariates requires more research for verification.

The advantage of this review over previous ones[40] lies first in systematically summarizing the newly proposed covariates in recent studies, providing a clear and comprehensive reference basis for subsequent research. Meanwhile, we also reviewed the simulations and drug administration protocol optimizations proposed in the included studies,

attempting to provide direct and referenceable information for clinical practice. In addition, by adopting an integrated checklist, this review conducted a systematic quality assessment of the included studies, pointing out the completion status of each study item by item to help researchers quickly grasp the completeness and quality level of each study.

In terms of limitations. Firstly, in this review, we only included English literature and excluded studies in other languages, which might lead to selection bias. Secondly, due to the inability to obtain the original data, we are unable to verify the predictive performance of the included model, which limits our ability to evaluate the relative superiority or inferiority of the model. Finally, the high heterogeneity of the model in terms of structure setting, software selection and covariate inclusion means that we can only conduct qualitative synthesis and are unable to provide aggregated quantitative estimates.

Conclusion

In summary, a review of the 16 included studies indicated that recent research has focused predominantly on critically ill patient populations. Although a wide range of covariates influencing tigecycline pharmacokinetics have been reported, our systematic analysis suggests that the most significant factors can be broadly categorized into three groups: liver function indicators, renal function markers, and body weight–related parameters. With respect to dose optimization, most studies have conducted simulation analyses based on the site of infection or the causative pathogens and have consistently recommended high-dose regimens for low-sensitivity bacterial, cSSI and VAP infections. Individualized dose adjustment should be based on liver function and the degree of drug resistance of the pathogen, without considering renal function. However, these recommendations require validation through studies with larger sample sizes or randomized controlled trials. Finally, none of the existing models underwent external validation, raising concerns about their robustness and generalizability in clinical settings.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no potential conflicts of interest.

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