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Population pharmacokinetics of piperacillin in non-critically Ill hospitalized patients: A study from Pakistan

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Abstract: **Background**: Piperacillin/tazobactam is commonly used for the treatment of severe infections in hospitalized patients. While its pharmacokinetics have been extensively studied in critically ill patients, data on non-critically ill hospitalized patients remain limited. **Objectives**: This study aimed to characterize the population pharmacokinetics of piperacillin in non-critically ill Pakistani patients and to identify significant covariates influencing drug disposition. **Methods**: This prospective, single-center study was conducted at Ayub Teaching Hospital. Serial plasma samples were collected at multiple post-dose time points to quantify piperacillin concentrations using high-performance liquid chromatography. Demographic, clinical and laboratory data were systematically recorded. Population pharmacokinetic modeling was performed using Monolix 2024R1 and model selection was guided by standard diagnostic criteria, the Akaike Information Criterion and objective function values. **Results**: Twenty-five non-critically ill patients (median age: 54 years) were enrolled. The pharmacokinetic profile of piperacillin was adequately described by a two-compartment model with first-order elimination. The estimated glomerular filtration rate by the CKD-EPI 2021 equation, significantly influenced clearance, which was estimated at 15.58 L/h. The central volume of distribution was 27.06 L, the peripheral volume of distribution was 4.48 L and the intercompartmental clearance rate was 4.16 L/h. **Conclusion**: Piperacillin pharmacokinetics in non-critically ill patients are primarily influenced by renal function, with the CKD-EPI 2021 equation providing the most reliable estimates of clearance. Despite the limited sample size, these findings provide a foundation for future individualized and model-informed precision dosing approaches, particularly in Pakistan.

Keywords: β-lactams; Pharmacokinetics; Population pharmacokinetics; Piperacillin

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INTRODUCTION

Bacterial infections remain a major cause of hospital-associated morbidity and mortality (Abban *et al.,* 2023). In particularly, infections caused by Gram-negative pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are among the most frequently implicated microorganisms (Abban *et al.,* 2023; Mahmoud *et al.,* 2025). The global emergence of multidrug-resistant (MDR) organisms has complicated treatment strategies and emphasized the need to optimize broad-spectrum antibiotics therapy based on pharmacodynamics (PD) and pharmacokinetics (PK) principles (Marino *et al.,* 2025). Piperacillin/tazobactam (Pip/Taz) exhibits time-dependent bactericidal activity and is commonly used in the management of severe nosocomial infections. Its PD efficacy is primarily determined by the duration for which the unbound concentration of piperacillin remains above the minimum inhibitory concentration ($fT_{>MIC}$). Current PD targets generally recommend achieving at least 50% $fT_{>MIC}$ (Alikhani *et al.,* 2025; Pokludova, 2025; Viscardi *et al.,* 2024).

Despite the widespread use of Pip/Taz in general clinical practice, PK studies have primarily focused on critically ill patients (Kong *et al.,* 2025; Veillette *et al.,* 2021) or specific populations, such as neonates (Kong *et al.,* 2025; Pokorná *et al.,* 2025), the elderly (Kong *et al.,* 2025) and obese individuals (Veillette *et al.,* 2021). Although these studies (Kong *et al.,* 2025; Pokorna *et al.,* 2025; Veillette *et al.,* 2021) have provided useful insights, their findings are not readily generalizable to the broader population of non-critically ill hospitalized patients. These patients, although physiologically more stable than intensive care unit (ICU) patients (Morales *et al.,* 2023), may nevertheless exhibit substantial PK variability due to factors such as renal function, age, comorbidities, body composition and overall clinical status (Maluangnon *et al.,* 2023). Therefore, dosing strategies developed for the critically ill population may lead to either subtherapeutic exposure or toxicity in non-ICU patients, highlighting the urgent need for targeted PK studies in this population.

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Existing population pharmacokinetic (Pop-PK) models (Cojutti *et al.,* 2021; Hites *et al.,* 2014; Klastrup *et al.,* 2020; Bohorquez *et al.,* 2021; Obrink *et al.,* 2015) have several methodological limitations. These include study designs based on sparse sampling, with data often restricted to trough concentrations derived from therapeutic drug monitoring (TDM) in clinical practice, thereby limiting the ability to fully characterize piperacillin PK. Moreover, small sample sizes and relatively homogeneous patient populations reduce the external validity of these findings (Hites *et al.,* 2014; Bohorquez *et al.,* 2021). Additionally, covariate identification has often been incomplete, particularly with respect to renal function, which is the primary determinant of piperacillin clearance. Most studies have relied solely on creatinine clearance (CR_{CL}) estimated using the Cockcroft-Gault equation, without comparing the performance of alternative renal markers, such as estimated glomerular filtration rate (eGFR) calculated using CKD-EPI or MDRD equations, or the Jelliffe equation for patients with unstable renal function. This narrow assessment limits the identification of the most predictive renal function metric for piperacillin clearance (El-Haffaf *et al.,* 2021; Kong *et al.,* 2025).

Another gap in the available literature is the scarcity of PK data from ethnically and geographically diverse populations. Despite significant global progress in the field of Pop-PK, to date, no studies have been published on non-critically ill patients in the Pakistani healthcare setting. Such data are particularly warranted, as genetic variability, environmental factors, patterns of comorbidities and the healthcare environment have all been shown to significantly affect drug metabolism and clearance (Banerjee *et al.,* 2019; Ngcobo, 2025; Theuretzbacher, 2024).

To address these limitations, the present study aimed to evaluate the Pop-PK of piperacillin and to identify factors associated with variability in drug disposition among non-critically ill hospitalized patients in Pakistan. Although this study does not provide specific dosing recommendations, the developed model establishes a foundation for future precision dosing strategies. By identifying factors contributing to interindividual variability in piperacillin concentrations in this understudied population, the findings may inform the optimization of Pip/Taz therapy and support antimicrobial stewardship in South Asian healthcare settings.

MATERIALS AND METHODS

Study design and population

This prospective observational study was conducted at Ayub Teaching Hospital, Khyber Pakhtunkhwa, Pakistan, between March and August 2024. Written informed consent was obtained from all patients prior to enrollment and ethical approval was granted by the Institutional Review Board (IRB) of Ayub Teaching Hospital (RC-EA-2024/041).

Inclusion and exclusion criteria

Hospitalized Pakistani adults (≥18 years) admitted to medical wards as non-critical cases and receiving intravenous Pip/Taz treatment were enrolled within 24 hours of the first dose administration. Exclusion criteria included pregnant women and patients receiving either extracorporeal membrane oxygenation or renal replacement therapy.

Demographic parameters, including age, sex, height and weight, were recorded. Laboratory parameters, including serum albumin, serum bilirubin, serum creatinine, urea and platelet count, were also recorded.

Sample size calculations

The sample size and sampling design were determined a priori using PFIM 4.0 (Bazzoli *et al.,* 2010), a software tool designed to optimize Pop-PK study designs based on the Fisher information matrix. As all available PK models developed in non-critically ill patients were based on one-compartment structures, these models were considered insufficient to inform the design of a study intended to characterize two-compartment drug disposition. Therefore, fixed- and random-effects parameter estimates from a two-compartment model reported in critically ill patients (Udy *et al.,* 2015) were used as reference values for the simulation. The results indicated that enrolling 25 subjects, with 5–8 blood samples per subject collected at time points covering both the distribution and elimination phases, would provide sufficient information for precise two-compartment parameter estimation.

Study drug and blood sample collection

Pip/Taz 4.5 grams every 8 hours was prescribed to the patients in accordance with the dosing recommendations provided in the product information (Pfizer 2024). The treatment regimen and intensity of infection were determined by the treating physicians. Each dose was administered as an intermittent infusion over 30 minutes and diluted in 100 mL of normal saline (Pfizer 2024). Venous blood samples (volume 3 mL per sample) were collected *via* a separate venous catheter. Two sampling groups were defined: extensive sampling (n=10), in which eight samples were collected and a non-extensive group (n=15), in which five samples were collected. Blood sampling was initiated at least 24 hours after the first dose of Pip/Taz. For patients undergoing intensive PK sampling, eight blood samples were collected pre-dose (time 0) and at 0.5, 1, 2, 4, 5, 6 and 7–8 hours post administration. For patients in the non-intensive sampling group, 5 blood samples were collected within the following time windows: pre-dose (time 0), 0.5 hours, 0.5–2 hours, 2.1–4 hours and 4.1–8 hours post-dose. All samples were

collected in heparinized tubes without gel. The exact start and end times of the infusion, as well as the precise sampling times, were recorded. Immediately after collection, blood samples were centrifuged at 4000 rpm for 5 minutes and the plasma was stored at −22°C until analysis (Hatami and Saadatmand, 2022).

Bioanalysis

Piperacillin was purchased from Biosynth Ltd., UK, while the ZOYSN sample was provided by Global Pharma, Pakistan. Methanol and water were purchased from Dae-Jung Chemicals and Metals, Korea. Sodium dihydrogen phosphate, tetrabutylammonium hydroxide solution (40% w/w) and orthophosphoric acid were purchased from Merck, (Darmstadt, Germany). Plasma piperacillin concentrations were quantified using a previously validated protein-precipitation HPLC-UV method, as described in an earlier study (Ahmad *et al.,* 2025), and the same analytical conditions were employed in the present study. Briefly, plasma samples were mixed with acetonitrile (1;3, v/v)., vortexed by using (Z258415 Vortex-Genie® 2 mixer) for 3 minutes and centrifuged at 4000 rpm by using (800-1 Electric Centrifuge Machine, China) for 10 minutes. The supernatant was subsequently re-centrifuged at 12,000 rpm for 10 minutes at 10°C using Dlab Model D3024 Centrifuge (Beijing, China). The resulting supernatant was reconstituted with 300 µL of mobile phase, filtered through a 0.25 µm nylon membrane and transferred into HPLC vials for analysis (Ahmad *et al.,* 2025).

Chromatographic analysis was performed using a Waters Alliance 2695 system (Zellik, Belgium) equipped with a Waters 2996 Photodiode Array Detector and controlled by Empower® software (Waters). Separation was achieved on an XSelect HSS C18 column (250 × 4.6 mm, 5 µm) fitted with a guard column and maintained at 25°C. A 20 µL injection volume was used, with the autosampler maintained at 5 ± 1°C. The run time was set at 27 minutes with a flow rate of 1.0 mL/min and ultraviolet (UV) detection was carried out at 218 nm (Ahmad *et al.,* 2025).

The isocratic mobile phase (pH 5.5) was comprised methanol, water, buffer and Solution A in the ratio of 510:432:50:8. The buffer was prepared by dissolving 27.6 g/L of monobasic sodium phosphate in water and Solution A was prepared by diluting 80 mL of 40% tetrabutylammonium hydroxide to a final volume of 100 mL. Each plasma sample was analyzed in triplicate to ensure accuracy (Ahmad *et al.,* 2025).

Population PK analysis

Pop-PK analysis was performed using the Stochastic Approximation Expectation Maximization (SAEM) algorithm. The analysis was conducted using Monolix 2024R1 (Lixoft, Orsay, France; http://www.lixoft.com) (Simulations Plus, 2026). The input dataset was structured according to Monolix requirements and included subject identifiers (ID), time after dose (Time), administered dose (AMT), dosing history (including dose timing, frequency and route of administration), observed plasma concentration (DV) and infusion duration along with relevant covariates (Traynard *et al.,* 2020). Initial estimates for the structural pharmacokinetic parameters, inter-individual variability and residual error were derived from previously published piperacillin population pharmacokinetic models (Udy *et al.,* 2015) and refined through the iterative SAEM estimation process. One- and two-compartment models with first-order elimination kinetics were evaluated as structural models. Interindividual variability (IIV) in model parameters was assumed to follow a log-normal distribution and this variability was described using exponential error models (Traynard *et al.,* 2020). Residual variability was assessed using proportional, additive Combined[1] (additive + proportional) and Combined[2] (quadratic combination of additive + proportional) error models. After the development of the base model, the effects of covariates were evaluated using a stepwise approach consisting of forward inclusion followed by backward elimination approach (Traynard *et al.,* 2020).

A total of twenty-one covariates were examined, of which eleven were related to renal function. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2009 and 2021 (CKD-EPI 2009 and CKD-EPI 2021), Modification of Diet in Renal Disease (MDRD), Jelliffe (Jelliffe, 2002) and CKD-EPI-Pakistan (Ahmed *et al.,* 2017) equations. In addition, creatinine clearance (CR_{CL}) was estimated using the Cockcroft-Gault (CG) equation. The remaining covariates included demographic and anthropometric factors, namely age, sex, height, adjusted body weight, ideal body weight, lean body weight, total body weight, body surface area (BSA) and body mass index (BMI).

Continuous covariates were normalized to the median of the dataset prior to inclusion in the model. During forward selection, covariates were retained if the decrease in the objective function value (OFV) was at least 3.84 units ($p < 0.05$, 1 df). During backward elimination, covariates were retained in the model if the increase in the OFV was at least 6.63 units ($p<0.01$). According to the guidelines of the U.S. Food and Drug Administration (FDA), eGFR is normally referenced to a BSA of 1.73 m^2 and is commonly reported in units of mL/min/1.73 m^2. Therefore, for dosage recommendations in adult patients with renal impairment, the use of eGFR expressed in mL/min is recommended rather than eGFR normalized to a BSA of 1.73 m^2 (U.S. FDA, 2020). To obtained eGFR in mL/min, eGFR referenced to a BSA of 1.73 m^2 should be multiplied by the patient's BSA value calculated using the BSA Mosteller formula ($BSA\ (m^2) = \sqrt{([Height\ (cm) \times Weight\ (kg)] /$

3600)) (Zheng, 2022) and then divided by 1.73 m^2 (U.S. FDA, 2020).

Model adequacy was assessed using standard goodness-of-fit diagnostics, including plots of observed concentrations versus population predictions (PRED) and individual predictions (IPRED), as well as individual weighted residuals (IWRES) and normalized prediction distribution errors (NPDE) versus time. Prediction-corrected visual predictive checks (pcVPC) were performed to evaluate the predictive performance of the final model. Parameter precision and model robustness were further assessed using a non-parametric bootstrap procedure with 1,000 replicates. Median parameter estimates and corresponding 95% confidence intervals obtained from the bootstrap analysis was compared with estimates from the final model. Descriptive statistics, including frequency, interquartile range and median were calculated using Microsoft Excel.

RESULTS

Patient characteristics

This study was conducted on 25 patients admitted to the medical wards of Ayub Teaching Hospital. A dose of 4.5 g of Pip/Taz was administered every 8 hours as a 30-minute intermittent infusion. The median age of the patients was 54 years (IQR: 46–63 years), of whom 52% were female. Anthropometric measurements indicated generally normal body composition, with a median BMI of 24.7 kg/m² and a median BSA of 1.7 m². The median mean arterial pressure (MAP) was 83.3 mmHg (IQR: 71.6–94 mmHg), indicating adequate hemodynamic status in the study population. The median platelet count was 170,000/µL (IQR: 138,000-248,000/µL), with values largely within the normal range. The median total bilirubin level was 0.5 mg/dL (IQR: 0.4-0.85 mg/dL) and the median albumin level was 3.1 g/dL (IQR: 2.7-3.4 g/dL). Renal function was generally preserved across the study population, with median eGFR values within the normal to mildly reduced range. However, interindividual variability was evident across equations, with the CKD-EPI-Pak equation yielding lower estimates than international formulas. Baseline characteristics are summarized in Table 1.

Population pharmacokinetic modeling

A total of 155 piperacillin plasma concentrations (range: 1.33–259 mg/L) were included in the analysis, with a median of six samples per patient. No concentrations were below the lower limit of quantification (LOQ). Piperacillin concentration− time profiles were best described by the two-compartment model with first-order elimination from the central compartment. A substantially better fit to the data was achieved with the two− compartment model compared to the one-compartment model, with an Akaike Information Criterion (AIC) difference of−84. Therefore, the two-compartment model was selected as the final structural model. The final model was parameterized in terms of clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp) and intercompartmental clearance (Q). Residual variability was best described by a combined additive and proportional error model.

Interindividual variability (IIV) was initially estimated for all structural parameters. However, the IIV estimates for Q and Vp were associated with poor precision (relative standard error [RSE] > 70%) and were found to contribute to model instability; therefore, these random effects were fixed to zero in the final model. During covariate analysis, all six formulas used to estimate renal function significantly improved model performance. Equations estimating absolute GFR values in mL/min provided greater predictive power than those involving BSA–normalized values in mL/min/1.73 m². Among the renal function metrics assessed, GFR estimated using the CKD-EPI 2021 equation was selected for subsequent model development. The reduction in objective function value (OFV) was comparable to that obtained with alternative metrics, although it was not greater. Nevertheless, this equation was selected based on clinical relevance, including its widespread adoption, routine reporting without the need for additional calculation and its established role in the staging of chronic kidney disease.

After incorporating GFR estimated using the $GFR_{CKD\text{-}EPI\ 2021}$ equation into the model, no additional covariates were found to affect the pharmacokinetics of piperacillin. During the backward deletion process, the removal of this covariate resulted in an increased in OFV of more than 6.63 units. Therefore, this covariate was retained in the final model. In the final model, CL was described as a function of GFR estimated using the CKD-EPI 2021 equation, as follows:

$$CL\ (L/h) = CLpop \times \left(\frac{GFR_{CKD-EPI}}{80}\right)^{0.19} \times e^{\eta CL}$$

CL_{pop} (L/h) = 15.58
Vc (L) = 27.06
Vp (L) = 4.48
Q (L/h) = 4.16

In this model, CL represents individual clearance and CL_{pop} is defined as the typical population clearance. $GFR_{CKD\text{-}EPI\ 2021}$ (mL/min) is defined as the absolute glomerular filtration rate calculated using the CKD-EPI 2021 equation. When only normalized eGFR values (mL/min/1.73 m²) were available, they were converted to absolute GFR by multiplying each patient's eGFR by their body surface area, i.e., eGFR × (BSA / 1.73 m²), to obtain mL/min. Vc and Vp are defined as the central and peripheral volumes of distribution, respectively and Q is defined as the intercompartment clearance. The term ηCL is used to represents interindividual variability and is assumed to have a mean of zero and variance ω^2_{CL} = 0.176 (CV% = 43.9%).

Table 1: Demographic and clinical data of the study population.

Characteristics	Patients (n=25)
Male, n (%)	12 (48%)
Age (years), median (Q1-Q3)	54 (46 - 63)
BW (kg), median (Q1-Q3)	65 (70 - 56)
IBW (kg), median (Q1-Q3)	57 (57 - 61.5)
BMI (kg/m^2), median (Q1-Q3)	24.7 (20.3 - 26.4)
BSA (m^2), median (Q1-Q3)	1.7 (1.5 - 1.8)
MAP (mmHg), median (Q1-Q3)	83.3 (71.6 - 94)
Platelets (x10^3/µL), median (Q1-Q3)	170000 (138000 – 248000)
Bilirubin (mg/dL), median (Q1-Q3)	0.5 (0.4 - 0.85)
Albumin (mg/dL), median (Q1-Q3)	3.1 (2.7 - 3.4)
$CR_{CL\text{-}CG}$ (mL/min), median (Q1-Q3)	73.7 (51.6 - 124)
$GFR_{MDRD\text{-}4\ variables}$ (mL/min), median (Q1-Q3)	85 (50.6 - 140.6)
$GFR_{MDRD\text{-}4\ variables}$ (mL/min/1.73 m^2), median (Q1-Q3)	79.02 (47.9 - 130)
$GFR_{CKD\text{-}EPI\text{-}2009}$ (mL/min), median (Q1-Q3)	93.7 (54.9 - 115)
$GFR_{CKD\text{-}EPI\text{-}2009}$ (mL/min/1.73 m^2), median (Q1-Q3)	84.8 (53.1 - 108.1)
$GFR_{CKD\text{-}EPI\text{-}2021}$ (mL/min), median (Q1-Q3)	93.2 (55.3 - 114.1)
$GFR_{CKD\text{-}EPI\text{-}2021}$ (mL/min/1.73 m^2), median (Q1-Q3)	87.8 (53.2 - 108.2)
$GFR_{CKD\text{-}EPI\text{-}Pak}$ (mL/min), median (Q1-Q3)	83.5 (48.1 - 103.5)
$GFR_{CKD\text{-}EPI\text{-}Pak}$ (mL/min/1.73 m^2), median (Q1-Q3)	78.8 (46.5 - 96.6)
$CR_{CL\ Jelliffe}$ (mL/min), median (Q1-Q3)	77.2 (52.1 - 132.7)
$CR_{CL\ Jelliffe}$ (mL/min/1.73 m^2), median (Q1-Q3)	82.2 (55.2 - 134.2)

Data were reported on the day of blood collecting for pharmacokinetic analysis; BW, body weight; IBW, ideal body weight; BMI, body mass index; BSA, body surface area; MAP, mean arterial pressure; CR_{CL}, Creatinine clearance; CG, Cockcroft-Gault equation; MDRD-4, Modification of Diet in Renal Disease equation 4-variable version; included age, sex, ethnicity and serum creatinine. The CKD-EPI-2009 and CKD-EPI-2021 (Chronic Kidney Disease Epidemiology Collaboration) equations from the years 2009 and 2021 were then multiplied by each person's body surface area divided by 1.73 m²; CKD-EPI-PAK refers to the eGFR Prediction Equations in the Pakistani Population.

Table 2: Parameters estimates of basic, final and bootstrap results.

	Base model	Final model	Bootstrap
Parameters	Estimate (%RSE)	Estimate (%RSE)	Median (95% CI) of bootstrap estimate
OFV	1099.96	1092.67	1080.97
Fixed effect parameter			
CL (L/h)	15.35 (10.3)	15.58 (8.67)	15.53 (13.21-18.75)
Vc (L)	26.81 (10.9)	27.06 (10.9)	26.39 (16.31-33.43)
Vp (L)	4.66 (16.6)	4.48 (16.8)	5.21 (3.42-12.53)
Q (L/h)	4.48 (46.1)	4.16 (40.7)	4.21 (1.98-71.96)
$\beta_{GFR\text{-}EPI}$	-	0.19 (35.2)	0.19(0.055-0.29)
Inter-individual variability (IIV)			
%IIV on CL	53.43 (13.8)	43.92 (14.3)	41 (32.83-52.12)
%IIV on Vc	55.71 (14.6)	55.66 (15.0)	54 (42.80-94.68)
Corr Vc and CL	0.97	0.97	0.97 (0.96-0.98)
Residual unexplained variability			
Proportional (%)	3.82 (10.2)	3.82 (9.89)	3.81 (2.1-5.08)
Additive (mg/L)	0.002 (26.0)	0.06 (24.3)	0.064 (0.00014-0.12)

CL, Clearance; Vc, Central volume of distribution; Vp, Peripheral volume of distribution; Q, intercompartmental clearance; $\beta_{GFR\text{-}EPI}$, reflecting the influence of absolute value of glomerular filtration rate (GFR) calculated by CKD-EPI 2021 equation on CL (mL/min); %RSE, Percentage of relative standard error; OFV, minimum value of objective function; CI, confidence interval; Corr, Correlation.

The Pop-PK parameters estimated in the final model are summarized in table 2. Adequate precision was demonstrated for most parameter estimates, except for Q, for which relatively high uncertainty was observed (RSE: 40.7%). However, this parameter was shown to be stable in bootstrap analysis and did not compromise overall model performance, as indicated by satisfactory goodness-of-fit plots and predictive checks. Good agreement

between observed and predicted concentrations at both the population and individual levels is demonstrated in fig. 1, where data points are distributed closely around the line of unity. Satisfactory diagnostic plots are represented in fig. 2, in which residuals are randomly distributed around zero and most data points are located between -2 and +2, indicating the absence of systematic bias. The pcVPC of the final model is shown in fig. 3. The 5^{th}, 50^{th} and 95^{th} percentiles of the observed concentrations were contained within the corresponding 95% confidence intervals of the model predictions. These results indicate that the concentration-time data were adequately described by the model. Bootstrap analysis further demonstrated that the final model parameters were consistent with the bootstrapping medians and fell within the corresponding 95% confidence intervals.

DISCUSSION

This study provides important insights into the Pop-PK of piperacillin in non-critically ill hospitalized Pakistani adults, addressing a significant gap in the literature. Among patients treated with intermittent piperacillin, a two-compartment model with first-order elimination best described drug disposition and demonstrated excellent predictive performance. Renal function was identified as the primary predictor of clearance. Absolute eGFR expressed in mL/min, performed better than BSA-normalized values and GFR estimated using the CKD-EPI 2021 equation was retained based on model fit, clinical relevance and routine availability in clinical practice. These findings contribute to the limited data available for this population and may facilitate the individualization of antibiotic therapy, thereby reducing the risks of suboptimal dosing and toxicity.

The structural pharmacokinetic model selection process revealed that a two-compartment model with first-order elimination provided the best fit for the observed data. The concentration-time profile of piperacillin was adequately described by this model, which is consistent with findings reported in previous PK studies conducted in both critically ill and non-critically ill populations (Dhaese *et al.,* 2018; Hites *et al.,* 2014; Obrink-Hansen *et al.,* 2015; Roberts *et al.,* 2014). Although an improvement in model fit was achieved, high IIV estimates for Vp and Q were observed, reflecting instability and limited reliability of these parameters. High %RSEs values are typically associated with limitations in the dataset, particularly small sample size in terms of both the number of subjects and concentration measurements. In addition, the rapid elimination of piperacillin results in a shortened distribution phase. When sparse or missed sampling occurs during this phase, accurate estimation of parameters such as Q or Vp may be compromised. In contrast, if high IIV were observed in conjunction with low %RSE values, this would indicate true variability, potentially arising from differences in body composition, fluid status, or protein binding. Such variability is important for individualized dosing (Fratoni *et al.,* 2021).

Most patients in this study had normal renal function, which had a significant effect on piperacillin clearance. This finding is consistent with previous studies in which renal function was identified as the primary determinant of piperacillin clearance (Dhaese *et al.,* 2018; Obrink-Hansen *et al.,* 2015; Roberts *et al.,* 2014). The results also indicated improved model performance when multiple renal function equations were evaluated, supporting the usefulness of the 2021 CKD-EPI equation in dose adjustment strategies (Fratoni *et al.,* 2021). The CKD-EPI-Pak equation, which is more specific to the population in Pakistan, did not demonstrate superior performance in estimating piperacillin clearance. This finding suggested that globally derived models may be useful as predictive tools in clinical settings. However, its consistently lower GFR estimates need further evaluation in more representative patient cohorts. The present findings supported previous evidence that piperacillin clearance in non-critically ill patients is strongly correlated with CR_{CL} derived from multiple models, indicating that renal function is the major determinant of piperacillin disposition. However, variability in renal function estimation suggests that multiple models should be explored to support careful patient stratification across different clinical settings and health statuses, particularly when selecting renal function estimation models are selected (Mirkov *et al.,* 2024).

Compared with critically ill patients, a lower volume of distribution (Vd) and higher CL were observed in the non-critically ill patients enrolled in this study. Although augmented renal clearance (ARC) is frequently observed in critically ill patients and is often associated with sub-therapeutic antibiotic concentrations, ARC was not observed in the present patient group (Hefny *et al.,* 2022). When the estimated piperacillin CL in the present population (≈ 15 L/h with median CR_{CL} of 80 mL/min) was compared with the values reported in previous models, variability in CL appeared to be driven by renal function and other patient-specific covariates. Mean CL values have been reported to vary widely in previous studies, ranging from approximately 5 L/h in early sepsis patients with reduced GFR to more than 15 L/h in septic patients with ARC in the ICU (Alobaid *et al.,* 2017; Andersen *et al.,* 2018).

However, when published models were scaled to the median CR_{CL} of 80 mL/min observed in this study, the differences in predicted CL become negligible. For example, when the model developed previously was applied ($CL = 4.556 + 1.353 \times CR_{CL}$), an estimated CL of approximately 11 L/h was obtained (Bohorquez *et al.,* 2021).

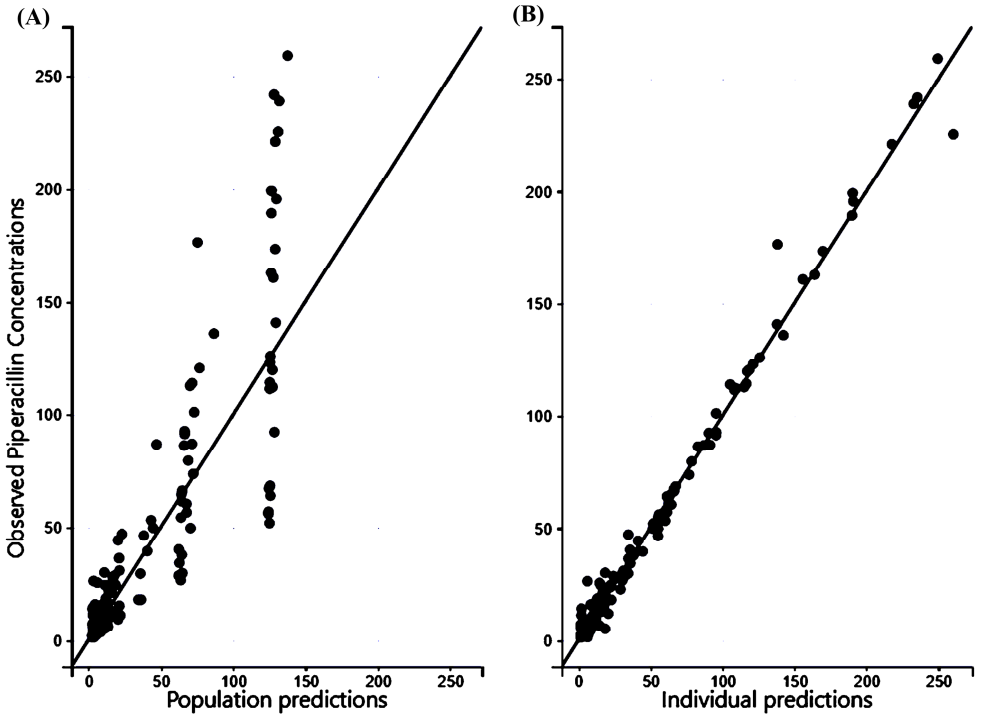

Fig. 1: Goodness-of-fit plots for the final population pharmacokinetic model of piperacillin. (A) Observed versus population-predicted concentrations; (B) Observed versus individual-predicted concentrations.

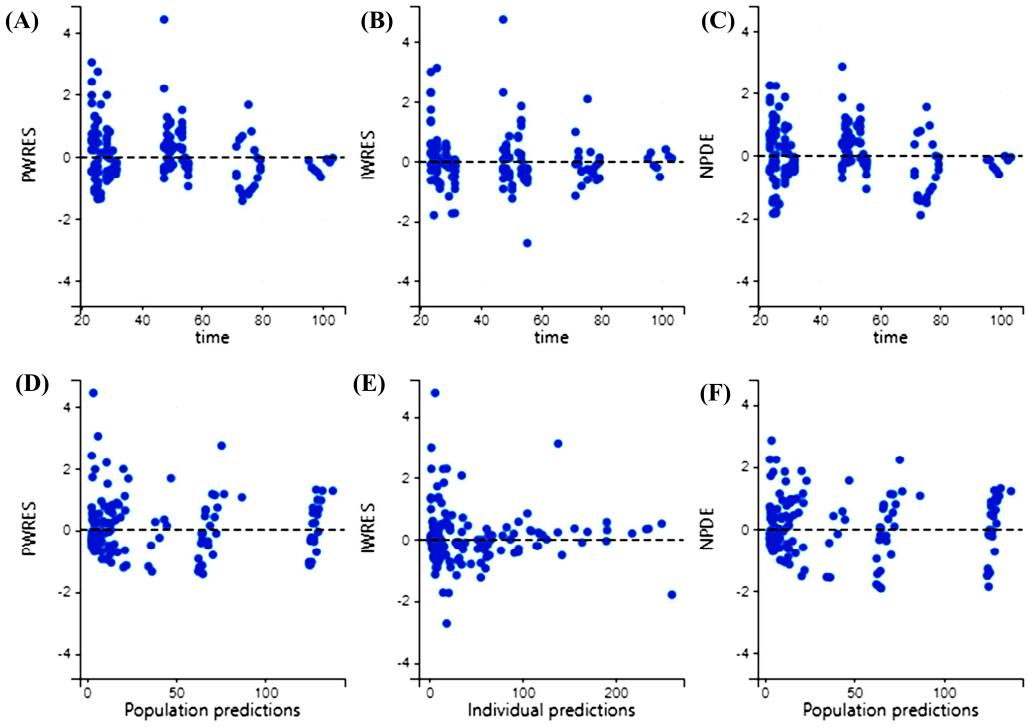

Fig. 2: Residual diagnostic plots for model evaluation. Top panels (A−C) show population weighted residuals (PWRES), individual weighted residuals (IWRES) and normalized prediction distribution errors (NPDE) versus time; bottom panels; (D–F) show these residuals versus population and individual predictions.

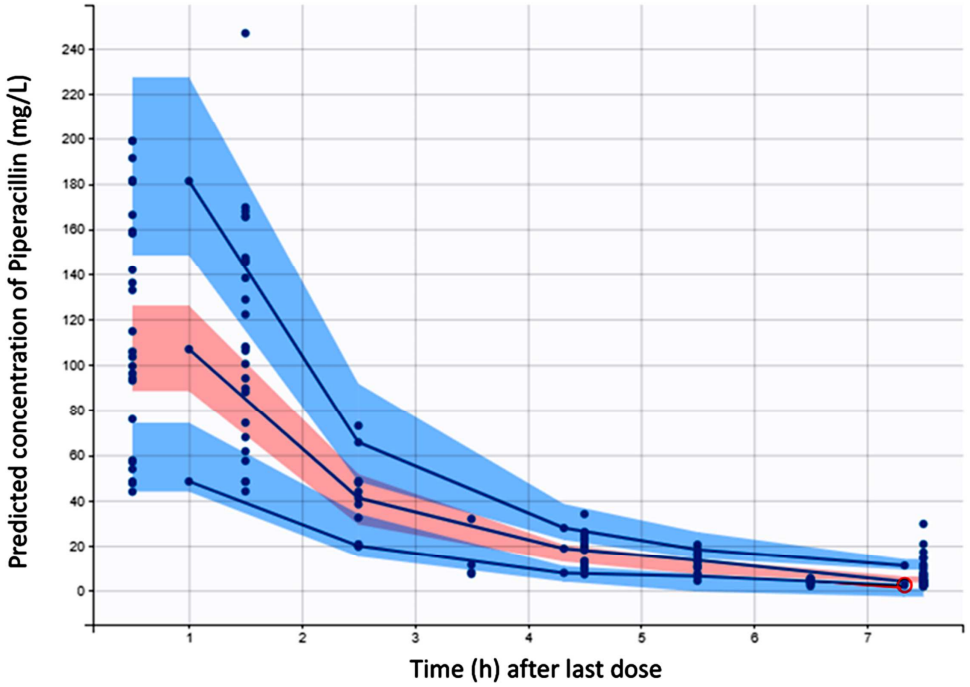

Fig. 3: Prediction-corrected visual predictive check (pcVPC) for the final piperacillin population pharmacokinetic model. Blue dots show individual observed drug concentrations. The solid blue line represents the 5th, 50th and 95th percentiles of the observed data. Shaded areas show 95% confidence intervals for the corresponding simulated percentiles.

Across previous studies, CL values in critically ill populations have generally been reported to range from approximately 5 to 9 L/h (Barreto *et al.,* 2025; Dhaese *et al.,* 2018; Tsai *et al.,* 2016; Sukarnjanaset *et al.,* 2019). In contrast, a substantially higher CL of 15.58 L/h was observed in the present study, which is consistent with more efficient renal elimination in non-critically ill patients. Variability in Vd has also been described, particularly in studies of critically ill patients, where factors such as age, fluid shifts and organ dysfunction contribute to an expanded Vd (Kong *et al.,* 2025; Dhaese *et al.,* 2018). Vd values had generally been reported to range between 9 and 26 L in previous studies; however, a Vd of 27.06 L was found in the present study, representing the upper end of this range and reflecting physiological differences between critically ill and non-critically ill populations. Overall, the comparisons indicate that the higher CL and relatively large Vd observed in this study are likely to reflect enhanced renal function and less severe illness compared with critically ill patients described in earlier studies.

When the findings are compared with previous piperacillin PK studies conducted in non-critically ill or obese patient populations, consistent trends are observed, although notable differences in magnitude remain. In general, lower CL values have been reported in earlier studies (Bohórquez *et al.,* 2021; Hites *et al.,* 2014; Cojutti *et al.,* 2021). These differences are likely explained by factors such as older age, variability associated with obesity, or reduced renal function. In contrast, a higher clearance (15.58 L/h) was observed in the present study population, which was consistent with younger age and preserved renal function, with GFR identified as a significant covariate. Regarding distribution, a wide range of Vd values has been reported in obese patients (Veillette *et al.,* 2021). In comparison, the central volume of distribution estimated in the present study (26.81 L) falls within previously reported ranges but is associated with less variability. Collectively, these comparisons reinforced that the PK of piperacillin are influenced by patient-specific factors, particularly renal function, age, BMI and body size, thereby contextualizing the higher clearance estimates observed in the present model.

One of the major strengths of this study is the application of multiple renal function estimation techniques to characterize piperacillin CL, thereby improving the precision and reliability of the results. Second, although previous PK studies of piperacillin have primarily been conducted in ICU populations and studies in non-ICU setting have often focused on specific groups such as elderly patients or those with renal dysfunction, the present study was conducted in non-critically ill patients. This population, which commonly receives piperacillin in general hospital wards, provides insights that better reflect typical clinical scenarios. Therefore, this study addresses a gap in the literature, which has often been biased toward

ICU populations and provides valuable information that is more representative of stable hospitalized patients in general healthcare settings.

Limitations

The relatively small sample size is acknowledged as a limitation of this study, as it may increase the risk of model overfitting and limit the generalizability of findings. To mitigate this, a parsimonious modeling approach was adopted, retaining only clinically and biologically plausible covariates. IIV for parameters with poor precision (Q and Vp) was fixed to zero to reduce model complexity. Model robustness was evaluated using goodness-of-fit diagnostics, bootstrap analysis and pcVPC, which indicated acceptable performance without substantial overfitting. Furthermore, the study was conducted in patients from a single hospital and patients with severe renal impairment or those requiring intensive care were excluded. Finally, clinical outcomes and the impact of pharmacokinetic variability on treatment efficacy were not evaluated in this study and should be investigated in future research.

CONCLUSION

This study provides a Pop-PK characterization of piperacillin in non-critically ill patients from Pakistan, addressing a notable gap in regional pharmacokinetic data. The pharmacokinetics of piperacillin were best described by a two-compartment model with first-order elimination. Renal function, particularly creatinine clearance, was identified as the primary determinant of piperacillin clearance, highlighting the importance of renal function-guided dosing. Despite these findings, the relatively small sample size represents a limitation of the study. Therefore, larger studies with more extensive sampling are required to further validate the model and support evidence-based dose optimization of piperacillin in non-critically ill patients' population.

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Authors' contributions

TA data collection, samples analysis and wrote the initial draft of the entire manuscript. SS and SP: Supervised the project, formal analysis, study conceptualization and funding support to conduct this study; AB: Contributed in initial analysis, review and formatting of manuscript; SAK: Contributed in HPLC analysis. All authors have read, approved and agreed to submit the final manuscript for publication.

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Data availability statement

Data are provided within the manuscript; however, if additional raw data are required, they can be made available upon request to the corresponding author.

Ethics approval and consent to participate

This study received ethical approval from the Institutional Review Board (IRB) of the Ayub teaching hospital, under approval reference number (RC-EA-2024/041). Informed consent was obtained from all patients prior to the commencement of the study. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interests

The authors declare no conflicts of interest.

Supplementary data

https://www.pjps.pk/uploads/2026/07/SUP1783151523.pdf

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