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# Population Pharmacokinetics and Dosing Regimen Analysis of Nirmatrelvir in Chinese Patients with COVID-19 Infection

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**Purpose:** Nirmatrelvir/ritonavir (N/R) is the first drug to receive emergency authorization for the treatment of COVID-19 infection. We aimed to develop a population pharmacokinetic (PopPK) model to evaluate the effects of potential covariates and explore dosing regimen.

**Patients and Methods:** Sparse data of serum concentrations of N/R were obtained from 129 patients with COVID-19 infection receiving oral 300/100 mg N/R twice daily for 5 days. Plasma samples were assayed using ultra-high-performance liquid chromatography–tandem mass spectrometry. The PopPK model was developed using a nonlinear mixed effects approach utilizing the NONMEM 7.4 software. Monte Carlo simulation was conducted to optimize the dosage regimen.

**Results:** A one-compartment model with first-order absorption and first-order elimination provided the best fit for the data. Allometric scaling of parameters on creatinine clearance (CrCl) and body weight were identified as covariates that significantly influenced exposure-efficacy after oral administration of nirmatrelvir. Monte Carlo simulation using the final model generated concentration-time profiles for virtual patients (1,000 per group) with varying renal functions and body weight. Furthermore, we developed a web-based dashboard to visualize the dynamic changes in nirmatrelvir concentration and provide individualized dosage regimens.

**Conclusion:** This study showed that dosing regimen optimization of nirmatrelvir should be based on CrCl and body weight. Moreover, a web-based dashboard has been developed to facilitate individualized pharmacotherapy.

**Keywords:** population pharmacokinetics, nirmatrelvir, COVID-19, simulations, dosing regimen

## Introduction

Since 2019, the coronavirus disease 2019 (COVID-19) pandemic has led to substantial challenges to human health and economic losses worldwide.[1] Due to its highly mutable nature, COVID-19 has threatened the lives and health of affected individuals. According to the World Health Organization, there have been more than 767 million confirmed cases and 6.9 million deaths attributable to COVID-19 up through July 2023.[2,3] Governments and scientists worldwide have

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attempted to develop various preventive and control measures, including vaccines, biological agents, and therapeutic drugs.

Paxlovid (Pfizer Inc), an orally administered tablet containing nirmatrelvir and ritonavir (N/R), received emergency use authorization from the US Food and Drug Administration for the treatment of mild to moderate COVID-19 in December 2021.[4] Subsequently, the National Medical Products Administration approved paxlovid for the treatment of COVID-19 in February 2022. The recommended dose is 300 mg nirmatrelvir and 100 mg ritonavir twice daily for 5 days. Nirmatrelvir is the main protease inhibitor of COVID-19, which can block the processing of viral polyprotein precursors, thus preventing virus replication. Coadministration of ritonavir, an inhibitor of the cytochrome P450 3A4 (CYP3A4) enzyme, prevents premature metabolism and inactivation of nirmatrelvir, increasing nirmatrelvir levels in the body by approximately eight-fold and enhancing its therapeutic effects.[5–8] The goal of treatment is to maintain trough nirmatrelvir concentration above that at which 90% of SARS-CoV-2 viral replication is inhibited ($EC_{90}$) in vitro (292 ng/mL).[7–9]

Phase II–III clinical trials have demonstrated paxlovid's effectiveness in patients at high risk of severe disease, showing an 88% reduction in the risk of COVID-19-related hospitalization or death compared to placebo group.[10–12] A meta-analysis included 13 clinical studies showed that the efficacy of paxlovid in reducing mortality rate, hospitalization rate, hospitalization or death rate, and PCR negative conversion time in COVID-19 patients compared to the no-paxlovid group, but it was not effective in terms of emergency department (ED) visits and ICU admission.[13]

Currently, the use of N/R in Chinese patients is mostly guided by the prescribing information, with relatively fixed dosing, and individualized therapy is less frequently applied. However, the issue of drug exposure which insufficient exposure leading to reduced efficacy and excessive exposure causing adverse reactions in different patients urgently needs to be addressed. Additionally, the drug interactions of N/R also warrant our attention. Ritonavir is a potent CYP3A4 inhibitor, lead to increase in plasma levels of tacrolimus, cyclosporine, calcineurin inhibitors (CNIs), or mTOR inhibitors: everolimus and sirolimus in patient when coadministration.[14,15] Ritonavir is also an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and uridine diphosphate (UDP)-glucuronyltransferase (UGT), and consequently can reduce the exposure (area under the curve (AUC)) of drugs metabolized by these enzymes.[16,17]

Therefore, we aimed to assess the PopPK parameters of nirmatrelvir in Chinese patients with COVID-19 infection. Moreover, optimization of dosing regimens and establishment of individualized dosing prediction tools for Chinese patients based on final PopPK model.

# Materials and Methods

## Study Design

A single-center, retrospective pharmacokinetic (PK) trial was conducted at Changxing People's Hospital in Zhejiang, China, between December 2022 and June 2023. We enrolled patients aged ≥ 18 years who were diagnosed with mild to moderate COVID-19 based on laboratory parameters or clinical features and provided informed consent. We excluded patients with current or past positivity for hepatitis B surface antigen or hepatitis C antibody; positive results in a human immunodeficiency virus antibody test; who were unwilling or unable to adhere to the study protocol; with mental or legal incapacitation; and who used inhibitors or inducers of cytochrome P450 enzymes or P-glycoprotein within the prior week.[18]

Participants with mild to moderate COVID-19 infection received 300/100 mg N/R twice daily for 5 days. A sparse sampling strategy was used to collect 3–5 mL blood from patients to measure the N/R level.[1] The study protocol was approved by the Ethics Committee of Changxing People's Hospital (2023-KY-046). The study was conducted in accordance with the Declaration of Helsinki.

## Sample Processing

In total, 100 μL plasma sample was mixed with 300 μL mixed internal standard working solution (nirmatrelvir-D9 acetonitrile solution and $^{13}C$, $^{2}H_3$-ritonavir acetonitrile aqueous solution), vortexed to ensure appropriate mixing, and centrifuged at 12,000 rpm for 5 min. Then, 2 μL supernatant was obtained for analysis. All samples were promptly centrifuged, and the separated plasma was frozen at −80°C.[19]

## Laboratory Methods

N/R levels were assessed using a validated ultra-high-performance liquid chromatography–tandem mass (UPLC-MS/MS) method with deuterated internal standards. The biological reference standards for N/R and deuterated N/R were obtained from Shanghai Yuanye Bio-Technology Co., Ltd (Shanghai, China) and Shimadzu Global Laboratory Consumables Co., Ltd (Shanghai, China), respectively. In brief, samples were spiked with deuterated N/R as the internal standard (Nirmatrelvir/nirmatrelvir-D9 was dissolved in acetonitrile, ritonavir/$^{13}C$, $^{2}H_3$-ritonavir were dissolved in acetonitrile:water (50:50)), and proteins were precipitated using acetonitrile. After centrifugation, the supernatant (2 μL) was injected onto a Xevo TQ-S Cronos UPLC-MS/MS (Waters Corp, Milford, MA, USA) equipped with an Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm). Gradient elution was performed using mobile phases A (0.1% formic acid in water) and B (100% acetonitrile) at a flow rate of 0.3 $mL \cdot min^{-1}$. The electrospray ionization source plus mode was utilized, with a capillary voltage of 3,000 V, a desolvation temperature of 350°C, an $N_2$ flow rate of 600 L/h, and a scanning mode of multiple-reaction monitoring. Adduct transitions were monitored using positive electrospray ionization, with multiple-reaction monitoring for nirmatrelvir, nirmatrelvir-D9, ritonavir, and $^{13}C$, $^{2}H_3$-ritonavir indicating values of m/z 500.20→319.10, m/z 508.59→328.10, m/z 721.30→426.10, and m/z 725.30→426.10, respectively. The linear ranges of nirmatrelvir and ritonavir were 0.1–10.0 $\mu g \cdot mL^{-1}$ ($R^2$ = 0.9972) and 0.05–5.0 $\mu g \cdot mL^{-1}$ ($R^2$ = 0.9952), respectively. The within-run and between-run precision of N/R were < 10%. The matrix effect, stability, dilution effect, and residual effect of N/R in plasma did not affect the quantitative analysis.[19]

## Model Development

The PopPK of nirmatrelvir in plasma concentration-time data were analyzed based on a nonlinear mixed-effects modeling approach using NONMEM (version 7.4.1; Icon Development Solutions, Ellicott City, MD, USA). This approach involved the first-order conditional estimation method with η-Ɛ (FOCE-I), where η is the random interindividual variability and Ɛ is the random residual variability. Stepwise covariate modeling was used for covariate screening with Perl-speaks NONMEM (version 5.1.2). R (version 4.3.3) and RStudio (version 2022.07.0) were used for data pre- and post-processing to summarize and plot results.

A base model incorporating the interindividual variability (IIV) and residual error was developed. In the additive, proportional, or exponential model, the IIV of pharmacokinetic parameters was described based on the following exponential error equation:

$$P_i = P_{pop} \times e^{\eta i}$$

where $P_i$ is the hypothetical true value of the parameter for the *i*th subject, $P_{pop}$ is the population parameter value, and ηi is the IIV.

The IIV in pharmacokinetic parameters was assumed to follow a normal distribution with a mean of 0 and variance of $\omega^2$. Residual errors were evaluated using various residual variability models, including additive, proportional, and additive plus constant coefficient of variation models.

Subsequently, a priori allometric scaling was employed, with volume terms multiplied by (WT/70) and clearance terms multiplied by $(WT/70)^{0.75}$. The effects of the following potential covariates were evaluated: age; height; sex; creatinine clearance (CrCl); white blood cell, neutrophil, and lymphocyte counts; and levels of C-reactive protein, procalcitonin, alkaline phosphatase, glutamyl transpeptidase, alanine aminotransferase, and aspartate aminotransferase. During the stepwise forward-inclusion step and backward elimination procedure, covariates were considered significant for the model parameters if the objective function value decreased by more than 3.84 ($\chi^2$ test, degree of freedom [df] = 1, $p < 0.05$) or increased to > 10.84 ($\chi^2$ test, [df] = 1, $p < 0.001$).[1]

## Model Evaluation and Validation

The stability and robustness of the final model were evaluated using the condition number and a nonparametric bootstrap procedure with 1,000 replicates. The accuracy and applicability of the final models were assessed based on goodness-of-fit in diagnostic scatter plots for observed concentrations vs population predictions, observed concentrations vs individual predictions, conditional weighted residuals (CWRES) vs population predictions, and CWRES vs time.

## Simulation and Dosing Regimen Optimization

The final PopPK model was used to simulate plasma concentrations of nirmatrelvir under various dosing regimens. Monte Carlo simulations were conducted using NONMEM to optimize dosing strategies, achieving a balance between exposure, efficacy, and safety. The final model was based on twice daily doses of 150 and 300 mg oral nirmatrelvir. Each group simulated the area under the curve (AUC) of nirmatrelvir with different renal functions and body weights, including normal renal function (CrCl = 100 mL/min), mild renal impairment (CrCl = 70 mL/min), moderate renal impairment (CrCl = 45 mL/min), and severe renal impairment (CrCl = 15 mL/min). Furthermore, we developed a web-based dashboard based on parameters from the final model using the shiny package in R.

## Statistical Analysis

Data were analyzed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). P-values $< 0.05$ were considered indicative of statistically significant differences, and presented as mean ± standard deviation or median with interquartile range, as appropriate. Continuous variables were compared using the Student's *t*-test.

# Results

## Demographic Parameters

After excluding patients with missing baseline information, 130 plasma samples from 129 patients (65 males and 64 females) who provided informed consent were used to develop the PopPK model. The mean±standard deviation [SD] age and body weight of the 129 patients at sampling time were 73.2±14.7 (range, 18.0 to 97.0) years and 61.2±9.3 (range, 37.5 to 96.0) kg, respectively. Information related to N/R co-administration not collected. Table 1 presents the demographic characteristics of patients.

## Model Development

Using a sparse sampling strategy, a one-compartment model with first-order absorption and first-order elimination (ADVAN2 TRANS2) was found to provide the best fit for the data. The model-derived pharmacokinetic parameters for nirmatrelvir were apparent clearance (CL/F), apparent volumes of distribution (V/F), and the first-order absorption rate constant ($K_a$). Residual errors were described by additive plus constant coefficient of variation models, with values set at 10%.

Considering that the sampling time points mainly represent valley concentrations, typical values for V/F and $K_a$[1,2] were used to prevent over-parameterization or model failure. The V/F and $K_a$ values were set at 39 L and 0.8 $h^{-1}$. Following the forward inclusion and backward elimination processes, the model retained only CrCl (objective function value = 37.275; $\chi^2$ test, df = 1, $p < 0.001$) as a covariate for CL/F.[20] The inclusion of covariates for CL/F modestly reduced the IIV from 58.9% to 52.3%. The final model adopted $CL/F = 3.41 \times (WT/70)^{\circ 0.75} \times (CRCL/52.9)^{\theta} \times e^{\eta}$, where

**Table 1** Summary of Baseline Demographics of Patients

| Parameter | Value | |
|---|---|---|
| | **Mean ± SD** | **Median (Range)** |
| Body Weight, kg | 61.2 ± 9.3 | 61.1 (37.5–96.0) |
| Age, year | 73.2 ± 14.7 | 76.0 (18.0–97.0) |
| Height, cm | 164.6 ± 6.9 | 164.4 (148.0–182.0) |
| C-Reaction Protein, mg/L | 61.1 ± 63.1 | 42.6 (0.1–314.8) |
| White Blood Cell Count, *10^9 | 7.5 ± 5.9 | 5.9 (0.2–53.0) |
| Neutrophil Count, *10^12 | 5.4 ± 3.6 | 4.3 (0.1–20.0) |
| Lymphocyte Count, *10^9 | 1.0 ± 1.4 | 0.8 (0.1–15.4) |
| Procalcitonin, ng/mL | 1.2 ± 5.3 | 0.08 (0.01–45.3) |
| Creatinine Clearance, mL/min | 56.7 ± 33.1 | 52.9 (4.8–289.2) |
| Alkaline Phosphatase, U/L | 60.5 ± 83.0 | 50.2 (0.9–790.6) |
| Glutamyl Transpeptidase, U/L | 74.9 ± 271.1 | 32.5 (9.2–2324.5) |
| Aspartate aminotransferase, U/L | 55.8 ± 44.4 | 44.9 (12.1–256.7) |
| Alanine Aminotransferase, U/L | 41.9 ± 64.8 | 23.2 (5.7–447.3) |

**Abbreviation**: SD, standard deviation.

θ represents the effect of CrCl on CL/F and η represents the IIV. The final estimated PopPK parameters and bootstrap result for nirmatrelvir are presented in Table 2.

The close agreement (within ± 15%) between the population parameters from the final model and bootstrap medians supports the stability of the model and the accuracy of the parameter estimates. The 2.5–97.5 percentiles from the bootstrap and the relative standard errors from the model fitting indicated reasonable accuracy of the estimated fixed- and random-effect parameters.[20] The diagnostic plots demonstrated acceptable goodness-of-fit for the final PopPK model of nirmatrelvir (Figure 1). The CWRES vs time plot and predicted concentrations exhibited a roughly symmetrical distribution, with only a few points outside the range. The observed concentration vs predicted concentration plot demonstrated a good predictive performance at low concentrations and bias at high concentrations. The median CrCl was within or close to the 95% prediction interval of the median obtained from the model, indicating adequate model performance (Figure 2).

## Simulation and Dosing Regimen Optimization

We simulated populations receiving oral doses of 300 mg and 150 mg nirmatrelvir twice daily with varying renal functions and body weight based on the final model parameters (Figure 3). Furthermore, we summaried nirmatrelvir exposure in patients with varying renal functions (Tables 3). In subgroups received 300/100 mg N/R twice daily for 5 days, which simulated four groups of virtual patients with normal to severe renal impairment, the median (95% Cl) trough concentration ($C_{through}$) increased from 2.36 (0.48–4.72) to 4.74 (2.27–6.47) μg/mL after the first dose, the median (95% Cl) maximum observed concentration ($C_{max}$) increased from 8.31(4.99–16.16) to 16.00(8.10–29.07) μg/mL, and the median (95% Cl) $AUC_{tau}$ increased from 71.07 (30.32–153.21) to 164.30 (68.42–319.53) μg•h/mL. In the subgroups receiving 150/100 mg N/R twice daily for 5 days, the median (95% Cl) $C_{through}$, the median (95% Cl) $C_{max}$, and the median (95% Cl) $AUC_{tau}$ were significantly lower, besides the exposure profile in patients with severe renal impairment was similar to patients with normal renal impairment receiving 300/100 mg N/R twice daily for 5 days.

Using Monte Carlo simulations, we also evaluated the impact of body weight on nirmatrelvir exposure in virtual patients receiving 300/100 mg N/R twice daily for 5 days, detailed simulation is shown in Table 4. In virtual patients weighing 115 kg, the median (95% Cl) $C_{through}$ after first dose is 1.58 (0.39–2.88), the median (95% Cl) $C_{max}$ is 5.14 (3.05–9.76), and the median (95% Cl) $AUC_{tau}$ is 45.61 (19.73–101.41). The median (95% Cl) $C_{through}$, $C_{max}$, and $AUC_{tau}$ in 40 kg virtual patients were approximately twice those observed in 115 kg virtual patients, indicating considerable variability in drug exposure across different body weights.

To facilitate the monitoring of dynamic drug concentrations and provide individualized treatment, we developed a web-based dashboard using the shiny package in R. The dashboard recommends the dosage of nirmatrelvir and simulates the AUC based on individual patient characteristics. A screenshot of the dashboard is presented in Figure 4,

**Table 2** Parameter Estimates for Final Model and Bootstrap Values

| Parameter | Final model | | Bootstrap (n=1000) | |
|---|---|---|---|---|
| | Estimate | RSE (%) | Median | 2.5th-97.5th |
| CL/F, L/h | 3.41 | 4.00 | 3.36 | 3.16–3.92 |
| Effect of CrCl on CL/F | 0.429 | 28.00 | 0.40 | 0.21–0.81 |
| V/F, L | 39.00 (fixed) | | | |
| $K_a$, $h^{-1}$ | 0.80 (fixed) | | | |
| Interindividual variability, CV% | | | | |
| CL/F, L/h | 52.30 | 7.00 | 52.90 | 44.70–60.80 |
| Residual variability, CV% | | | | |
| $\varepsilon_1$ | 10.00 (fixed) | | | |
| $\varepsilon_2$ | 10.00 (fixed) | | | |

**Abbreviations**: RSE, relative standard error; CV, coefficient of variation; $K_a$, absorption rate constant; V/F, apparent volumes of distribution; CL/F, apparent clearance; CrCl, Creatinine Clearance; $\varepsilon_1$, $\varepsilon_2$, residuals error value.

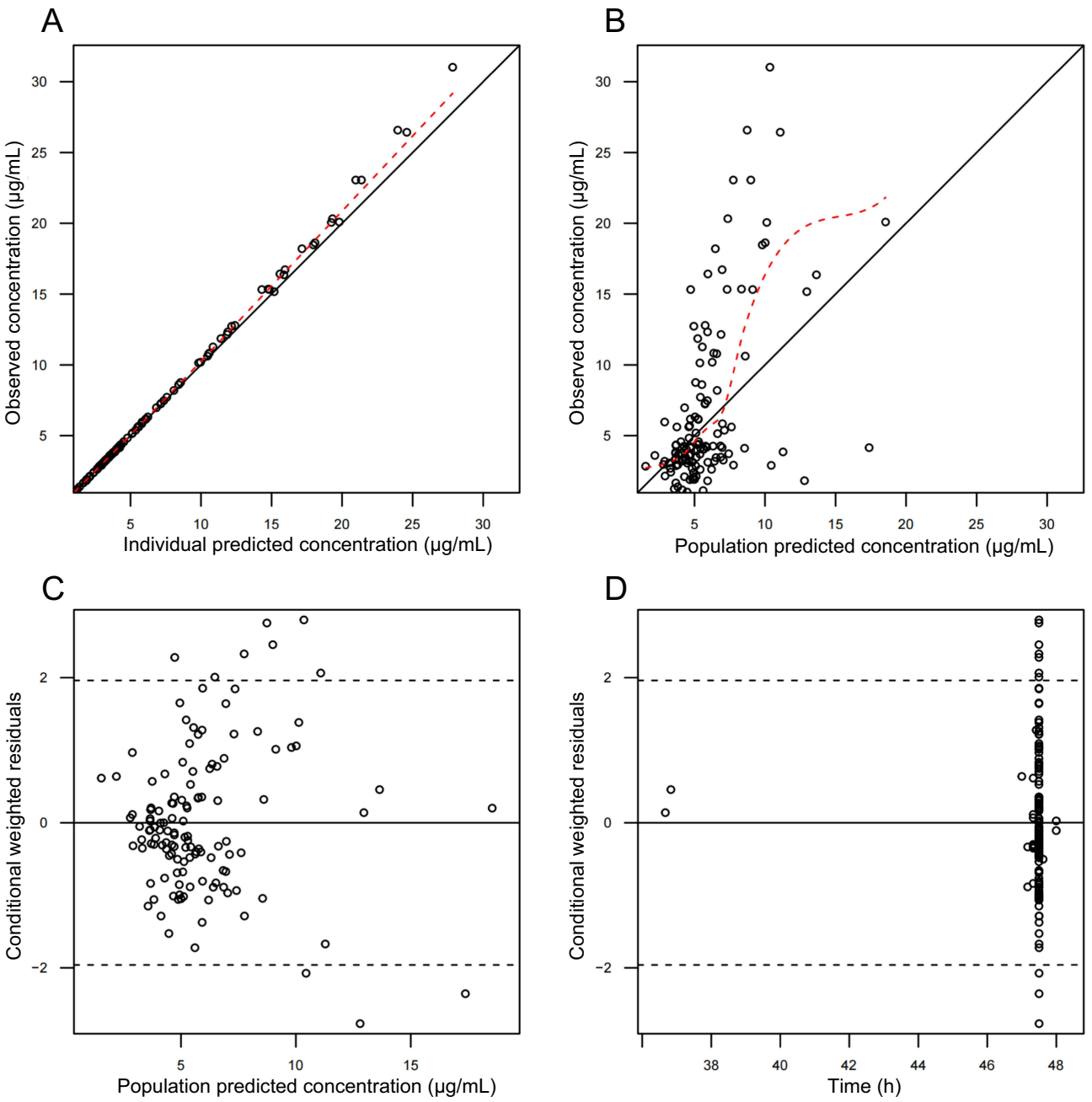


**Figure 1** Diagnostic plots of the final plasma nirmatrelvir population pharmacokinetic model. (**A**) observed concentrations versus individual predictions. (**B**) observed concentrations versus population predictions. (**C**) conditional weighted residuals versus population predictions. (**D**) conditional weighted residuals versus time.

illustrating an example of a patient with a body weight of 65 kg and CrCl of 100 mL/min who started taking 300 mg nirmatrelvir twice daily for 5 days postoperatively.[21]

## Discussion

This study objective was to describe the pharmacokinetics (PKs) profiles of nirmatrelvir in Chinses patients with COVID-19 infection, assess the effects of demographic, clinical, and biological elements on nirmatrelvir disposition, and establish an optimized regimen tool for individualised therapy. The results showed that a one-compartment model with first-order absorption and first-order elimination provided the best accuracy for determining the plasma level following oral administration of nirmatrelvir. In addition, simulation results showed that CrCl and body weight play a crucial role in adjusting the individualized medication regimen of patients.

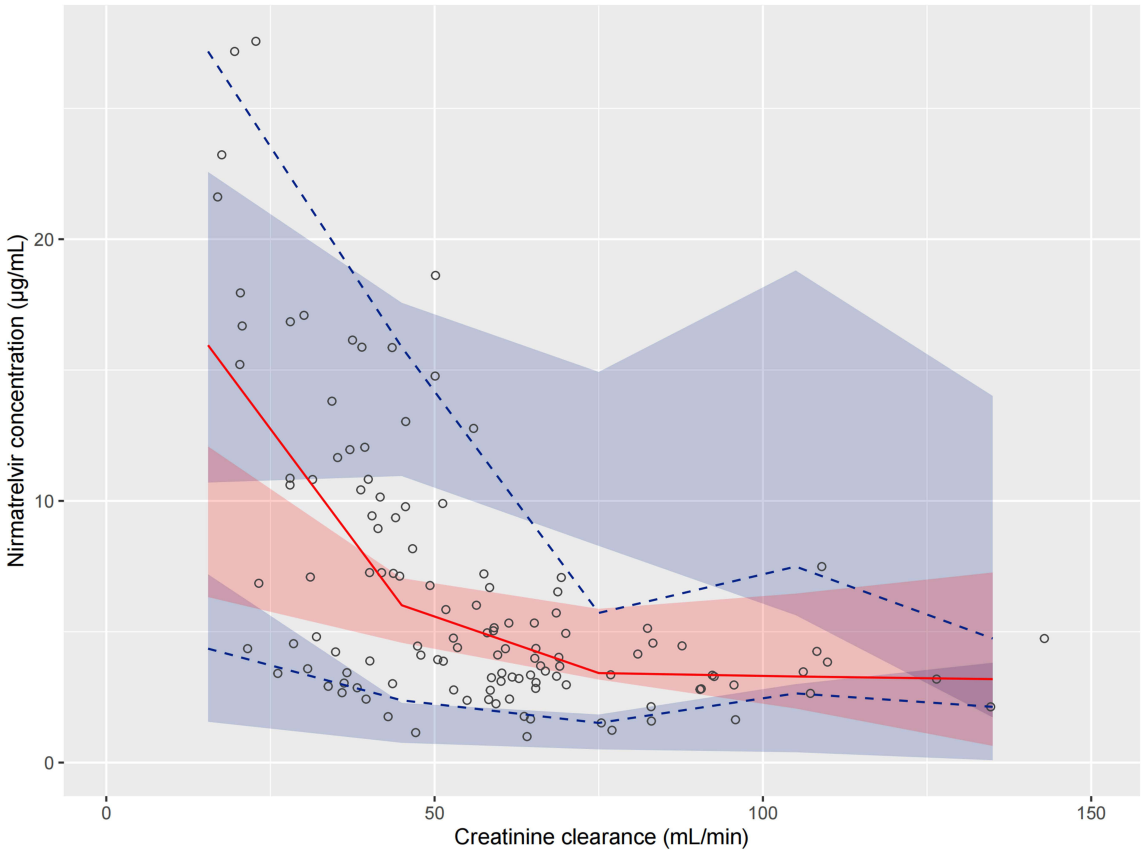


**Figure 2** Visual predictive check plot for final model showing nirmatrelvir concentrations. The lines are the 2.5$^{th}$ (blue dash), 50$^{th}$ (red solid) and 97.5$^{th}$ (blue dash) percentiles based on the observed data. The shaded areas are 95% confidence intervals for the 2.5$^{th}$, 50$^{th}$, and 97.5$^{th}$ percentile prediction intervals based on the simulated data.

During the model building process, due to sparse sampling, we fixed the typical values of V/F (39 L) and $K_a$ (0.8 $h^{-1}$) based on previous studies.[1,3,22] The typical value of CL/F was 3.41 L/h, similar to the one-compartment model[22] and lower than that of the two-compartment model of nirmatrelvir.[1,3] We employed standard allometric scaling of body weight to reduce collinearity among covariates, and CrCl was found to predict the variability in CL/F, explaining only 6.6% of the IIV. Aspartate aminotransferase and alanine aminotransferase did not significantly affect the CL/F of nirmatrelvir, indicating the primary role of renal excretion in nirmatrelvir elimination when the CYP3A4-mediated metabolism is inhibited by ritonavir.[3,7]

Compared to drug exposure in label of Paxlovid, Monte Carlo simulations based on the final model parameters revealed that patients receiving 300/100 mg N/R twice daily for 5 days exhibited higher exposure with normal renal function in this study. The median AUC vs time curve through the dosing interval ($AUC_{tau}$, 71.07 µg.h/mL) was approximately two-fold higher than that for Chinese and Western young adult volunteers (32.01 and 33.35 µg.h/mL, respectively).[11] Due to the advanced age of participants, our results are comparable to pharmacokinetic parameters of old Chinese patients.[1] The CL/F tended to decrease with age, and the mean age of our patients was 73.2 years. The age-related decline in P-glycoprotein and CYP3A4 function may reduce nirmatrelvir metabolism, thereby increasing drug exposure.[23,24] Therefore, in the present study, the CL/F was lower than that compared to models based on young patients.[3]

The CrCl and body weight emerged as significant influencing factors in the final model, and simulations were used to support dosing recommendations in special populations. The exposure of nirmatrelvir increased with a decline in renal function (Table 3), consistent with a previous study.[25] For patients with moderate to severe renal impairment, the median $C_{max}$ of nirmatrelvir exceeded 10 µg/mL, with a significant increase in $AUC_{tau}$ (44% and 131%). Considering the potential for adverse effects, 150 mg nirmatrelvir coadministered with 100 mg ritonavir twice daily for 5 days is suitable for patients with moderate to severe renal impairment, although there is a wide safety margin (26.4 µg/mL).[7,12] Even if the drug label by Pfizer recommends that nirmatrelvir should be avoided in patients with severe renal impairment, our simulations indicate that drug exposure with 150/100 mg N/R in patients with CrCl of 15 mL/min is comparable to that in patients with normal renal function taking 300/100 mg N/R orally. For

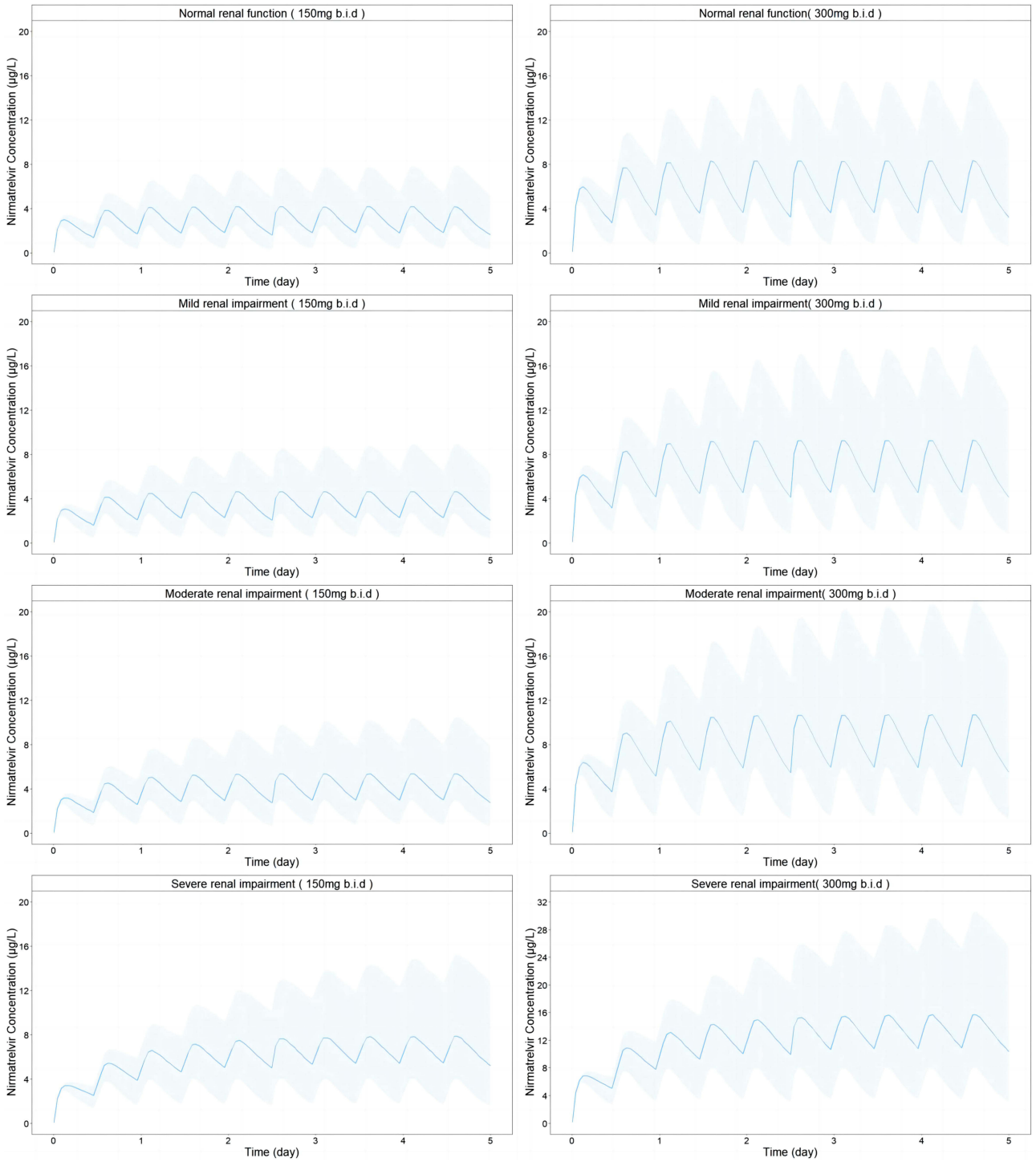


**Figure 3** Simulated the curves of nirmatrelvir concentration with different renal functions and dosage. The deepblue line depicts the median value. The lightblue-shaded areas depict the 95$^{th}$ prediction interval. Simulate patients' body weight as 65kg and based on 1000 simulated subjects per group.

adults with normal renal function who received oral doses of 300 mg nirmatrelvir and 100 mg ritonavir, simulations indicated that > 90% of participants achieve $C_{trough} \geq EC_{90}$ on days 1 and 5 and had an appropriate $C_{max}$ (8.31 μg/mL). Tables 3 and 4 present the Monte Carlo simulation of patient parameters.

Moreover, the CL/F of nirmatrelvir decreased with body weight reduction, resulting in higher exposure at lower body weights. This was attributed to allometric scaling in CL/F $((WT/70)^{\circ 0.75})$ and V/F (WT/70) in the PopPK model, where weight loss leads to a decrease in CL/F accompanied by a decrease in V/F. The participants of the present study (median

**Table 3** Simulated Nirmatrelvir Exposure in Patients with Varying Renal Functions and Dosage

| CrCl, mL/min | Dose Number | $C_{through}$, μg/mL | $C_{max}$, μg/mL | $AUC_{tau}$, μg•h/mL |
|---|---|---|---|---|
| **300 mg (b.i.d) for 5 days** | | | | |
| 100 | 1st (day 1) | 2.36 (0.48–4.72) | 8.31 (4.99–16.16) | 71.07 (30.32–153.21) |
| | 10th (day 5) | 3.10 (0.49–10.08) | | |
| 70 | 1st (day 1) | 2.82 (0.70–5.12) | 9.47 (5.44–17.08) | 85.21 (35.33–166.65) |
| | 10th (day 5) | 3.99 (0.75–12.17) | | |
| 45 | 1st (day 1) | 3.39 (1.06–5.57) | 10.92 (6.03–20.08) | 102.98 (42.71–212.81) |
| | 10th (day 5) | 5.33 (1.18–15.14) | | |
| 15 | 1st (day 1) | 4.74 (2.27–6.47) | 16.00 (8.10–29.07) | 164.30 (68.42–319.53) |
| | 10th (day 5) | 10.10 (2.97–24.37) | | |
| **150 mg (b.i.d) for 5 days** | | | | |
| 45 | 1st (day 1) | 1.70 (0.54–2.78) | 5.46 (3.01–10.04) | 51.48 (21.35–106.37) |
| | 10th (day 5) | 2.66 (0.59–7.56) | | |
| 15 | 1st (day 1) | 2.37 (1.13–3.23) | 8.00 (4.05–14.65) | 82.11 (34.2–159.79) |
| | 10th (day 5) | 5.05 (1.49–12.18) | | |

**Note**: Values presented as median (95% CI) for all. Simulate patients' body weight as 65kg and based on 1000 simulated subjects per group. Oral 300 or 150 mg nirmatrelvir twice daily coadministered with 100 mg ritonavir for 5 days.
**Abbreviations**: $AUC_{tau}$, area under the concentration versus time curve through the dosing interval (day 5); $C_{max}$, maximum observed concentration (day 5); $C_{through}$, through concentration; b.i.d, twice daily.

**Table 4** Simulated Nirmatrelvir Exposure in Patients with Different Body Weight

| Body Weight, kg | Dose Number | $C_{through}$, μg/mL | $C_{max}$, μg/mL | $AUC_{tau}$, μg•h/mL |
|---|---|---|---|---|
| **300 mg (b.i.d) for 5 days** | | | | |
| 115 | 1st (day 1) | 1.58 (0.39–2.88) | 5.14 (3.05–9.76) | 45.61 (19.73–101.41) |
| | 10th (day 5) | 2.22 (0.41–6.79) | | |
| 90 | 1st (day 1) | 1.88 (0.43–3.57) | 6.29 (3.78–11.85) | 54.82 (23.71–122.12) |
| | 10th (day 5) | 2.57 (0.45–8.06) | | |
| 65 | 1st (day 1) | 2.36 (0.48–4.72) | 8.31 (4.99–16.16) | 71.07 (30.32–153.21) |
| | 10th (day 5) | 3.10 (0.49–10.08) | | |
| 40 | 1st (day 1) | 3.27 (0.54–7.12) | 12.30 (7.70–22.54) | 100.34 (43.81–225.22) |
| | 10th (day 5) | 4.08 (0.55–14.01) | | |

**Note**: Values presented as median (95% CI) for all. Simulate patients' CrCl as 100 mL/min and based on 1000 simulated subjects per group. Oral 300 mg nirmatrelvir twice daily coadministered with 100 mg ritonavir for 5 days.
**Abbreviations**: $AUC_{tau}$, area under the concentration versus time curve through the dosing interval (day 5); $C_{max}$, maximum observed concentration (day 5); $C_{through}$, through concentration; b.i.d, twice daily.

of body weight: 61.1 kg) had a lower body weight than Chan et al study (median of body weight: 79.8 kg).[3] Simulation results (Tables 4) of patients showed that nirmatrelvir exposure varied significantly with body weight. In clinical practice, it is essential to consider the impact of body weight on nirmatrelvir exposure, and further studies are needed to elucidate the effect of body weight.

Based on our simulation results, the CrCl and body weight of patients can significantly influence exposure to nirmatrelvir. To facilitate individualized drug dosing and ensure optimal exposure, efficacy, and safety of nirmatrelvir, we developed a web-based dashboard based on the final model, providing rapid drug dose recommendations individualized according to the CrCl and body weight. This dashboard can provide guidance for nirmatrelvir treatment, enhancing its accuracy and safety (Figure 4).

This study had some limitations. First, due to sparse sampling and limited blood samples per patient, the original data could only be used to establish a one-compartment model, and some relevant parameters ($K_a$ and V/F) were derived from previous studies. Second, the study participants were relatively old, limiting the generalizability of the PKs obtained from our study to younger populations. Third, data on N/R coadministration and information about patient's past history (asthma, chronic

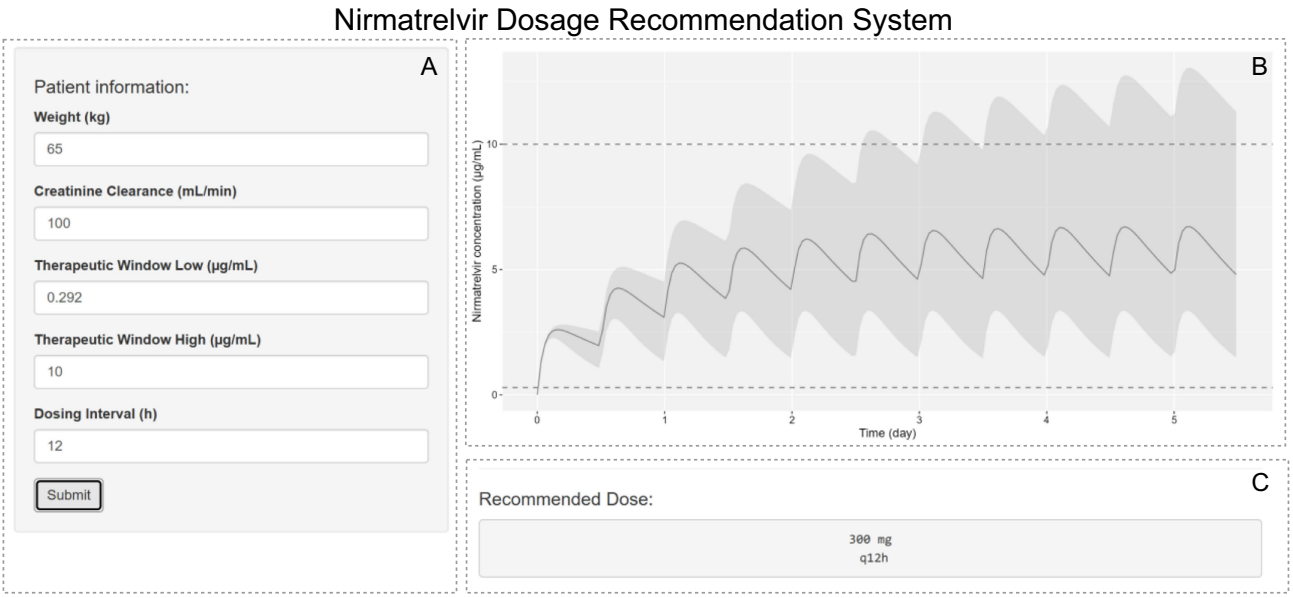


**Figure 4** The screenshot of the web-based dashboard for individual nirmatrelvir dose recommendations. (**A**) the input sidebar including patient demographics, therapeutic window low and high of nirmatrelvir, dosing interval. (**B**) the concentration-time curves of each regimen. (**C**) the text summary of the optimal regimen.

obstructive pulmonary disease, Chest Disease, etc.) was not collected and analysised. Finally, the use of the web-based dashboard to determine the recommended dosage regimen based on the final model should be validated.

## Conclusion

The PopPK model of nirmatrelvir was developed in Chinese patients with COVID-19 infection and elucidated the significant effects of CrCl and body weight on nirmatrelvir pharmacokinetics. Dose regimen optimization based on Monte Carlo simulations and a web-based dashboard were established to facilitate individualized therapy.

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## Disclosure

The authors declare no conflict of interest.

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