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ORIGINAL RESEARCH

Target Attainment and Population Pharmacokinetics of Nirmatrelvir/Ritonavir in Critically Ill Adult Patients

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Background: The population pharmacokinetics of nirmatrelvir/ritonavir (NIR/RIT) has not yet been described for critically ill adult patient.

Purpose: This was a prospective observational population pharmacokinetic study of nirmatrelvir/ritonavir (NIR/RIT) in critically ill adult patients and identify optimal dosing regimens.

Patients and Methods: The prescription of NIR/RIT is determined by the attending physician and ranges from 150mg/100mg to 300mg/100mg twice a day. Two to three serial blood samples were collected for each patient after the second doses. We developed and validated PK model for plasma NIR and plasma RIT. Monte Carlo dosing simulations were performed to assess target attainment.

Results: We analyzed 89 plasma samples from 31 adult patients. The data were best described by a one-compartment model. Among the covariates tested on pharmacokinetic parameters, creatinine clearance (CrCL) and area under curve (AUC) of RIT had a significant effect on apparent clearance (CL/F) of NIR. Mean (SD) parameters estimates for the absorption rate constant (Ka), apparent distribution (V/F) and CL/F were 0.42 (0.10) h^{-1}. 36.5 (8.5) L, 3.6 (0.26) L/h, respectively. Dosing simulations showed that the target in vitro 90% effective concentration (EC_{90}) was more likely to be achieved twice a day than once a day at the same daily dose of NIR. High CrCL, low AUC of RIT were associated with a reduced likelihood of NIR reaching the target EC_{90}.

Conclusion: Based on our dosing simulations, the initial dosage of NIR/RIT was 300mg/100mg twice a day in critically ill patients with CrCL>45 mL/min; When CrCL in critically ill patients is between 15 and 45 mL/min, NIR/RIT is 150mg/100mg twice a day. The maintenance dose is adjusted according to CrCL and AUC of RIT, with the dosages varying between 75mg/100mg and 300mg/100mg.

Keywords: nirmatrelvir, ritonavir, pharmacokinetics, critically ill, creatinine clearance

Introduction

Nirmatrelvir/ritonavir (NIR/RIT, Paxlovid) is a novel oral medication designed to inhibit the 3-chymotrypsin-like cysteine protease (M^{pro}) of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] NIR is metabolized primarily by cytochrome P450 3A4 (CYP3A4), and RIT, a CYP3A4 inhibitor, is co-administered to maintain effective plasma concentrations of NIR. When CYP3A metabolism is suppressed by RIT, the primary route of NIR elimination is through renal excretion.[2] The World Health Organization (WHO) strongly recommends NIR/RIT for high-risk hospitalized patients to effectively reduce the risk of progressing to severe disease.[3] This recommendation is particularly

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pertinent for patients who are critically ill or have severe symptoms that began more than five days ago, with a SARS-CoV-2 nucleic acid ct value less than 30. Despite the delay in treatment initiation, there is still a potential benefit from the use of antiviral drugs in these cases.[4]

A Phase I study evaluating the pharmacokinetic effects of renal impairment on NIR/RIT demonstrated that systemic exposure to NIR increased with increased renal impairment, and apparent clearance (CL/F) was positively correlated with creatinine clearance (CrCL). Compared with the normal renal function group, the moderate renal impairment group was 47% lower and the severe renal impairment group was 80% lower.[5] In patients with end-stage renal disease treated with intermittent hemodialysis, in these patients, NIR/RIT 150mg/100mg twice a day, measured peak plasma concentrations of NIR were 4 times higher than the median levels in patients with normal renal function and a full NIR/RIT dose.[6] Another study in hemodialysis patients found that when NIR 150mg once daily and RIT 100mg twice daily were given, the measured trough plasma concentration of NIR were 7.7 times higher than the up-limitation of the in vitro 90% effective concentration (EC_{90}) and 2.3 times higher than that in the control group.[7,8] In a study of eight continuous renal replacement therapy (CRRT) supported critically ill patients, NIR valley concentrations ranged from 3325.34 to 15625.46 ng/mL. The concentration was 7 times higher than in patients with normal kidney function and 2 times higher than in patients with end-stage renal disease receiving hemodialysis.[9]

Although NIR/RIT was not approved for critically ill patients, it remains one of the main antiviral drugs of SARS-CoV-2 in clinical use for critically ill patients. The primary aims of this study were to evaluate the population pharmacokinetics of NIR/RIT and to provide an individualized dosing regimen for critically ill patients.

Patients and Methods

Study Design and Population

Between January 2023 and June 2023, a study was conducted at the First Affiliated Hospital of Zhejiang University School of Medicine, focusing on patients meeting specific inclusion criteria. Eligible participants were adults aged 18 or older admitted to the Intensive Care Unit (ICU) due to a COVID-19 infection, confirmed by SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) and supported by a compatible pulmonary computed tomography scan. Additionally, patients had to have received more than two doses of NIR/RIT, with at least one measurement of NIR and RIT concentrations. The administration of NIR/RIT was managed by the attending physicians. The study excluded patients undergoing CRRT or extracorporeal membrane oxygenation.

Nirmatrelvir/Ritonavir Assay

NIR and RIT were determined by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS), as in our previous studies.[9] In simple terms, the linear ranges of NIR and RIT are 100.41 to 52991.51 ng/mL and 2.03 to 961.37 ng/mL, respectively. The intraday and intraday precision of the quality control samples was less than 5%, and the accuracy was between 89.2% and 112%.

Data Collection

Demographic data were registered and collected for each patient form the electronic hospital information system, including Nirmatrelvir/Ritonavir dose and administration details, age, height, body weight, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, blood creatinine, CrCL (calculated using the CKD-EPI equation), Acute Physiology and Chronic Health Evaluation (APACHE) II score, sequential organ failure assessment (SOFA), with CYP3A inducer or inhibitor (https://drug-interactions.medicine.iu.edu/MainTableaspx).

Population Pharmacokinetic Modelling

Population pharmacokinetic parameters were determined using Phoenix NLME software (version 8.1; Pharsight, Mountain View, CA), employing either one- or two-compartmental models. The first-order conditional estimation method (FOCE) was utilized for model estimation. Model assessment was based on criteria such as the precision of parameter estimates (standard error), goodness-of-fit plots, and the likelihood ratio test (−2 log likelihood [−2LL]). For

the one-compartment model, basic parameters included the absorption rate constant (Ka), volume of the central compartment distribution (V), and central compartment clearance (CL). In the two-compartment model, the parameters encompassed the volume of the peripheral compartment distribution (VP) and intercompartmental clearance (Q).

In the initial model, interindividual variability was characterized using an exponential-error model. Intraindividual variability, also known as residual error, was described by proportional, additive plus proportional, or log-additive models. The covariate selection process was assessed through a stepwise approach. For forward selection, a decrease in the objective function value (OFV; −2LL) by more than 6.635 (p=0.01) served as the criterion for covariate inclusion. Conversely, during backward selection, an increase in OFV greater than 10.828 (p=0.001) was the threshold for covariate exclusion. Ultimately, based on the scatter plot and a drop in OFV of more than 6.63 (ΔOFV), the pertinent population pharmacokinetic parameters were incorporated into the diagonal or off-diagonal elements of the variance-covariance matrix to finalize the model.

The final model's adequacy was evaluated through the use of goodness-of-fit plots. To assess the model performance, a prediction-corrected visual predictive check (pcVPC) was conducted, encompassing 1000 replicates. Furthermore, the precision of the parameter estimates was scrutinized using bootstrap analysis, which involved 1000 samples. These comprehensive evaluations ensured the robustness and reliability of the model's predictions and parameter estimations.

Monte Carlo Dosing Simulations

Base on NIR/RIT final population PK models, the plasma concentration-time profile of 1000 individuals was simulated. For critically ill patients, it is presumed that>90% of individual first dose predicted trough concentration (C_{trough}) values were above EC_{90} for SARS-CoV-2 (292 ng/mL), and >95% of individual steady-state C_{trough} above EC_{90}. The predicted peak concentration (C_{peak}) of all individuals on steady-state was lower than human no observed adverse effect levels (NOAELs, 79,700ng/mL).[1,5] The dose regimens were set at 37.5mg-450mg dose twice or once daily for NIR, with 100mg dose twice daily for RIT, the CrCL ranged from 15mL/min to 100 mL/min, and area under curve of RIT (AUC_{RIT}) from 10%th to 90%th were carried out for simulation.

Statistical Analysis

Statistical analyses were conducted utilizing IBM SPSS Statistics version 26. Patient demographic data were presented through descriptive statistics. The normality of the distribution for continuous variables was assessed using the Kolmogorov–Smirnov test. These continuous variables were reported either as the mean ± standard deviation (mean ± SD) or as the median with the interquartile range (IQR) from the 25th to the 75th percentile, depending on their distribution. Discrete variables, on the other hand, were expressed in terms of counts and percentages.

Results

Patients and Sample

In the study, a total of 31 patients were enrolled, providing 89 plasma samples for analysis, with demographic and clinical details summarized in Table 1. The median age was 69 years (IQR: 63–77), and 65% of participants were male. The mean body weight was 60.6 kg (SD: 12.8 kg). Clinical scores included a median APACHE II score of 14 (IQR: 11–21) and a median SOFA score of 6 (IQR: 3–9). Creatinine clearance (CrCL), calculated using the CKD-EPI equation, had a median value of 78.5 mL/min, with an IQR ranging from 10.4 to 146.3 mL/min. NIR/RIT was administered at 300mg/100mg twice a day for 27 patients (87%), and at 150mg/100mg twice a day for 4 patients (13%). 29 patients (94%) received NIR/RIT by nasal feeding and 2 patients (6%) by oral administration, all patient for a duration of more than 5 days. Measured concentrations of NIR ranged from 1214.31 to 21342.06 ng/mL, and RIT ranged from 21.71 to 4966.72 ng/mL.

Population PK Model Development

In the preliminary analysis of the RIT base model, the OFVs for the one- and two-compartment pharmacokinetic models were 193.6 and 193.2, respectively. Guided by the OFV, CV values, and diagnostic scatter plots, a one-compartment

Table 1 Demographic and Clinical Characteristics of the Study Population

Characteristics	All Patients (n=31)
Male sex, %	20 (65)
Age, years	69 (63–77)
Weight, kg	60.6±12.8
Body mass index (BMI)	22.3±3.8
Admission details	
APACHE II score, mean	14 (11–21)
SOFA score, mean	6 (3–9)
Laboratory values	
Serum creatinine, μmol/L	100.2±79.9
Creatinine clearance [a], mL/min	78.5±34.4
Total protein, g/L	54.8±6.0
Albumin, g/L	33.4±2.8
Alanine aminotransferase, U/L	21 (16–37)
Aspartate transpeptidase, U/L	25 (18–39)
Alkaline phosphatase, U/L	76 (51–100)
Tablets taken manner, Nasal feeding, %	29 (94)
Dosage regimen, nirmatrelvir/ritonavir	
300mg/100mg, q12h, %	27 (87)
150mg/100mg, q12h, %	4 (13)
Concomitant CYP3A4/5 inducer or inhibitor [b]	
Weak inhibitor	7 (22.6)
Weak inducer	10 (32.3)

Notes: [a]Creatinine clearance was calculated using the CKD-EPI equation. [b]CYP3A4/5 inducer or inhibitor, drug-interactions.medicine.iu.edu/MainTableaspx.

model with a log-additive error option was selected as the base model. During the covariate model building step, no significant covariate effects were identified. Importantly, a correlation between CL and V was observed and incorporated into the off-diagonal elements of the variance-covariance matrix, which resulted in a significantly improved OFV of 174.5 (P<0.01). The final pharmacokinetic (PK) parameters are presented in Table 2.

In the preliminary analysis of the NIR base model, the OFVs for the one- and two-compartment pharmacokinetic models were 125.5 and 125.7, respectively. Based on the OFV, coefficient of CV values, and diagnostic scatter plots, a one-compartment model with a log-additive error option was selected as the base model. During the covariate model building step, CrCL and the area under the RIT concentration-time curve (AUC_{RIT}) were identified as covariates for CL, as depicted in Figure 1. No covariate effect was identified for V of distribution. Additionally, a correlation between CL and V was observed and incorporated into the off-diagonal elements of the variance-covariance matrix, resulting in a significantly improved OFV of 95.0 (P<0.01). The final PK model parameters are presented in Table 3 and Equation 1.

$$CL = tvCL \times (CrCL/80)^{dCLdCrCL} \times (AUCRIT/12.2)^{dCLdRIT} \times \exp(nCL) \quad (1)$$

AUC_{RIT}: AUC of ritonavir, mg/L·h, calculated by Equation 2

$$AUC = \frac{DOSE}{CL/F} \quad (2)$$

Table 2 Parameters Estimates, Bootstrap Medians, and Confidence Intervals for Ritonavir

Parameter	Final Model		Bootstrap of Final Model	
	Estimate, Mean	CV, %	Estimate, Median	95% CI
tvKa, h^{-1}	0.64	37.4	1.10	0.13–9.99
tvV, L	84.9	29.2	82.4	10.1–158.4
tvCL, L/h	10.3	14.7	10.3	7.5–13.7
Inter-individual variability				
ω^2V	1.27	-	1.64	-
ω^2CL	0.57	-	0.53	-
CorrV-CL	0.73	-	0.71	-
Residual variability (σ)				
Stdev0	0.34	12.7	0.34	0.24–0.44

Abbreviations: CV%, percent confidence of variation; CI, confidence interval; tvKa, typical value of absorption rate constant; tvV, typical value of central compartment distribution; tvCL, typical value of central compartment clearance; ω^2V, variance of the interindividual variability of V; ω^2CL, variance of the interindividual variability of CL; CorrV-CL, correlation between random effects for V and CL; stdev, standard deviation.

The goodness-of-fit plots for the final model, which are displayed in Figures 2 and 3, demonstrate that the observed concentrations are in alignment with the population predictions (PRED) and individual predictions (IPRED). The distribution of conditional weighted residuals (CWRES) over time and against predictions is shown to be normal. The estimated covariates and bootstrap replicates, presented in Tables 2 and 3, indicate that the final model possesses adequate stability. Furthermore, in the pcVPC diagrams depicted in Figure 4, the majority of the observed data points are found within the 95% prediction intervals, signifying a robust model performance.

Monto Carlo simulations

The once-daily NIR regimen is considered inappropriate because the probability of the once-daily NIR regimen reaching in vitro EC_{90} is lower than that of the twice-daily NIR regimen (Figure 5). Second, RIT needs to be administered twice a day, which complicates dosing and potentially increases the chance of noncompliance.

The initial dosing regimen for critically ill patients is based on the expectation of EC_{90} more than 90% from C_{trough} of the very first dose. The maintenance dose is adjusted based on the expectation of EC_{90} more than 95% for steady-state

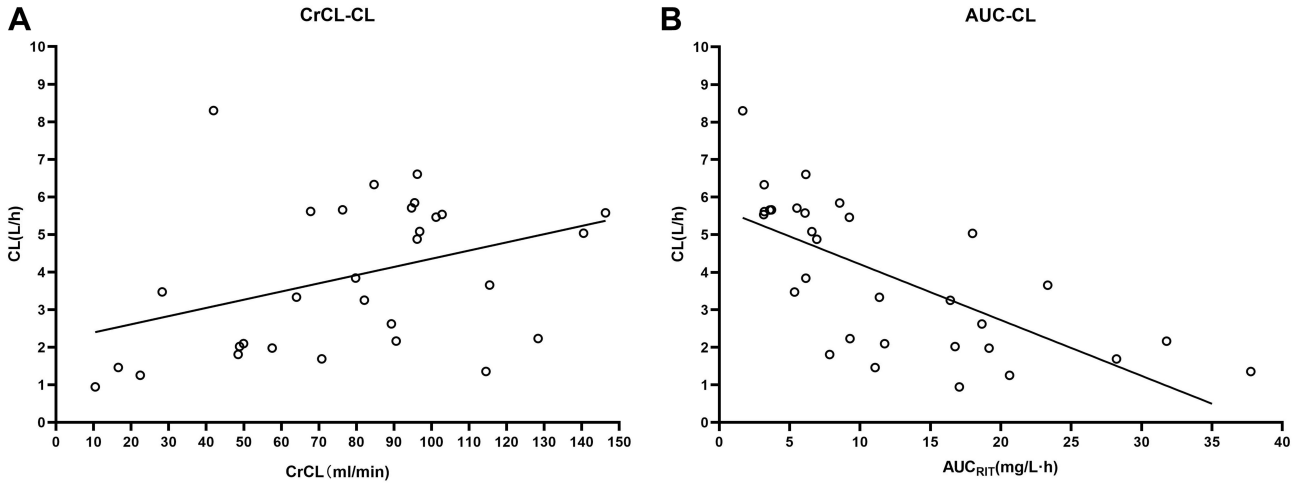

Figure 1 Linear regression plots of individual nirmatrelvir CL/F. (**A**) The relationship between NIR vs CrCL; (**B**) The relationship between NIR vs AUC of RIT.
Abbreviations: CL/F, apparent clearance of drug; CrCL, Creatinine clearance, calculated using the CKD-EPI equation; AUC, area under curve of ritonavir base on 100mg.

Table 3 Parameters Estimates, Bootstrap Medians, and Confidence Intervals for Nirmatrelvir

Parameter	Final Model		Bootstrap of Final Model	
	Estimate, Mean	CV, %	Estimate, Median	95% CI
tvKa, h^{-1}	0.42	24.9	0.61	0.09–085
tvV, L	36.5	23.3	34.0	5.5–60.5
tvCL, L/h	3.6	7.1	3.2	2.6–3.7
dCLdCrCL	0.53	21.7	0.58	0.23–1.15
$dCLdAUC_{RIT}$	−0.45	−18.0	−0.44	−0.62-(−0.10)
Inter-individual variability				
ω^2V	0.64	-	0.60	-
ω^2CL	0.086	-	0.086	-
CorrV-CL	0.12	-	0.12	-
Residual variability (σ)				
stdev	0.26	17.4	0.26	0.16–0.37

Abbreviations: CV%, percent confidence of variation; CI, confidence interval; tvKa, typical value of absorption rate constant; tvV, typical value of central compartment distribution; tvCL, typical value of central compartment clearance; dCLdCrCL, fixed parameter coefficient of creatinine clearance (CrCL, mL/min/1.73m^2) to CL; $dCLdAUC_{RIT}$, fixed parameter coefficient of ritonavir concentration (RIT, mg/L·h) to CL; ω^2V, variance of the interindividual variability of V; ω^2CL, variance of the interindividual variability of CL; CorrV-CL, correlation between random effects for V and CL; stdev, standard deviation.

C_{trough}. The recommended dosage regimen for critically ill patients with various CrCL and AUC_{RIT} is presented in Table 4. The steady-state C_{peak} of all recommended dosage regimen was lower than NOAELs.

Discussion

The current study describes the pharmacokinetic profile of NIR/RIT in critically ill patients and establishes the dosing regimen for NIR to achieve the target probability. In a phase I study, the Ka, V/F and CL/F of NIR in healthy adults aged 18–60 were reported as 1.11 h^{-1}, 111 L, 8.2 L/h, respectively.[8] In contrast, our study observed these parameters in in critically ill patients to be 0.42 h^{-1}, 36.6 L and 3.6 L/h. Notably, the majority of our patient cohort (81.2%) exceeded 60 years of age. A population pharmacokinetic study of NIR/RIT in Chinese patients aged 60 and above indicated typical patient parameters of 0.776 h^{-1}, 39.1 L and 4.16 L/h for Ka, V/F and CL/F of NIR, respectively.[10]

Secondly, Bayesian feedback analysis applied to our critically ill patients, based on established population pharmacokinetics, revealed the AUC for a 300mg dose of NIR was 107.1 μg·h/mL, approximately five times higher than that observed in Chinese and Western young adult volunteers.[8,11] In healthy young adults administered a large dose of NIR/RIT (2250mg/100mg) once, the V/F, CL/F and AUC of NIR were 40.06 L, 3.97 L/h and 188.2 μg·h/mL, respectively, with significantly lower V/F and CL/F compared to normal dose.[8] This suggests that NIR may exhibit non-linear pharmacokinetic properties with a substantial dose escalation and AUC increase. However, due to the limited dosage range of NIR, we were unable to confirm the presence of non-linear pharmacokinetic properties of NIR at therapeutic doses. A single-compartment compartment model with first-order absorption and elimination was utilized as the structural model to prevent overparameterization of the fit.

In combination with RIT, the primary elimination pathway of NIR shifts from liver to kidney. Consistent with previous studies,[5,10] as CrCL decreases, the CL/F of NIR diminishes, thus considered a a covariate of CL/F. This study is the first to construct AUC_{RIT} as covariate described the pharmacokinetics of NIR. No crossover pharmacokinetic trials evaluating NIR with varying doses of RIT were identified in the literature. Among other protease inhibitors that require RIT boosting, saquinavir[12] and fosamprenavir[13] were equally boosted by lower (50–100mg) and higher doses of RIT, whereas indinavir,[14] tipranavir[15] and lopinavir[16] responded better to higher RIT doses.

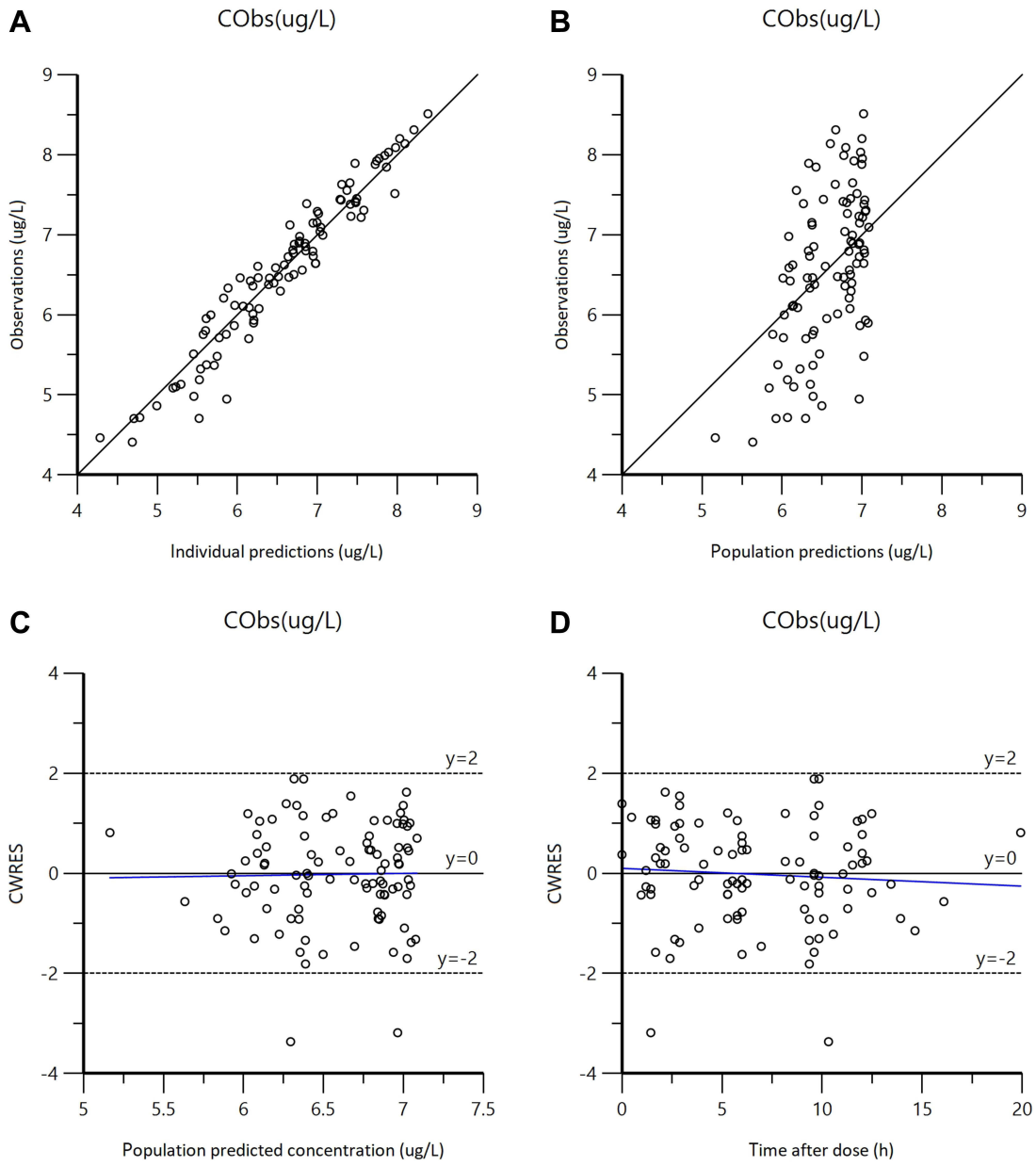

Figure 2 Goodness-of-fit plots for the final population pharmacokinetic model of ritonavir. (**A**) Observed versus individual predicted concentrations (DV vs IPRED); (**B**) Observed versus population predicted concentration (DV vs PRED); (**C**) Conditional weighted residuals versus population predicted concentrations (CWRES vs PRED); (**D**) Conditional weighted residuals versus time after dose (CWRES vs TAD); The reds lines in panels (**C** and **D**) represent smoothed regression lines.

Hepatic impairment may influence the pharmacokinetic parameters of NIR and RIT. A Phase 1 study evaluating mild to moderate hepatic impairment indicated that the median plasma concentration and AUC of NIR were comparable to those with normal hepatic function.[17] Additionally, aging is known to reduce the function of P-gp[18] and CYP3A4,[19] which are relevant for NIR disposition. In our study, the number of young patients and hepatic impairment patients were insufficient to assess the impact of age and liver function on NIR pharmacokinetic parameters. Concurrent administration of voriconazole, dexamethasone, methylprednisolone and omeprazole can induce or inhibit CYP3A4/5 or P-gp activity, potentially interacting with NIR. Ritonavir, a strong inhibitor of CYP3A4/5 and P-gp, may obscure the induction or inhibition effects of other drugs.

In the NIR/RIT combination tablets, the inhibitory effect of RIT on NIR metabolism is achieved at a dose of 100mg. Given the absence of published CYP3A inhibitory IC50 for RIT against NIR, we maintained our simulation based on a RIT dose of 100mg twice daily.[20] a common regimen for boosting protease inhibitors.

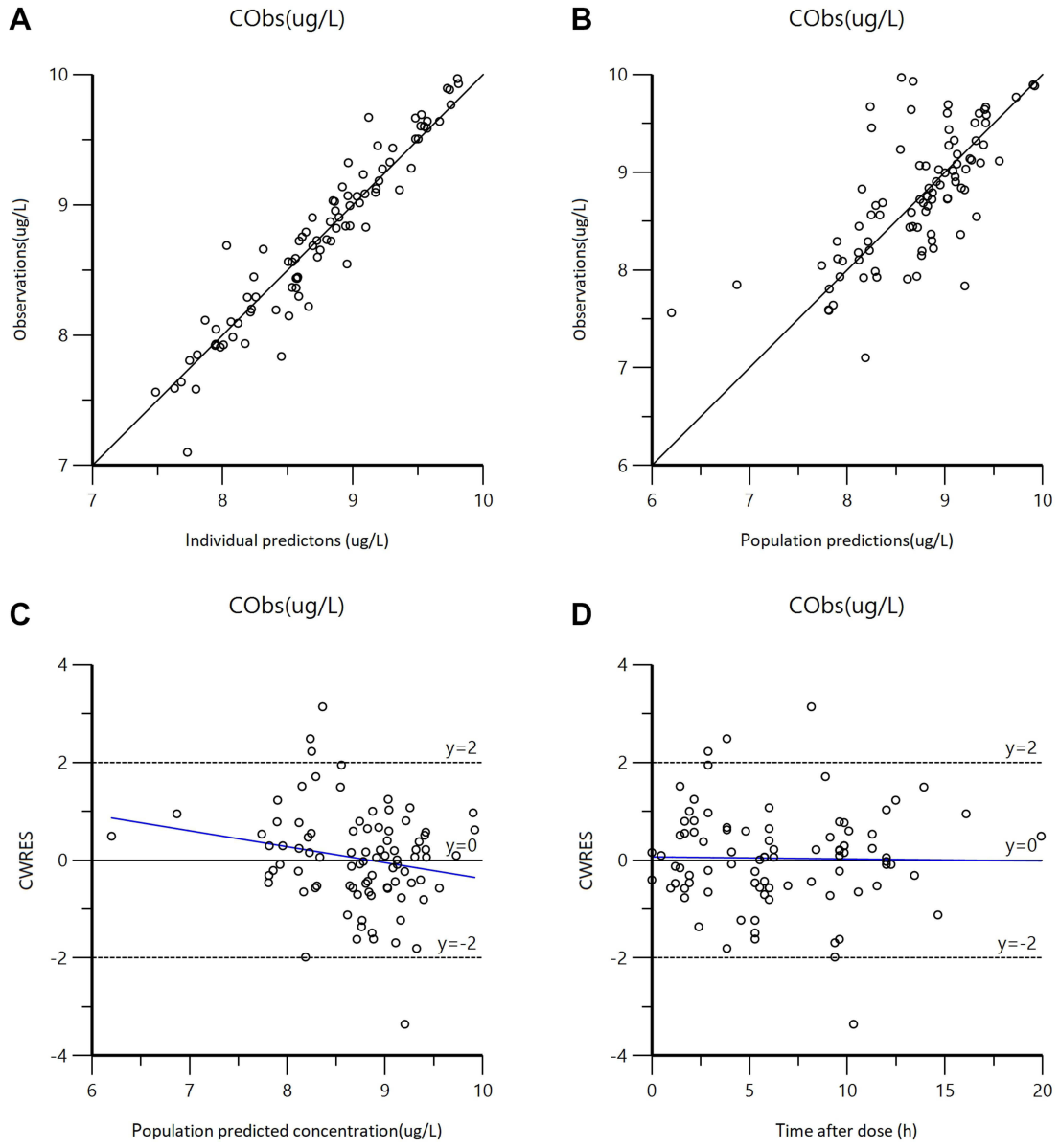

Figure 3 Goodness-of-fit plots for the final population pharmacokinetic model of nirmatrelvir. (**A**) Observed versus individual predicted concentrations (DV vs IPRED); (**B**) Observed versus population predicted concentration (DV vs PRED); (**C**) Conditional weighted residuals versus population predicted concentrations (CWRES vs PRED); (**D**) Conditional weighted residuals versus time after dose (CWRES vs TAD); The reds lines in panels (**C** and **D**) represent smoothed regression lines.

Free exposure to NIR remained multiple times above in virto EC_{90} (90.5ng/mL, 181 nM),[1] providing a potential barrier against resistance development and proven antiviral efficacy.

With approximately 70% protein binding, the total EC_{90} for NIR is 292 ng/mL.[1,21] Base on previous research, the concentration at 12h postdose (C_{trough}) above efficacious concentration in >90% of simulation for the very first dose, and >95% of simulation for the steady-state.[1,8] According to the simulation results, the median C_{trough}>5.7 times the total EC_{90} at steady-state, which was similar to the Phase 1 study for NIR/RIT dosing regimen selection.

While this study presents valuable findings, several limitations are acknowledged. Due to the small sample size and the sporadic nature of sampling, our analytical approach was confined to employing a one-compartment model, which simplifies the representation of NIR's complex pharmacokinetic profile. Our efforts to explain the elevated levels of NIR exposure observed in critically ill patients included a thorough consideration of factors such as age and the implications of non-linear pharmacokinetics. Despite these efforts, there is a clear need for further in-depth research. This additional

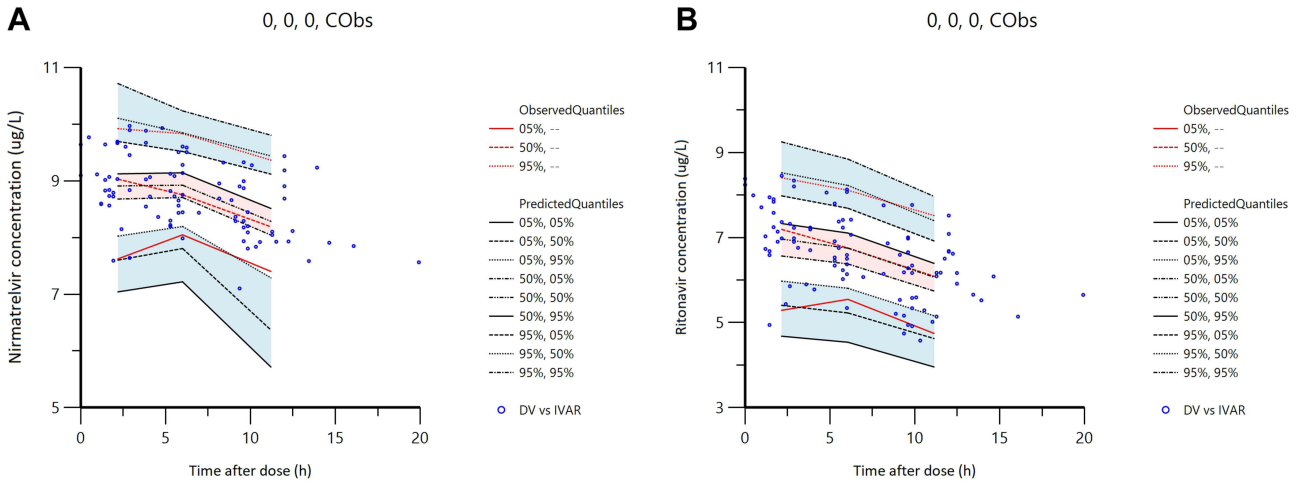

Figure 4 Prediction-corrected visual predictive check of the final model. (**A**) Prediction-corrected visual predictive check for Nirmatrelvir; (**B**) Prediction-corrected visual predictive check for ritonavir.

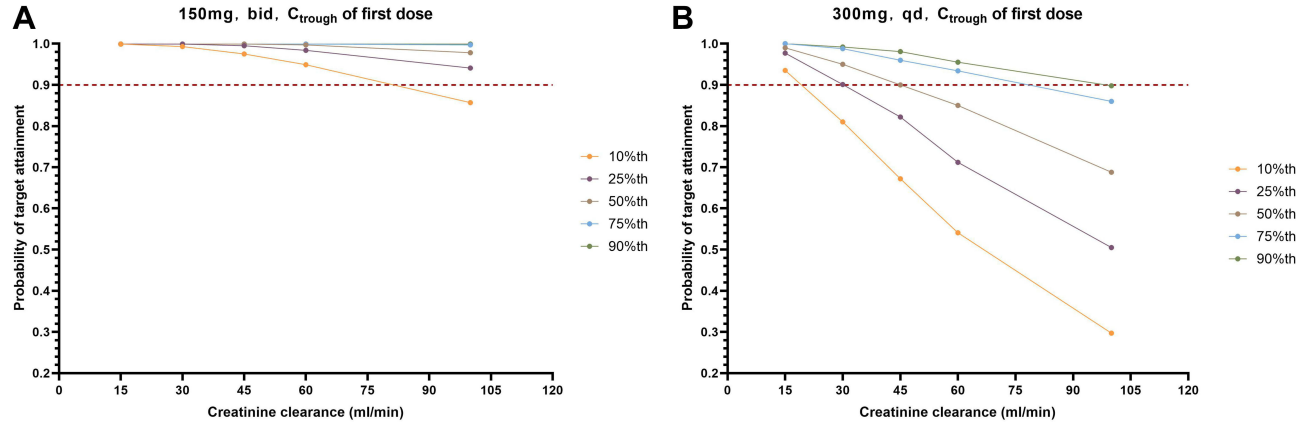

Figure 5 Probability of target attainment for (**A**) nirmatrelvir/ritonavir 150mg/100mg twice a day and (**B**) nirmatrelvir/ritonavir 300mg once a day, 100mg twice a day.

work will be crucial for achieving a more profound comprehension of the observed phenomena and for significantly enhancing our understanding of how NIR behaves pharmacokinetically within the context of diverse patient populations, particularly those who are critically ill.

Table 4 Recommendation of Nirmatrelvir Dosage by Monte-Carlo Simulation Based on Ritonavir 100mg Twice a Day

CrCL [a]	Initial Treatment	Dose adjustment for AUC_{RIT} [b]			
		≥3.2–5.8	≥5.8–9.2	≥9.2–17.5	≥17.5–23.3
≥15–30	150mg, bid	150mg, bid	75mg, bid	75mg, bid	75mg, bid
>30–45	150mg, bid	150mg, bid	75mg, bid	75mg, bid	75mg, bid
>45–60	300mg, bid	300mg, bid	150mg, bid	75mg, bid	75mg, bid
>60	300mg, bid	300mg, bid	300mg, bid	150mg, bid	75mg, bid

Notes: [a]CrCL, creatinine clearance, CKD-EPI equation, mL/min. [b]AUC_{RIT}, area under curve of ritonavir, mg/L·h.

Conclusion

This study enrolled 31 critically ill patients, providing insights into the pharmacokinetics of NIR/RIT. A one-compartment model was developed, identifying CrCL and AUC_{RIT} as covariates for CL of NIR. In our study, NIR significantly reduced CL/F and V/F in critically ill patients compared to healthy young volunteers. Based on our dosing simulations, NIR/RIT was 300mg/100mg twice a day in critically ill patients with CrCL>45 mL/min; When CrCL in critically ill patients is between 15–45 mL/min, NIR/RIT is 150mg/100mg twice a day. The maintenance dose is adjusted according to CrCL and AUC_{RIT}, with the dosage varying between 75mg/100mg and 300mg/100mg. Despite valuable findings, the study's small sample size and sparse sampling limit the generalizability of the results, highlighting the need for larger, more comprehensive studies.

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Zhejiang University School of Medicine (No. IIT20230056B). The patients/participants provided their written informed consent to participate in this study. This study was in compliance with Declaration of Helsinki.

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

All authors declare that they have no competing interests.

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