Developing SARS-CoV-2 viral dynamic model in patients with COVID-19 based on amount of viral RNA and viral titer

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Introduction

- Some viral dynamic models for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported [1-5], however these studies mainly used patients' data in early phase of the pandemic and only the information on the amount of viral RNA (viral load), including both the infectious and non-infectious virus data.
- The environment surrounding this infection has dramatically changed from early phase, such as most people have been vaccinated for coronavirus disease 2019 (COVID-19) [6-9] and the change of major SARS-CoV-2 variants [10].
- We have obtained observed viral load and viral titer from patients with COVID-19 in the clinical trial for ensitrelvir (product code S-217622) [11-14], and the circumstance in our clinical trial would reflect that in current clinical practice during the Omicron epidemic.
- The aims of this study are to develop SARS-CoV-2 viral dynamic model using observed viral load and viral titer and to explore the covariates that have an impact on the viral dynamics.

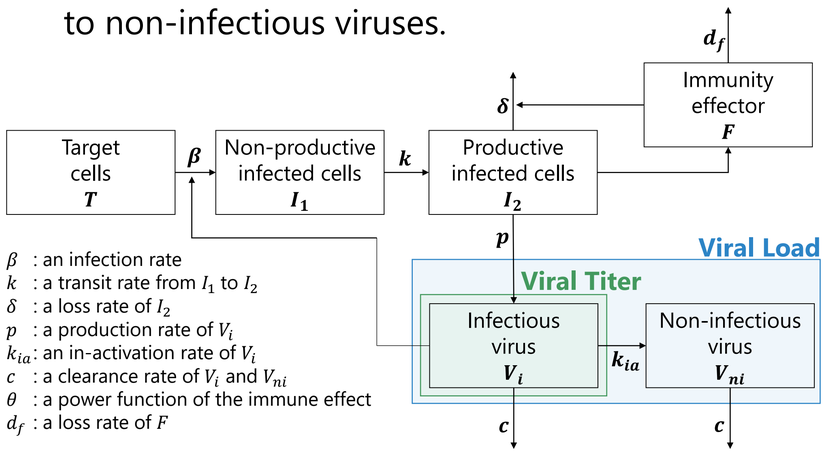
Methods

Clinical Trial Data

- Data from the placebo group in the phase 2/3 study (phase 2a, 2b, and 3 parts) for ensitrelvir [12-14] were used for our study.
  - ✓ The patients with mild-to-moderate COVID-19 based on the US Food and Drug Administration guidance [15] and who tested positive for SARS-CoV-2 within 120 hours prior to randomization were collected.
  - ✓ The investigated intrinsic or extrinsic factors in the patients (e.g. age, history of vaccination, and SARS-CoV-2 variants) were collected.
  - ✓ The time from symptom onset to randomization was reported as categorical data every 24 hours, and the median value for each category was used in our analysis.

Viral Dynamic Model and Parameter Estimation

- Our model (Figure 1) modified the previous target cell-limited model with immune function [1] to characterize SARS-CoV-2 dynamics and immune reactions for the infection.
  - ✓ Our model assumed that "productive infected cells" produce only infectious viruses (viral titer) and then some infectious viruses transit to non-infectious viruses.



Model equation

$$\frac{dT}{dt} = -\beta V_i T$$
$$\frac{dI_1}{dt} = \beta V_i T - kI_1$$
$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$
$$\frac{dV_i}{dt} = pI_2 - k_{ia}V_i - cV_i$$
$$\frac{dV_{ni}}{dt} = k_{ia}V_i - cV_{ni}$$
$$\frac{dI_2}{dt} = kI_1 - \delta(1 + F^{\theta})I_2$$
$$\frac{dF}{dt} = I_2 - d_f F$$

Figure 1 Scheme of the viral dynamic model for SARS-CoV-2.

- The dynamic parameters were estimated using both observed data.
  - ✓ Only post symptom onset data were available, so the time from infection to symptom onset (T_{inf}) was estimated in each patient based on the viral dynamics.
  - ✓ The investigated intrinsic or extrinsic factors in the patients were evaluated to identify the covariates which affect the dynamics.
  - ✓ The model structure and covariates were selected based on Bayesian information criterion and visual prediction accuracy.
  - ✓ The parameter estimation was performed by the likelihood maximized using the stochastic approximation expectation–maximization algorithm implemented in NONMEM ver.7.4.4 [16].

Results

Analysis Data

- Consecutive 3330 viral load and 3332 viral titer data from 464 patients with COVID-19 were obtained and we used only observed data above the limit of quantitation for our analysis (Figure 2).
- The analysis population included patients aged 13 to 69 years old who were mainly vaccinated (90.1%) and infected with Omicron variant (91.6%).

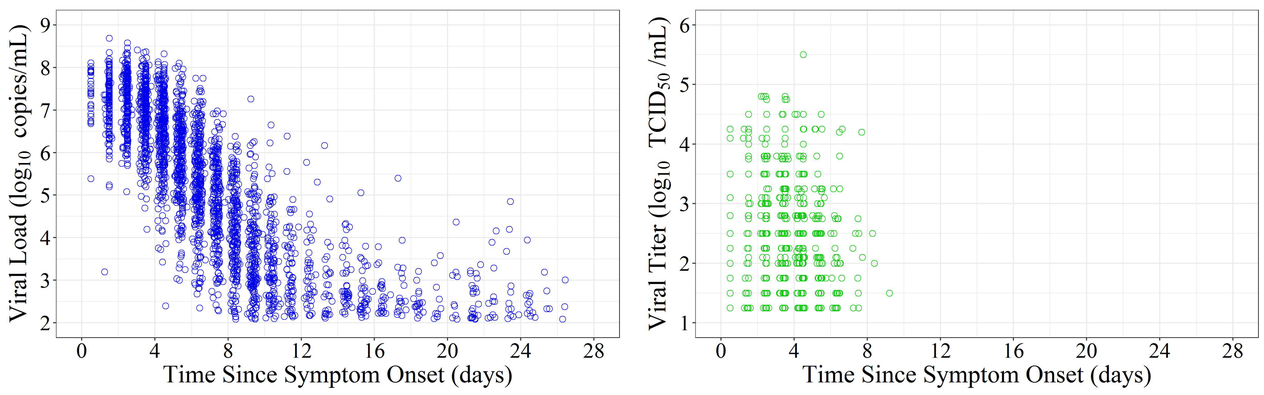


Figure 2 Observed data of viral load (left) and viral titer (right).

Parameter Estimation

- Estimated model parameters were shown in Table 1.
- Vaccination status was identified as a significant covariate for T_{inf} and the immune function parameter (θ).
  - ✓ T_{inf} of the unvaccinated patients was estimated as 2.8 days and shorter than that of the vaccinated patients (3.3 days).
  - ✓ Immune strength (the elimination rate of infected cells) in the vaccinated patients was 1.1 times stronger than that in the unvaccinated patients.

Table 1 Estimated model parameters.

Parameters	Units	Values (RSE)
$T_{inf\_Unvaccinated}$	day	2.8 (8%)
$T_{inf\_Vaccinated}$	day	3.3 (7%)
β	day^{-1}	1.50×10^{-3} (12%)
p	day^{-1}	3.34×10^{3} (41%)
δ	day^{-1}	0.0220 (85%)
k	day^{-1}	3 fixed
c	day^{-1}	3.76 (15%)
k_{ia}	day^{-1}	9.09×10^{4} (37%)
$\theta_{Unvaccianted}$	-	0.315 (23%)
$\theta_{Vaccianted}$	-	0.335 (20%)
d_f	day^{-1}	0.4 fixed
BSV_T_{inf}	%	14.0 (14%)
BSV_p	%	14.1 (27%)
BSV_θ	%	8.1 (59%)
RUV_load	$\log_{10}$ copies/mL	0.653 (3%)
RUV_titer	$\log_{10}$ $TCID_{50}$/mL	0.910 (4%)

RSE: Relative standard error (accuracy of parameter estimates).
BSV: Between subject variability.
RUV: Residual unidentified variability.

Model Diagnosis

- The model prediction was evaluated visually.
  - ✓ The individual predicted values were approximately similar to the observed values (Figure 3).
  - ✓ The results of simulations using estimated model parameters were well described both observed dynamics of viral load and viral titer (Figure 4).

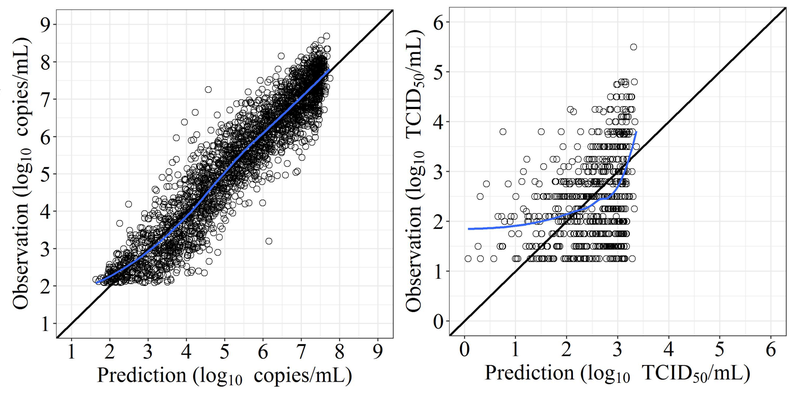
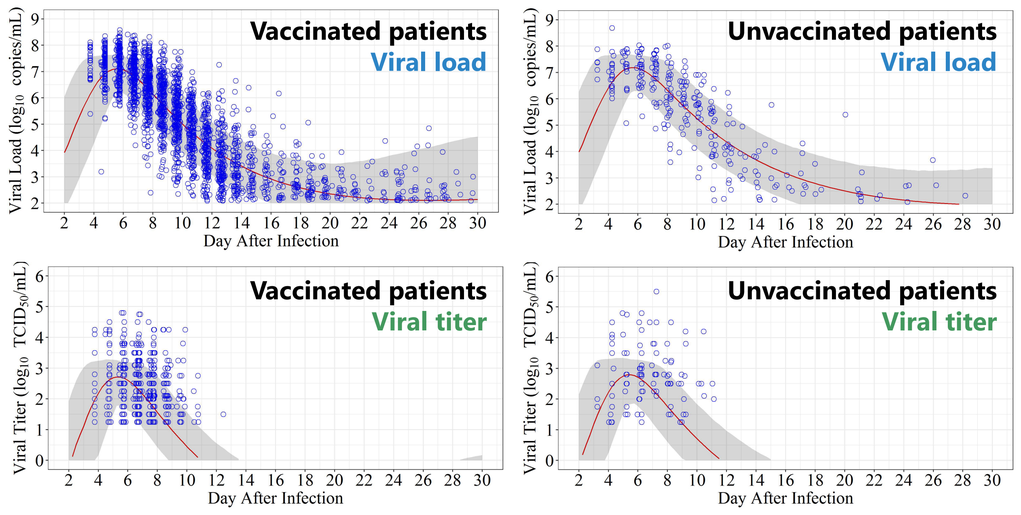


Figure 3 Goodness of fit plots for viral load (left) and viral titer (right).



Viral simulations were perfumed each 1000 virtual vaccinated and unvaccinated patients.

Red lines represent mean values.
Gray-shaded areas represent 90% percentile intervals.

Figure 4 Comparison of observed values and simulated results.

Conclusion

- We characterized the SARS-CoV-2 dynamics using both viral load and viral titer in the population who mainly included vaccinated and Omicron-infected patients.
- Our model allows to predict the viral dynamics in patients with COVID-19, including the time from infection to onset.
- Vaccination status was identified as a factor influencing the time from infection to symptom onset and the immune function.

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31st Population Approach Group in Europe, 28-30 June, 2023, A Coruña, Spain