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ARTICLE

Association between SARS-CoV-2 viral kinetics and clinical score evolution in hospitalized patients

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Abstract

The role of antiviral treatment in coronavirus disease 2019 hospitalized patients is controversial. To address this question, we analyzed simultaneously nasopharyngeal viral load and the National Early Warning Score 2 (NEWS-2) using an effect compartment model to relate viral dynamics and the evolution of clinical severity. The model is applied to 664 hospitalized patients included in the DisCoVeRy trial (NCT04315948; EudraCT 2020-000936-23) randomly assigned to either standard of care (SoC) or SoC + remdesivir. Then we use the model to simulate the impact of antiviral treatments on the time to clinical improvement, defined by a NEWS-2 score lower than 3 (in patients with NEWS-2 <7 at hospitalization) or 5 (in patients with NEWS-2 ≥7 at hospitalization), distinguishing between patients with low or high viral load at hospitalization. The model can fit well the different observed patients trajectories, showing that clinical evolution is associated with viral dynamics, albeit with large interindividual variability. Remdesivir antiviral activity was 22% and 78% in patients with low or high viral loads, respectively, which is not sufficient to generate a meaningful effect on NEWS-2. However, simulations predicted that antiviral activity greater than 99% could reduce by 2 days the time to clinical improvement in patients with high viral load, irrespective of the NEWS-2 score at hospitalization, whereas no meaningful effect was predicted in patients with low viral loads. Our results demonstrate that time to clinical improvement is associated with time to viral clearance and that highly effective antiviral drugs could hasten clinical improvement in hospitalized patients with high viral loads.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral dynamics is associated with risk of death in hospitalized patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

We address the association between SARS-CoV-2 viral dynamics and clinical evolution in hospitalized patients.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

We modeled the association between viral dynamics and clinical evolution, relying on the National Early Warning Score 2 score. Our model can be used to predict the impact of antiviral treatment on time to recovery as well as identifying patients that could most benefit from therapy.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The model can be used to bridge virological and clinical dynamics and anticipate the clinical benefit of an antiviral treatment.

INTRODUCTION

Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, many studies have been published on the association between viral loads and outcomes in hospitalized patients, particularly the relation between high viral loads at admission and risk of death.[1–3] Using a joint model linking viral dynamics and the instantaneous hazard of death, we previously demonstrated that not only the viral load at hospital admission but also the whole viral dynamics after admission was associated with the risk of death. This association

was particularly strong in high-risk patients, that is, those 65 years or older, male, or with chronic pulmonary disease.[4] Accordingly, we projected that strategies that accelerate viral clearance (e.g., antiviral drugs) could reduce mortality, in particular in these patients.[5] However, the clinical benefit of antiviral treatments in hospitalized patients remains controversial, with no studies showing an indisputable clinical benefit of antiviral treatments in hospitalized patients.

Clinical evolution in hospitalized patients can be followed using several scores. One of them is the National Early Warning Score (NEWS-2), developed to standardize the identification process of patient deterioration in different clinical contexts.[6–8] In the context of coronavirus disease 2019 (COVID-19), the National Institute for Health and Care Excellence and the World Health Organization recommended the use of the NEWS-2 score to routinely monitor hospitalized patients to identify as early as possible those who may deteriorate.[9,10] NEWS-2 evaluates six physiological parameters: respiratory rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness, and temperature. Each parameter is scored from 0 to 3, and the sum gives a global score ranging from 0 to 20 (the lower the better).

In this study, we developed a model to characterize the association between viral kinetics and NEWS-2 scores evolution using data from the European randomized controlled DisCoVeRy trial.[11,12] Data on viral loads were centralized and normalized to ensure consistency throughout centers, and NEWS-2 scores were collected daily from patient inclusions to hospital discharge by clinicians. We used the model to characterize the impact of viral dynamics on disease evolution and to identify profiles that could most benefit from effective antiviral treatments.

PATIENTS AND METHODS

Study design and data collection

Hospitalized adult patients, with a laboratory-confirmed SARS-CoV-2 infection, were enrolled in the DisCoVeRy trial (NCT 04315948; EudraCT 2020-000936-23),[12] sponsored by the Institut national de la santé et de la recherche médicale (Inserm), with written informed consent from all of them (or their legal representatives if unable to consent). We analyzed the results obtained from patients allocated to receive either standard of care (SoC) alone or SoC plus remdesivir between March 2020 and January 2021 and hospitalized in 48 different sites from France, Belgium, Portugal, Austria, and Luxembourg and for whom nasopharyngeal swabs were available. Remdesivir was administered intravenously at a loading dose of 200 mg on Day 1 followed by 100 mg infusions once daily for up to 10 days. More details on study design, ethics approval, and inclusion/exclusion criteria can be found in a previous publication.[12] Importantly, these data were collected before the emergence of variants of concern and before vaccination.

Viral load and NEWS-2 scores

Normalized viral loads in nasopharyngeal swabs were measured at randomization and at Days 3, 5, 8, 11, 15 ± 2, and 29 ± 3. The normalized SARS-CoV-2 viral load was determined by real-time quantitative reverse transcriptase polymerase chain reaction blinded to treatment arm, divided by the number of cells measured (quantification of *hypoxanthine phosphoribosyltransferase 1* housekeeping gene), and expressed in copies per 10^4 cells. All samples were centralized and analyzed in the same laboratory at the National Centre for Viral Respiratory Infections (Hospices Civils de Lyon) and the limit of detection was estimated at 1 $\log_{10}$ copies/10^4 cells.[13]

The clinical course was assessed using NEWS-2, measured daily from randomization to discharge, as well as on Day 15 and Day 29 in patients that were discharged before. We used the NEWS-2 cutoff value of 7 to define the degree of clinical severity at hospitalization. Patients with NEWS-2 scores lower than 7 were considered to have a low risk of clinical deterioration, and patients with NEWS-2 scores greater or equal than 7 were considered to have a high risk of clinical deterioration.[7–14]

Viral kinetics/NEWS-2 dynamics model

Model equations

We developed a model to characterize the relationship between the viral dynamics and NEWS-2. For that, viral load and NEWS-2 data were fitted simultaneously and NEWS-2 measurements were treated as a continuous quantitative variable.

Viral load data were described by a target-cell limited model with an eclipse phase previously described in Lingas et al.[13] This model assumes that target cells are infected at a constant rate β. Once infected, cells enter an eclipse phase and become productively infected at a rate k and are cleared at a rate δ. We assumed that an age above or below 65 years of age on the δ parameter, as previously published.[4] Infected cells produce viral particles per day at rate p but only a fraction of them μ, are infectious. Viral particles, infectious viral particles (V_i), and noninfectious viral particles (V_{ni}), are cleared at the same rate c.

The equations describing the viral dynamic model are as follows:

$$\frac{dT}{dt} = -\beta V_i T$$

$$\frac{dI_1}{dt} = \beta V_i T - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2 \quad (1)$$

$$\frac{dV_i}{dt} = p\mu I_2 - cV_i$$

$$\frac{dV_{ni}}{dt} = p(1-\mu)I_2 - cV_{ni}$$

The basic reproductive number R_0, defined by the number of secondary infected cells resulting from one infected cell in a population of fully susceptible cells, T_0, is defined by $R_0 = \frac{\beta p T_0 \mu}{c\delta}$, infected cells in an eclipse phase (I_1) and productively infected cells (I_2).

To link the viral load to NEWS-2, we added a compartment effect model (E), assuming that the NEWS-2 variation is driven by the viral load into E.

The relationship is expressed as follows:

$$\frac{dE}{dt} = k_{1e}\left(V_i + V_{ni}\right) - k_{e0}E \quad (2)$$

k_{1e} is the rate transfer constant between viral load and the hypothetical compartment effect, and k_{e0} represents the rate loss constant from the effect compartment. We assumed for simplification that $k_{1e} = k_{e0}$.

The NEWS-2 evolution was associated to viral load evolution over time using a Hill model between the two variables. In this model, we assumed that NEWS-2 could vary between a baseline value (N_0), which corresponds to the score before infection, and 20, which is the maximum value. The equation for the relationship between NEWS-2 and log viral load (LVL) is:

$$\text{NEWS} - 2 = N_0 + \left(20 - N_0\right) \times \frac{\left(\log_{10}E\right)^n}{\left(\log_{10}E\right)^n + \text{LVL}_{50}{}^n} \quad (3)$$

where LVL_{50} is the log viral load value leading to 50% of maximal NEWS-2, and n is the Hill coefficient that determines the steepness of the viral load/NEWS-2 relationship.

The remdesivir effect has been modeled as follows: remdesivir reduces viral production p by a factor ε, a parameter between 0 (no activity) and 1 (full viral suppression), leading to the following equation:

$$\frac{dV_i}{dt} = (1-\varepsilon)p\mu I_2 - cV_i \quad (4)$$

$$\frac{dV_{ni}}{dt} = (1-\varepsilon)p(1-\mu)I_2 - cV_{ni}$$

Assumptions on parameter values

At the time of infection, we assumed that there is exactly one productively infected cell I_2 in the entire nasopharyngeal tract, thus $T = T_0$, $I_1 = 0$, $I_2 = 1$, $V_i = 0$, and $V_{ni} = 0$; the initial number of target cells, T_0, was fixed at 4×10^6 cells. We used a scaling factor, f, to convert V into a normalized viral load and we note $V_{obs} = f \times V$. As only the parameter $p \times f$ can be estimated, we assumed without loss of generality that the proportion of susceptible cells in the biological sample was on average 10-fold lower than in the nasopharyngeal compartment, that is, 0.1%. Thus, we fixed f to $\frac{10^{-3} \times 10^4}{4 \times 10^6} = 2.5 \times 10^{-6}$. We also fixed the k, c, and μ parameters at 4 days^{-1}, 10 days^{-1}, and 10^{-4}, respectively, based on previous studies.[4,15,16] Time of infection was estimated, assuming a prior lognormal distribution for the incubation period with a median time of 5 days and a standard deviation of 0.125, meaning that 90% of patients have an incubation period ranging between 4 and 6 days. We also fixed the interindividual variability of R_0 to 50%. N_0 was bounded from 0 to 3 using a logistic-type transformation, consistent with the fact that patients had to be nonhospitalized prior to SARS-CoV-2 infection.

Parameter estimation and fitting assessment

All biological parameters were assumed to follow a lognormal distribution, whereas the treatment efficacy parameter was assumed to follow a logistic distribution to ensure values between 0 and 1. We used an additive error model for the log viral load as previously described, and we tested different error models (additive, proportional, and combined) for the NEWS-2 scores.

The parameters were estimated using the stochastic approximation expectation maximization algorithm implemented in Monolix2020R1 (http://www.lixoft.eu). The Fisher information matrix, log likelihood, and Bayesian information criterion (BIC) were obtained without approximation (no linearization method). The BIC value was used to discriminate between hierarchical models.

Effects on individual characteristics

Relying on the model given by Equation (1) and using only data from the SoC arm, we analyzed the effects of risk factors on both viral and NEWS-2 dynamics. We focused on covariates identified in a large cohort study of

hospitalized patients only using data from patients with less than 10% missing values and who belonged to patient groups representing more than 10% prevalence in our data.[17] Thus, only data from the following patient groups were analyzed: age ≥ 65, male sex, presence of chronic cardiac disease, presence of chronic pulmonary disease, and obesity. These covariates were screened using empirical Bayes estimates (EBEs) of individual parameters using nonparametric tests, and only covariates with $p < 0.1$ were evaluated in the model. Among the selected covariates, a forward procedure was applied, and $p < 0.05$ was considered statistically significant.

Once the covariate model was built, we assessed a specific effect of remdesivir on NEWS-2 parameters that would not be modulated by viral load. Using the same approach as before, an effect of remdesivir on NEWS-2 parameters was evaluated only if the EBE of individual parameters were different between the two arms (Wilcoxon test). If the difference was statistically significant ($p < 0.05$), the treatment effect on this parameter was then tested in the model.

Impact of antiviral treatment on NEWS-2 score

Finally, we used the model to assess the impact of antiviral treatment on the NEWS-2 score. We used the estimated parameter values to simulate 5000 individual profiles without antiviral treatment keeping the same sex (male) and age (<65 years old) proportions as in the studied population. We then considered fixed antiviral efficacies of 80%, 90%, 99%, and 99.9%, assuming a treatment initiation time sampled from the fitted Gamma distribution of observed times between infection and randomization in the population. For each scenario and for each simulated individual, we then calculated the time to obtain a score lower than 3 (for simulated individuals with NEWS-2 <7 at randomization) or 5 (for simulated individuals with NEWS-2 ≥7 at randomization) and the time to reach viral clearance since randomization. Then, we computed the cumulative incidence of the clinical improvement time for each treatment scenario and for the four different patient profiles according to the viral load (< or ≥3.5 $\log_{10}$ copies/10^4 cells) and NEWS-2 scores (< or ≥7) at randomization. These two thresholds represent the levels of viral culture[18] and risk of severe disease, respectively.[14]

Subgroup analyses

We previously demonstrated that the remdesivir effect was stronger in patients with viral loads at admission greater or equal than 3.5 $\log_{10}$ copies/10^4 cells. Thus, we performed the same analysis as described previously in two subpopulations using the cutoff of 3.5 $\log_{10}$ copies/10^4 cells as described in our previous analysis.[13]

Modeling NEWS-2 dynamics without adjusting for viral dynamics

As a means to verify that the relationship between viral load and NEWS-2 was not artefactual, we quantified to whether NEWS-2 dynamics is deteriorated when ignoring individual viral dynamics. For that purpose, we used the model including covariates to fit only NEWS-2 data, and we compared the BIC and the predictions obtained in two different scenarios: (i) individual viral load profiles were those predicted by the EBE from the final model, and (ii) individual viral load profiles were identical in all patients with individual viral parameters fixed to the mean population values from the final model. If the NEWS-2 and viral loads are independent, then one would expect the models to be equivalent in terms of fitting criterion and variability of random effects.

RESULTS

Baseline characteristics, viral load, and NEWS-2 data

From the 833 patients included in the primary modified intention-to-treat analysis, 684 had at least one nasopharyngeal viral load available (Figure S1). Among them, 20 were excluded: patients who were randomly assigned more than 20 days after symptoms onset ($N = 17$) and patients without any NEWS-2 data ($N = 3$). Consequently, a total of 664 patients (SoC alone, $N = 329$; SoC + remdesivir, $N = 335$) were included in this analysis. The majority of patients were male ($N = 456$, 68.7% of the total population) and younger than 65 years old ($N = 349$, 52.5% of the total population). The baseline characteristics of the population are summarized in Table 1.

Model parameters

The model was then applied to fit simultaneously both viral load and NEWS-2 trajectories. Viral dynamic parameters and their variability were estimated with a good precision (Table 2). The loss rate of infected cells, δ (see Patients and Methods), was estimated at 0.84 d^{-1} in individuals aged <65 years old and 0.74 d^{-1} in those ≥65 years old (Table 2). R_0 was estimated at 6.71, and the viral production, p, was estimated at 1.56×10^5 viruses per day. Following the

TABLE 1 Characteristics of the analyzed population at randomization.

Characteristics	Standard of care ($N=329$) Median (IQR) or n (%)	Standard of care + remdesivir ($N=335$) Median (IQR) or n (%)
Male sex	222 (67.5%)	234 (69.9%)
Age, y	64 (53–72)	63 (55–73)
<65	169 (51.4%)	180 (53.6%)
≥65	160 (48.6%)	155 (46.3%)
Time since symptom onset, days	9 (7–11)	9 (7–11)
Patients with viral load		
<3.5 $\log_{10}$ copies/10^4 cells	107 (32.5%)	129 (38.5%)
≥3.5 $\log_{10}$ copies/10^4 cells	91 (27.7%)	92 (27.5%)
Missing data	131 (39.8%)	114 (34.0%)
Patient NEWS-2		
<7	73 (22.2%)	97 (29.0%)
≥7	245 (74.5%)	227 (67.7%)
Missing data	11 (3.3%)	11 (3.3%)

Abbreviations: IQR, interquartile range; NEWS-2, National Early Warning Score 2.

TABLE 2 Final model population parameters of viral kinetics and NEWS-2 dynamics in the SoC and remdesivir arms.

Parameter estimates (RSE, %)		
	Parameter estimates	
Parameter	Fixed effects	SD of the random effect[a]
R_0	6.71 (5.6)	0.50 (fixed)
$\delta_{<65}$ (days^{-1})	0.84 (4.3)	0.30 (9.9)
$\delta_{\geq 65}$ (days^{-1})	0.74 (31.6)	
p (10^5 virus.cells^{-1}.days^{-1})	1.56 (22.4)	1.56 (9.4)
$k_{e0<65}$ (days^{-1})	0.82 (17.7)	1.42 (9.9)
$k_{e0\geq 65}$ (days^{-1})	0.37 (21.4)	
n	1 (8.4)	0.23 (34.6)
LVL_{50} ($\log_{10}$ RNA copies/10^4 cells)	4.81 (4.0)	0.72 (8.6)
N_0	0.86 (26.1)	3.35 (25.1)
ε (%)	22 (67.1)	2.43 (29.8)
Additive error ($\log_{10}$ RNA copies/10^4 cells)	1.23 (2.5)	–
Additive error (NEWS-2)	1.53 (2.8)	–
Proportional error (NEWS-2)	0.04 (10.5)	–

Abbreviations: LVL, log viral load; NEWS-2, National Early Warning Score 2; RSE, relative standard error; SoC, standard of care.

[a]Parameters follow a log-normal distribution except ε and N_0, which follow a logit-normal distribution, and N_0 was bound from 0 to 3.

procedure for covariate selection, only age ≥65 years old was found to be associated with a NEWS-2 dynamic parameter, k_{e0}, which was estimated at 0.82 d^{-1} for patients aged <65 years old and 0.37 d^{-1} for patients aged ≥65 years old, corresponding to a slower decrease in NEWS-2 for patients aged ≥65 years old after peak viral load. LVL_{50} was estimated at 4.81 $\log_{10}$ RNA copies/10^4 cells, and N_0 was estimated at 0.86.

Because viral load was missing in many patients at randomization, we used the model to reconstruct the virological and clinical characteristics at randomization. Overall, 37.8% of patients had high viral loads at randomization, with 9.2% having NEWS-2 <7 and 28.6% having NEWS-2 ≥7; 62.2% of patients had low viral loads at randomization, with 28.9% having NEWS-2 <7 and 42.5% having NEWS-2 ≥7.

Regarding the impact of remdesivir in the overall studied population, it reduced viral production by 22%. In patients with a high viral load at admission, remdesivir reduced viral production by 78% (95% confidence interval [CI]: 62%–89%), whereas this effect was only equal to 15% (95% CI: 3%–45%) in patients with a low viral load (Tables S1 and S2). However, we found no differences in the distribution of individual parameters characterizing the association between viral load and NEWS-2 (i.e., k_{e0} and LVL_{50}) between treated and untreated patients (Table S3), and no additional effect of remdesivir was therefore introduced in the model.

We finally assessed to what extent viral load improved the evolution of NEWS-2 (see Patients and Methods). When the individual viral load parameters were fixed, the variability of the NEWS-2 parameters was slightly reduced, but we obtained an improvement in BIC of 169 units compared with the model in which the viral load parameters were set to mean population estimates (Table S4). Visual predictive checks of the final model are not represented because to bias induced by the presence of dropouts, but by looking into the individual fits, a good description of the data is obtained by the model (Figure 1).

Antiviral treatment simulation

To get a better sense of a putative, more potent antiviral therapy impact on NEWS-2, we simulated a large cohort of individuals with the same characteristics than in the original population. Then we considered that antiviral therapy was initiated on hospital admission and capable

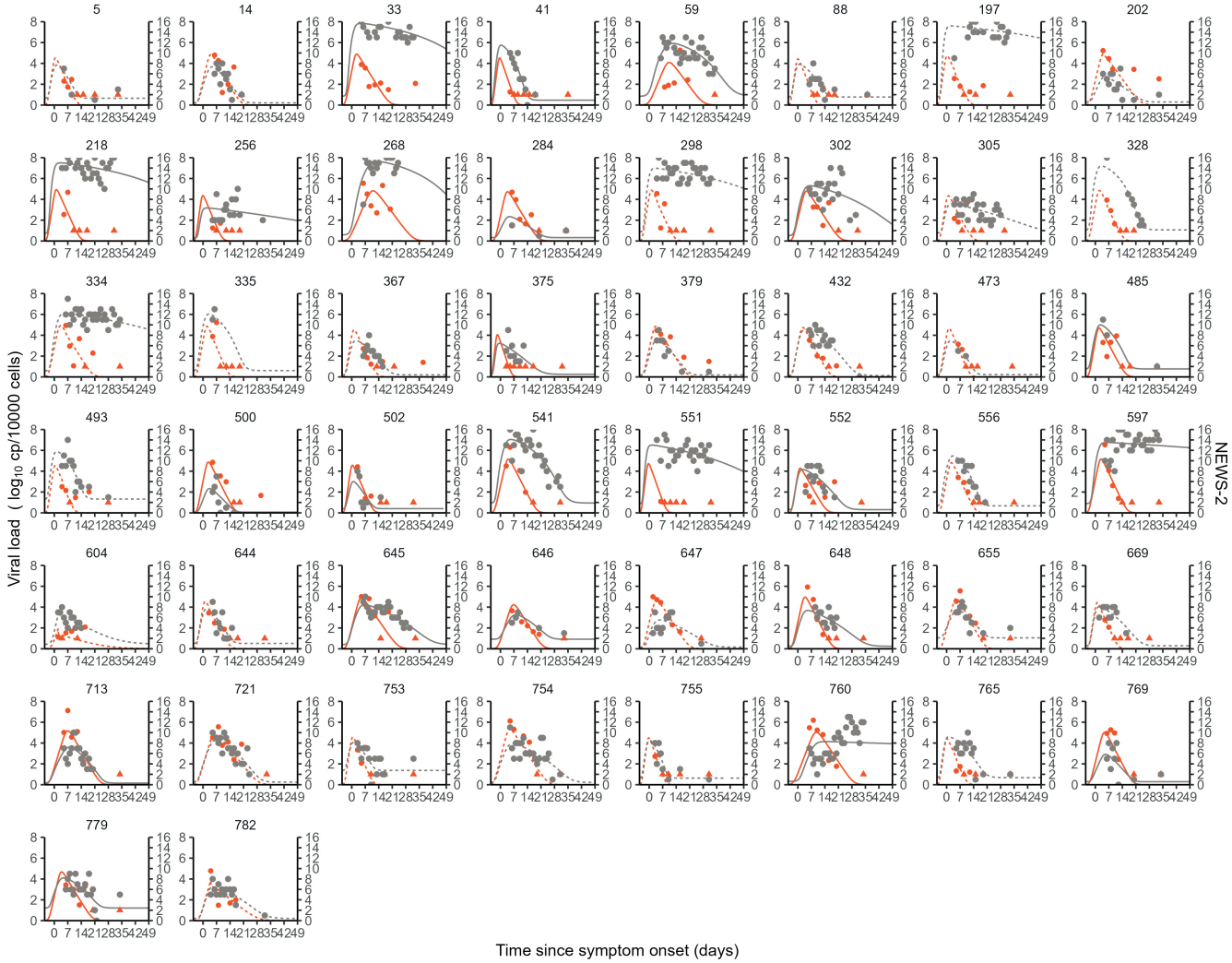

FIGURE 1 Model-based individual fits. Patients represented here are the patients with six viral load data points admitted within the first week of symptom onset. Circles represent detectable viral load, and triangles represent data below the limit of quantification. Orange: individual predictions of nasopharyngeal viral kinetics. Gray: individual predictions of National Early Warning Score 2 (NEWS-2). Solid lines: patients receiving standard of care (SoC) only. Dashed lines: patients receiving remdesivir + SoC.

of reducing viral production, p, by different values, respectively, 0% (no treatment), 80%, 90%, 99%, or 99.9%. Times to clinical improvement were compared with those obtained in the absence of treatment.

In the absence of treatment, the median predicted time to clinical improvement in patients with low viral load at admission was 5.8 days (interquartile range [IQR]: 5.3–6.2) for patients with a low risk of clinical deterioration and 11.4 days (IQR: 11.0–11.9) for patients with a high risk of clinical deterioration. The time to clinical improvement was much longer in patients with high viral loads, with a time to obtain clinical improvement of 14.6 days (IQR: 13.4–14.9) for patients with a low risk of clinical deterioration and 18.6 days (IQR: 18.2–19.2) for patients with a high risk of clinical deterioration (Figure 2). Thus, regardless of the clinical status, the model predicted that time to improvement is delayed by about 7 days in patients admitted with a high viral load compared with those arriving with a low viral load.

As a sanity check, we verified that these numbers were close to those observed in predicted individual trajectories of untreated patients. In patients with low viral loads, the median time to clinical improvement was equal to 5.8 days (IQR: 5.1–6.2) and 9.6 days (IQR: 8.6–10.9) in patients with a low or high risk of clinical deterioration, respectively. In patients with high viral loads, the median time to clinical improvement was equal to 12.7 days (IQR: 10.2–18.8) and 17.1 days (IQR: 15.8–18.4) in patients with a low or high risk of clinical deterioration, respectively.

As a consequence, simulations showed that antiviral treatment did not help time to clinical improvement in patients with low viral loads at admission, regardless of interindividual variability. Indeed, with treatment, the time gain was less than 0.2 days in all scenarios, irrespectively

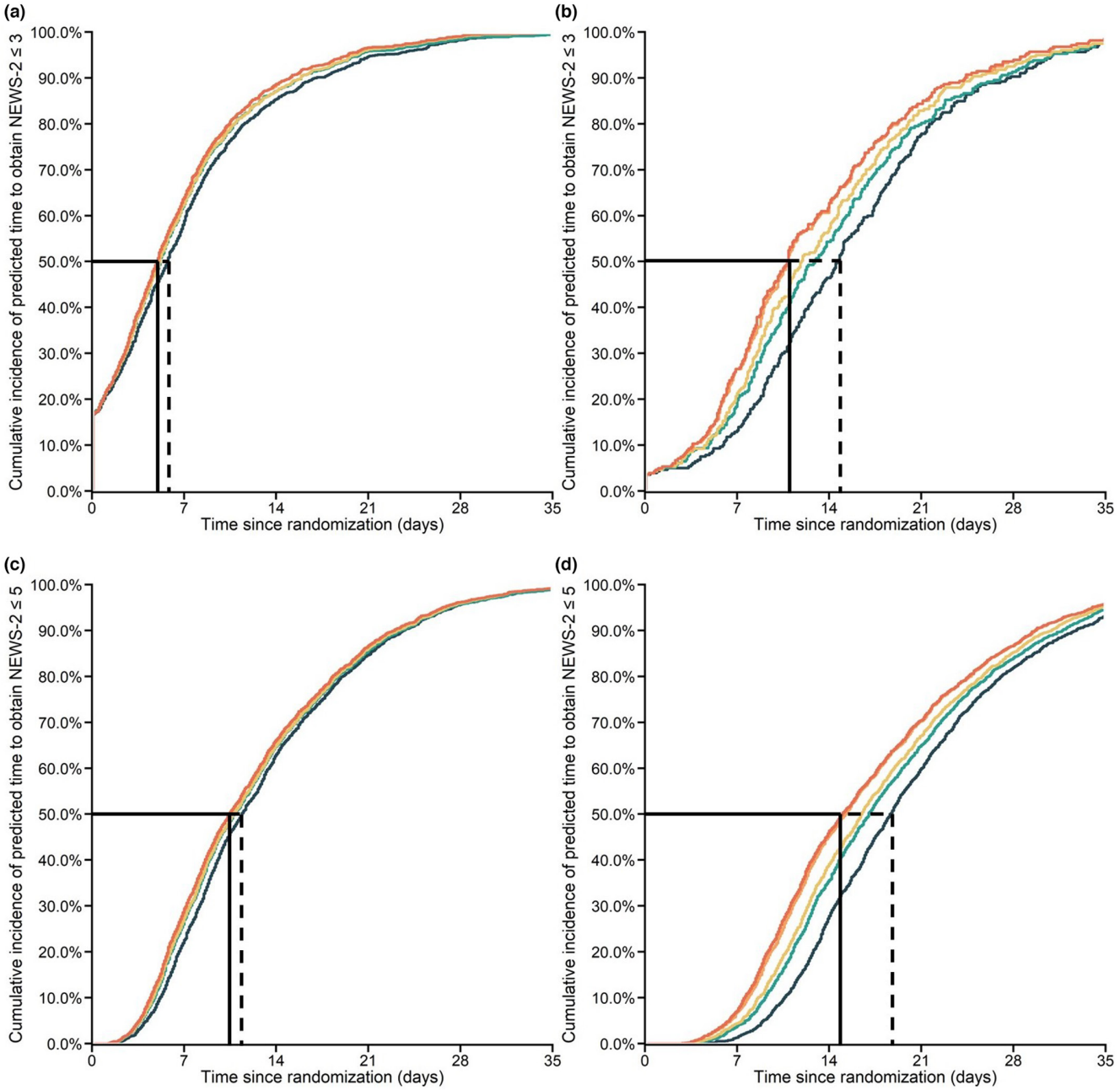

FIGURE 2 Predicted impact of antiviral treatment on the time to clinical improvement according to clinical status and viral load at admission. Top row: patients with low clinical risk of deterioration (NEWS-2 <7) with low (a) or high viral load (b) at admission. Bottom row: patients with high risk of clinical deterioration (NEWS-2 ≥7) with low (c) or high viral load (d) at admission. Time to clinical improvement was calculated as the time to achieve NEWS-2 <3 or NEW-2 <5 in patients with low and high risks of clinical deterioration, respectively, and a cutoff of 3.5 $\log_{10}$ copies/10^4 cells was used to define low and high viral loads. Treatment was assumed to be initiated on admission, with efficacy of 0% (no treatment, blue), 80% (green), 90% (yellow), 99% (orange), or 99.9% (red). The solid black line represents the median time to clinical improvement with a treatment efficacy of 99.9%, and the broken black line represents the median time to clinical improvement without treatment.

of disease severity at inclusion and/or treatment antiviral efficacy. However, the impact of treatment was greater in patients with high viral loads. Simulations showed that an 80% antiviral treatment effect decreased median time to clinical improvement by 1.3 days (IQR: 0.5–2) in patients with a low risk of clinical deterioration and 1.4 days (IQR: 1–4.5) in patients with a high risk of clinical deterioration. The clinical improvement was larger when assuming an antiviral treatment effect of 99.9%, with a reduction in the time to clinical improvement of 2.0 days (IQR: 0.8–3.6) and 2.2 days (IQR: 1–4.5) for patients with low and high risks of clinical deterioration, respectively.

DISCUSSION

In this study, we characterized the link between viral loads and NEWS-2 scores using data from 664 hospitalized COVID-19 patients from the DisCoVeRy trial included for remdesivir evaluation. This is the first time that viral loads and NEWS-2 scores have been modeled simultaneously in COVID-19 patients. The model that we developed captures the heterogeneity of the observed NEWS-2 score and viral patterns and then reconstructs individual trajectories of viral loads and NEWS-2 scores. We found that there is an association between the time to viral clearance and the time to clinical improvement, suggesting that therapeutic strategies reducing viral load levels could have an effect on patient outcome, especially in patients with high viral loads on hospitalization.

The model fits very well various association profiles between viral dynamics and NEWS-2 evolution. From the covariate analysis, we showed an impact of age on the parameter quantifying the association between viral load and NEWS-2, noted k_{e0}, such that NEWS-2 decline was slower in older patients, even after adjusting for the fact that older patients have a longer duration of viral excretion.[13] This result is in agreement with previous studies showing that age is a risk factor associated with poorer clinical outcomes or mortality than younger patients.[19,20] The specific antiviral effect of remdesivir in reducing viral replication was estimated at 22% (95% CI: 0%–51.4%), which is lower than the 52% estimated previously using viral load data only; however, the estimate was poorly estimated (Table 2). In the subpopulation of patients with high viral loads at inclusion, we found an estimate of remdesivir efficacy of 78% (95% CI: 64%–92%), which is similar to the result obtained from our previous study.[13] This antiviral effect, albeit significantly different from 0, is nonetheless too small to generate a meaningful impact on NEWS-2 (Figures S2 and S3).

To study the conditions required for an antiviral effect to translate into a clinically meaningful effect, we conducted large simulations evaluating the impact of different putative effect of antiviral treatment on both the time to viral clearance and the time to clinical improvement, stratifying again our population according to their viral loads and NEWS-2 scores at randomization: low or high viral replication; low or high clinical risk. Using this approach, we showed that treatments would have virtually no benefit in patients with low viral loads on either the time to clearance or the time to clinical improvement, regardless of the level of antiviral efficacy. In patients having high viral loads, regardless of NEWS-2, the introduction of any antiviral treatment with 99.9% efficacy would result in a reduction of the time to clinical improvement of 2 days. This, therefore, confirms that an antiviral treatment could be more effective in patients with high viral loads when administered early in the infection process, while viral replication is very active, which is in line with a recent study showing the beneficial impact of the early initiation of antiviral treatments on mortality and disease progression in hospitalized patients.[5] This result is also consistent with previous studies in outpatients, showing the interest of treating patients as early as possible to obtain a greater efficacy[21,22] and that time to symptom resolution is associated with time to viral clearance.[23] Therefore, our study reinforces the fact that treatments are particularly useful early in the course of the disease, when the viral load is high.

It should be recognized that these results have been obtained using data collected in 2020 and 2021, before mass vaccination that dramatically reduced the risk of severe forms of the disease, at least in immune-competent individuals. The model was also built before the emergence of variants of concern, in particular Omicron variants. Clearly vaccination and more generally preexisting immunity have dramatically changed since 2020, changing the typology and the trajectories of patients, and will be studied in future arms of the trial. The more complex immunological status could require using more physiological models of immunity and inflammation.[24]

Although our study strengthens the understanding that early treatments may be particularly beneficial when viral loads are high, we acknowledge important limitations. In particular, our model does not demonstrate formally a causal association between viral load and symptoms, and this is attributed to the fact that remdesivir antiviral efficacy was too small to generate a genuine clinical effect (provided the model is correct). Furthermore, our model identifies that the link between viral load and symptoms is characterized by large interindividual variability, suggesting that other factors that are not present in our model impacts the clinical evolution. These parameters could be related to viral replication in other compartments (i.e., lower respiratory tract) or to other time-independent or time-dependent biomarkers.

In conclusion, the model developed allows the assessment of the link between viral clearance and clinical improvement and can be used to better anticipate the effect of antiviral treatments in hospitalized patients. Our results confirm that patients with high viral loads at randomization are more likely to benefit from an antiviral treatment, and they quantify the benefit of treating patients as early as possible to accelerate clinical improvement.

AUTHOR CONTRIBUTIONS

N.N. and J.G. wrote the manuscript. J.G., A.G., D.B., M.H., T.S., R.G., J-A.P., J.P., N.P-S., D.C., Y.Y., M.B-D., A.G-B., F.A., F.M., F.W., and C.B. designed the research. N.N.,

J.G., and G.L. performed the research. N.N. analyzed the data.

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Members of the DisCoVeRy study group are included in a supplemental file.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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As Editor-in-Chief of *CPT: Clinical Pharmacology & Therapeutics*, France Mentré was not involved in the review or decision process for this paper.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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