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Clinical relevance of nasopharyngeal SARS-CoV-2 viral load reduction in outpatients with COVID-19

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Early reduction of SARS-CoV-2 viral replication emerges as a new strategy to reduce COVID-related morbidity and mortality.¹ Notably, early observations² and models³ have revealed an association between high SARS-CoV-2 nasopharyngeal RNA levels and high risk of hospitalization or death. How much this relationship relies on confounding is unknown. For example, age influences both viral clearance and the risk of adverse outcomes.³ In clinical trials, testing the potential antiviral effect using SARS-CoV-2 RNA reduction endpoint appears as a logical first step, but pivotal trials must demonstrate an effect on a clinically meaningful aspect of the disease⁴—that is, a patient-oriented endpoint.⁵ To date, there is no established predictive relationship between the magnitude and timing of viral load reductions and the extent of clinical benefit. Nevertheless, Mitjà and collaborators⁶ recommended 7 days as the optimal time for measurement and 0.5 log₁₀ decrease or greater as the minimal threshold for significant reduction between arms.

As the number of trials in outpatients with COVID-19 grows, our understanding of the interplay between several endpoints will become clearer. We aimed to assess whether the effect of an antiviral therapy on the risk of hospitalization or death is predicted by the effect of a therapy on the nasopharyngeal SARS-CoV-2 viral load.

We searched for Phase 2/3 randomized controlled trials of drug therapies conducted amongst outpatients with COVID-19 reporting both: (i) the risk of hospitalization or death; and (ii) the nasopharyngeal SARS-CoV-2 viral load change from baseline to Day 5–7 (see details in the [Supplementary data](#), available as [Supplementary data](#) at JAC Online). The trial-level variability on the log-transformed relative risk (RR) of hospitalization or death explained by the treatment effects on the nasopharyngeal SARS-CoV-2 viral load was quantified by R^2 through a random-effect linear meta-regression model (using the *metafor* methods in R v4.1.0), weighted by the inverse of the effect size

variance, using the Maximum Likelihood variance estimator. We also established a Surrogate Threshold Effect (STE): the minimum treatment effect on nasopharyngeal viral load reduction (the surrogate outcome) necessary to predict a significant effect on hospitalization or death (the patient-oriented outcome). The STE was determined by the intersection of the upper 95% prediction limit and the horizontal line with a RR equal to one. Because pivotal trials stopped prematurely for benefit are associated with an overestimation of the effect size,⁷ we conducted a sensitivity analysis after excluding these trials, as recommended.⁸ The statistical codes are available on request to the corresponding author.

Sixteen studies testing 17 interventions in 14 010 COVID-19 outpatients reported both treatment effects on SARS-CoV-2 viral load and on RR of hospitalization or death. The baseline characteristics and extracted results from the included studies are shown in Table S1 and Table S2. The RR of hospitalization or death amongst outpatients with COVID-19 was significantly ($P=0.021$) predicted by the magnitude of nasopharyngeal SARS-CoV-2 viral load reduction (Figure 1), corresponding to a moderate R^2 of 0.53. The STE corresponding to a non-zero effect on hospitalization or death was 0.41 log₁₀ higher nasopharyngeal SARS-CoV-2 viral load reduction relative to placebo at Day 5–7. Without PINETREE, the RR of hospitalization or death amongst outpatients with COVID-19 was more strongly ($P=0.003$) predicted by the magnitude of SARS-CoV-2 viral load reduction (Figure S1), corresponding to a good R^2 of 0.68. The STE remained similar (0.38 log₁₀ reduction).

Reducing the SARS-CoV-2 viral load early is relevant and beneficial for outpatients with COVID-19. Of course, this benefit may vary according to viral factors such as the severity of the SARS-CoV-2 variant and host factors such as the immune status of the target population. We also acknowledge the measurement errors related to the quality of sampling specimen swab and the lack of a standardized quantitative PCR for nasopharyngeal SARS-CoV-2 RNA. However, these technical aspects can be controlled in the clinical research setting. Although the number of trials is small, this finding suggests that nasopharyngeal SARS-CoV-2 viral load reduction at Days 5–7 captures at least half of the subsequent disease progression in outpatient COVID-19 trials. In addition, this result complements the FDA recommendation to select virological outcome as a potential surrogate endpoint in Phase 2 trials⁴ to identify promising antiviral therapies against COVID-19⁹ by providing data and a threshold above which clinical benefit is expected in Phase 3 trials.

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Transparency declarations

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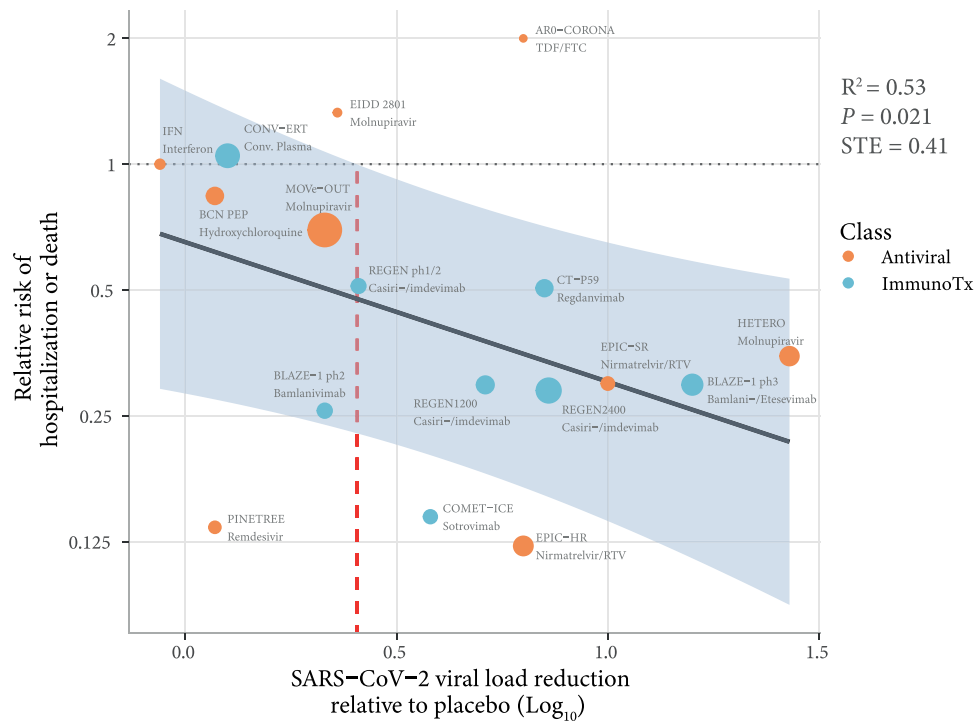


Figure 1. Clinical benefit (y-axis) by relative SARS-CoV-2 viral load reduction (x-axis) in outpatient COVID-19 trials. Point size is proportional to inverse of the effect size variance. The vertical red dashed line denotes the surrogate threshold effect (STE): the minimum increase in viral load reduction necessary to predict a significant reduction in hospitalization or death. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

Supplementary data

Methods, Tables S1 and S2 and Figure S1 are available as [Supplementary data](#) at JAC Online.

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