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

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17 Early reduction of SARS-CoV-2 viral replication emerges as a new strategy to reduce COVID-related
18 morbidity and mortality¹. Noteworthy, early observations² and models³ have revealed an association between high
19 SARS-CoV-2 nasopharyngeal RNA levels and high risk of hospitalization or death. How much this relationship relies
20 on confounding is unknown. For example, age influences both viral clearance and the risk of adverse outcomes³. In
21 clinical trials, testing the potential antiviral effect using SARS-CoV-2 RNA reduction endpoint appears as a logical
22 first-step, but pivotal trials must demonstrate an effect on a clinically meaningful aspect of the disease⁴—that is, a
23 patient-oriented endpoint⁵. To date, there is no established predictive relationship between the magnitude and timing
24 of viral load reductions and the extent of clinical benefit. Nevertheless, Mitjà and collaborators⁶ recommended 7 days
25 as the optimal time for measurement and 0.5 log₁₀ decrease or greater as the minimal threshold for significant
26 reduction between arms.

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

30 We searched for phase 2/3 randomized controlled trials of drug therapies conducted amongst outpatients
31 with COVID-19 reporting both: (i) the risk of hospitalization or death and (ii) the nasopharyngeal SARS-CoV-2 viral
32 load change from baseline to day 5-7 (see details in the [Supplemental appendix](#)). The trial-level variability on the log-
33 transformed relative risk of hospitalization or death explained by the treatment effects on the nasopharyngeal SARS
34 CoV-2 viral load was quantified by R² through a random-effect linear regression model, weighted by trial size. We
35 also established a Surrogate Threshold Effect (STE): the minimum treatment effect on nasopharyngeal viral load
36 reduction (the surrogate outcome) necessary to predict a significant effect on hospitalization or death (the patient-
37 oriented outcome). The STE was determined by the intersection of the upper 95% prediction limit and the horizontal
38 line with a relative risk (RR) equal to one. **Because pivotal trials stopped prematurely for benefit are associated with
39 an overestimation of the effect size⁷, we conducted a sensitivity analysis after excluding these trials, as recommended⁸.**

40 Sixteen studies testing 17 interventions in 14,010 COVID-19 outpatients reported both treatment effects on
41 SARS-Cov-2 viral load and on relative risk of hospitalization or death. The baseline characteristics and extracted
42 results from the included studies are shown in the [Table S1](#) and [Table S2](#). The relative risk of hospitalization or death
43 amongst outpatients with COVID-19 was significantly (P=0.021) predicted by the magnitude of nasopharyngeal SARS-
44 CoV-2 viral load reduction ([Figure 1](#)), corresponding to a moderate R² of 0.53. The STE corresponding to a non-zero
45 effect on hospitalization or death was 0.41 log₁₀ higher nasopharyngeal SARS-CoV-2 viral load reduction relative to
46 placebo at day 5-7. **Without PINETREE, the relative risk of hospitalization or death amongst outpatients with COVID-
47 19 was more strongly (P=0.003) predicted by the magnitude of SARS-CoV-2 viral load reduction ([Figure S1](#)),
48 corresponding to a good R² of 0.68. The STE remained similar (0.38 log₁₀ reduction).**

49 **Reducing the SARS-CoV-2 viral load early is relevant and beneficial for outpatients with COVID-19. We
50 acknowledge the measurement errors related to the quality of sampling specimen swab and the lack of a standardized
51 quantitative PCR for nasopharyngeal SARS-CoV-2 RNA. However, these technical aspects can be controlled in the
52 clinical research setting.** Although the number of trials is small, this finding suggests that nasopharyngeal SARS-CoV-
53 2 viral load reduction **at days 5-7** captures at least half of the subsequent disease progression in outpatient COVID-19
54 trials. In addition, this result complements the FDA recommendation to select virologic outcome as a potential
55 surrogate endpoints in phase 2 trials⁹ to identify promising antiviral therapies against COVID-19⁴ **by providing data
56 and a threshold above which clinical benefit is expected in phase 3 trials.**

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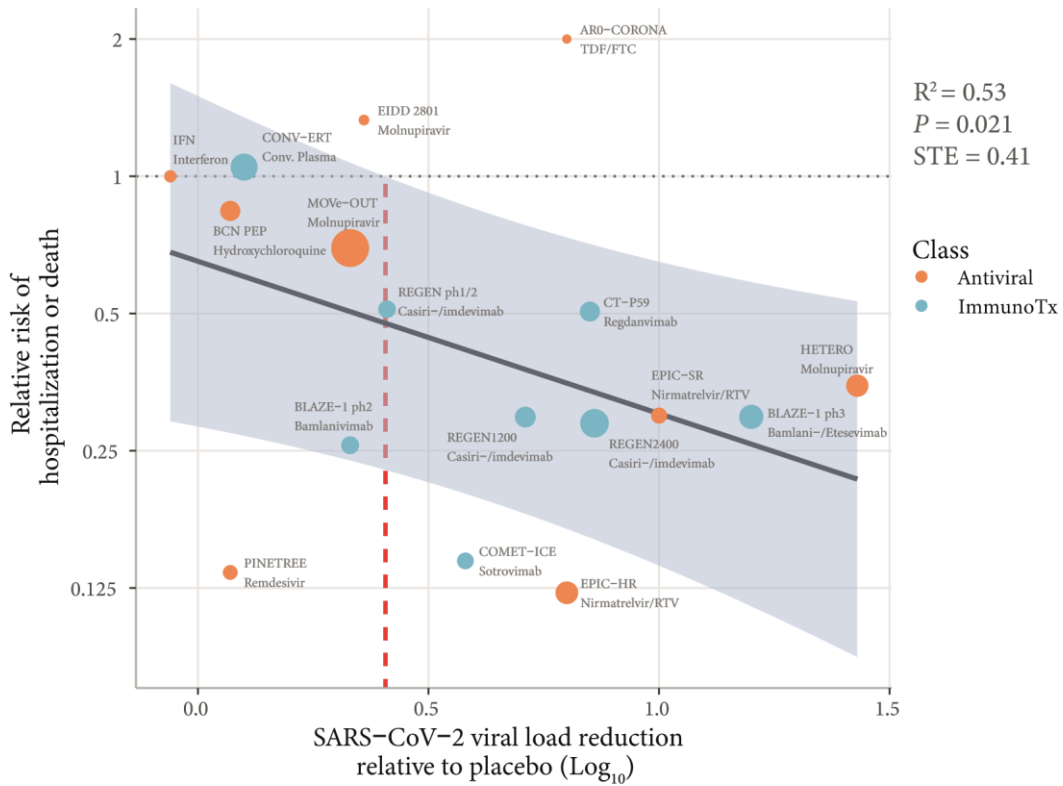
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90 Figure 1: Clinical benefit (Y-axis) by relative SARS-CoV-2 viral load reduction (X-axis) in outpatient COVID-19 trials.
 91 Point size is proportional to sample size. The vertical red dashed line denotes the surrogate threshold effect (STE):
 92 the minimum increase in viral load reduction necessary to predict a significant reduction in hospitalization or death.

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