Clinical evidence for viral load as surrogate endpoint for antivirals for COVID-19

Michael D. Hughes
Professor of Biostatistics
Harvard TH Chan School of Public Health, Boston, USA
(mhughes@sdac.harvard.edu)

Goals of Presentation

1. Natural history: Are SARS-CoV-2 RNA levels predictive of subsequent hospitalization/death in untreated patients with symptomatic mild-to-moderate COVID-19?
   - Illustrate using results from placebo recipients in the ACTIV-2 trial

2. Surrogacy: Is there an association between treatment effects on SARS-CoV-2 RNA levels and treatment effects on hospitalization/death among patients with mild-to-moderate COVID-19?
   - Review meta-regression analyses of RCTs that explored this association

Key limitation: Data used in these analyses largely from trials conducted in pre-omicron era when rates of hospitalization/death were higher

Natural History

Are SARS-CoV-2 RNA levels predictive of subsequent hospitalization/death in untreated patients with symptomatic mild-to-moderate COVID-19?

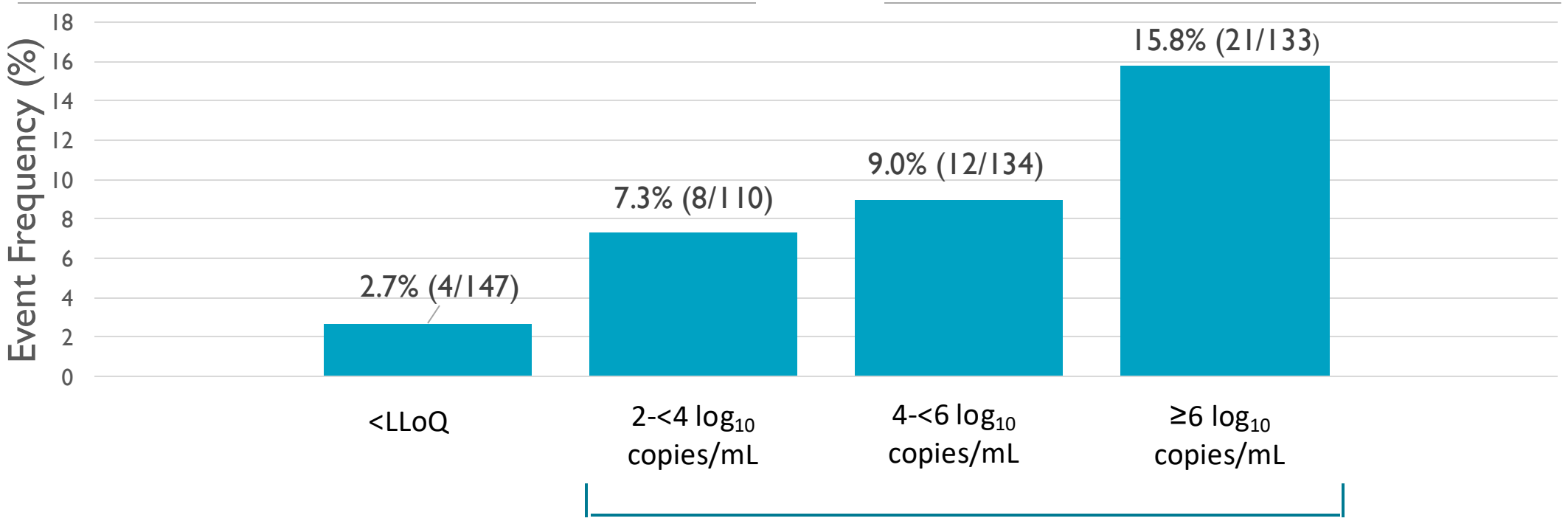
- Illustrate using results from placebo recipients in the ACTIV-2 trial

[Giganti et al. J Infect Dis. 2023;228:S117-25]

ACTIV-2 participants enrolled August 2020 to July 2021 who received placebo (n=561)	
Age (y): median (quartiles)	49 (38, 57)
Sex: % female	51%
Race: % white	77%
Ethnicity: % Hispanic/Latino	45%
Country: % U.S.	77%
SARS-CoV-2 vaccination: %	7%
Higher risk of severe COVID: %	79%
Days from symptom onset to study entry: Median (quartiles)	6 (4, 7)

ACTIV-2: Anterior nasal (AN) RNA level at Day 0 predicts hospitalization/death through Day 28 among untreated (placebo) adults

(n=524 with AN RNA values on day 0)



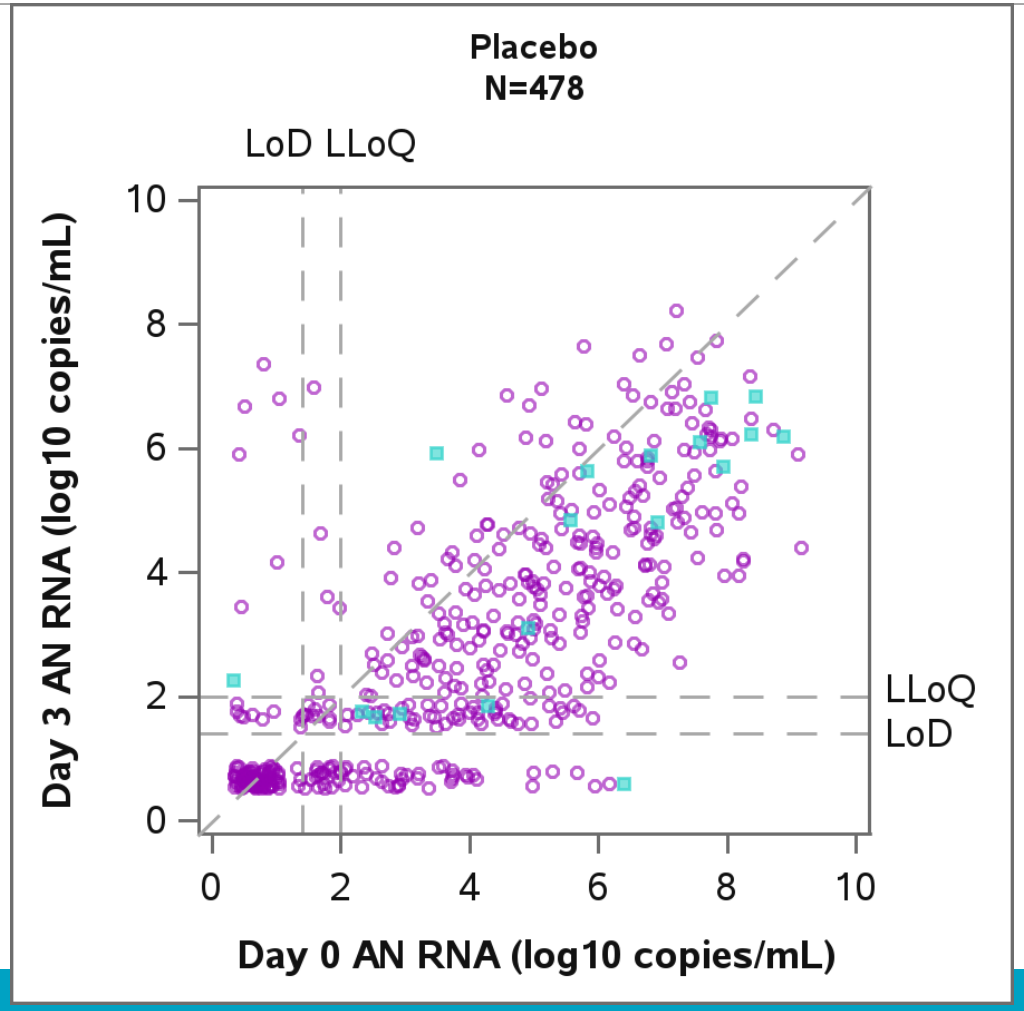
Relative Risk per 1.0 log_{10} copies/mL higher (95% CI):
1.24 (1.04, 1.49)

'< LLoQ' represents results below the lower limit of quantification (2 log_{10} copies/mL)

SARS-CoV-2 RNA levels on Days 0 and 3 showing participants who were hospitalized or died between Days 4 and 28

Untreated (Placebo) Participants Not Hospitalized by Day 3

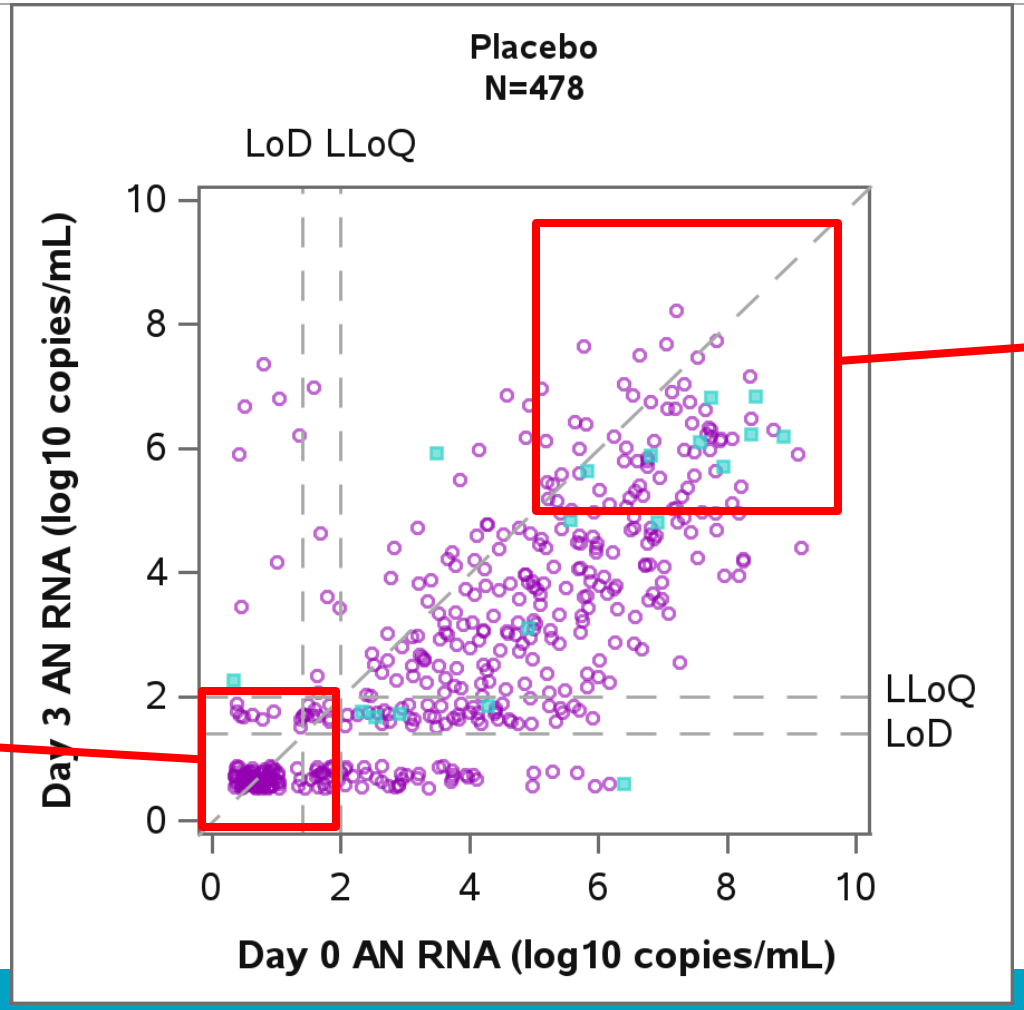
Teal squares = participants hospitalized/died between day 4 and day 28



SARS-CoV-2 RNA levels on Days 0 and 3 showing participants who were hospitalized or died between Days 4 and 28

Untreated (Placebo) Participants Not Hospitalized by Day 3

Teal squares = participants hospitalized/died between Day 4 and Day 28



RNA <LLoQ at both Day 0 and Day 3

0% (0/123) subsequently hospitalized/died

RNA ≥5 $\log_{10}$ copies/mL at both Day 0 and Day 3

10% (8/77) subsequently hospitalized/died

Multivariable analysis: Risk of hosp/death highest among those with persistently high RNA levels (at both Day 0 and Day 3)

Surrogacy

Is there an association between treatment effects on SARS-CoV-2 RNA levels and treatment effects on hospitalization/death among patients with mild-to-moderate COVID-19?

Four systematic reviews and meta-regression analyses of RCTs have explored this association:

- Parienti & de Grooth, J Antimicrob Chemother (2022); updated in J Infect Dis (2024)
- Elias et al., Lancet Microb (2024)
- Singh et al., J Antimicrob Chemother (2024) ← will focus primarily on this one
- Mateja et al., J Infect Dis (2025 – forthcoming)

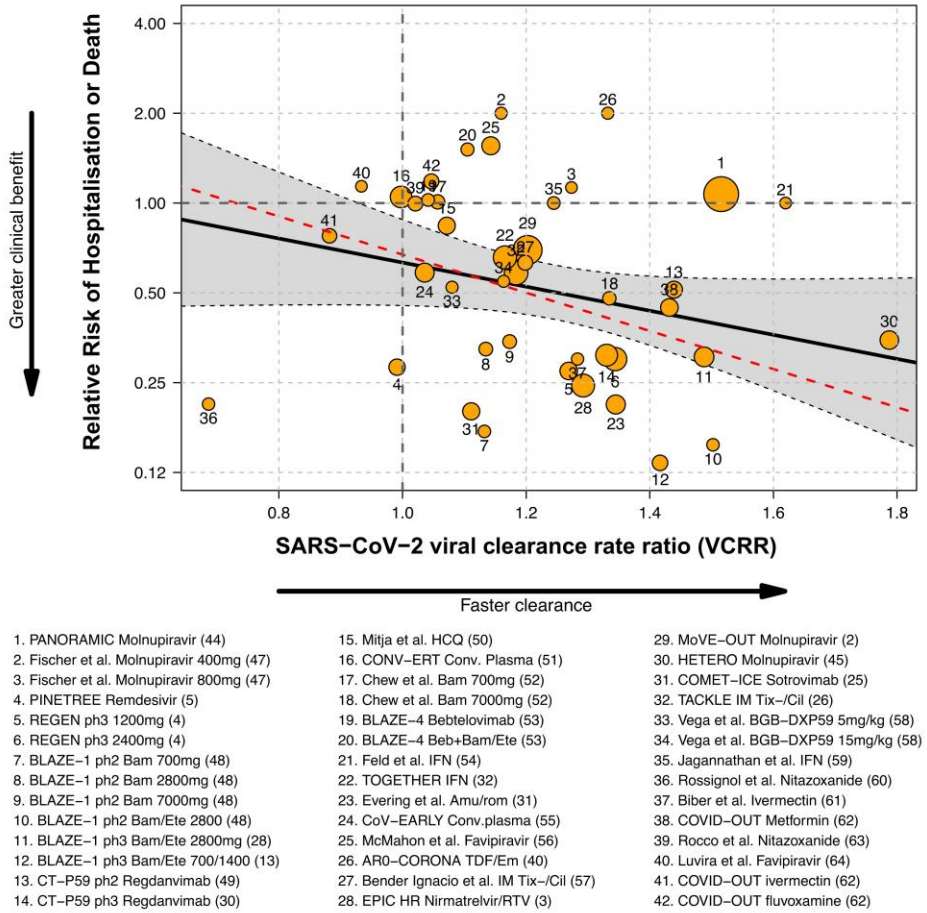
Systematic Review/Meta-Regression of Singh et al. (2024)

- RCTs of antiviral therapies in people with early symptomatic, uncomplicated SARS-CoV-2 infection within 8 days of symptom onset
  - Enrollment was between March 2020 and October 2022

- Clinical treatment effect: risk ratio comparing proportions hospitalized/dead during follow-up (min. 14 days)
  - all-cause hospitalization/death used if available

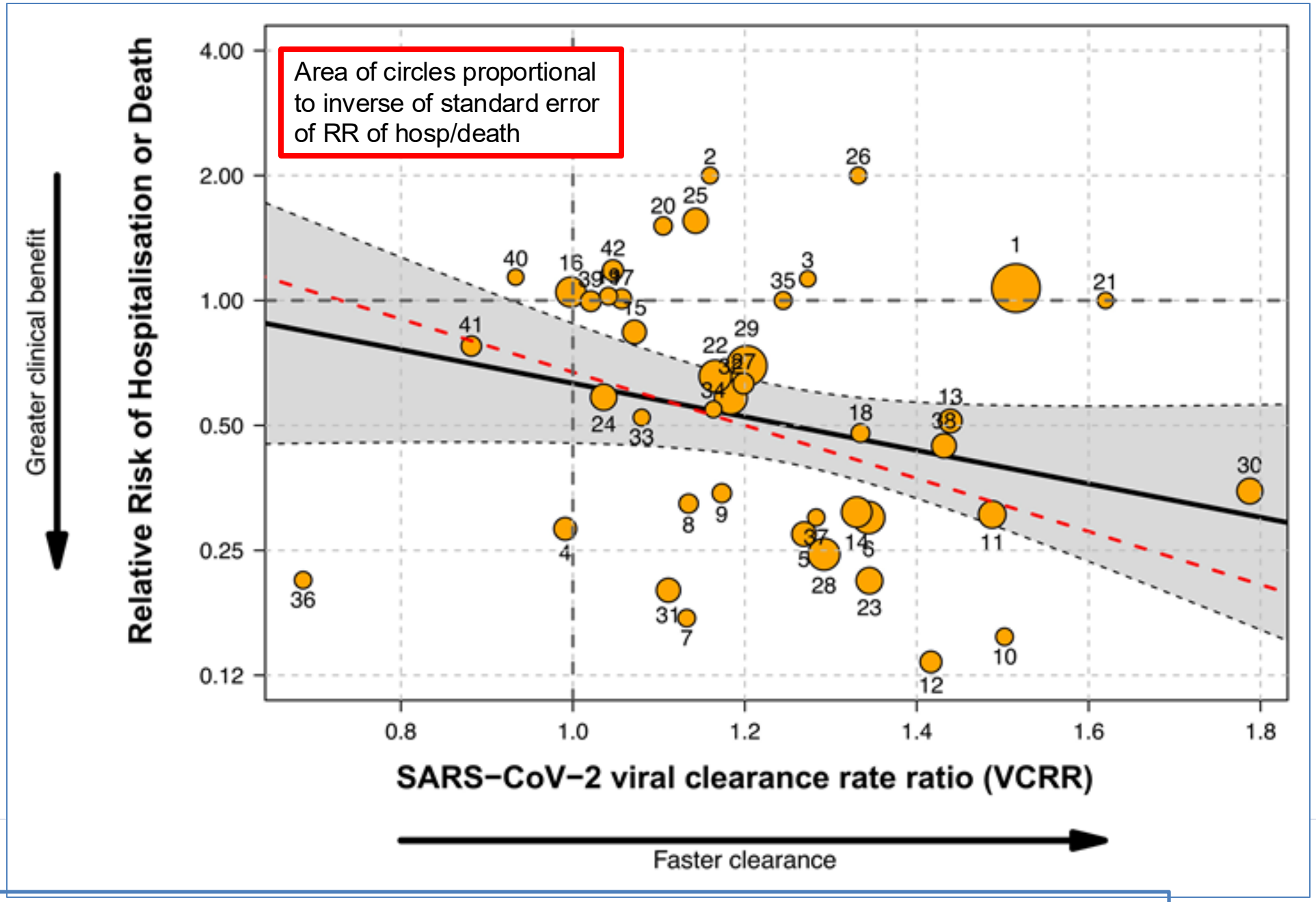
- Virologic treatment effect: ratio of viral clearance rates
  - Viral clearance rate expressed as $\log_{10}$ copies/mL per day in pharyngeal samples
  - RCT eligibility required measurements at baseline and at least one timepoint in the first week of follow-up

Singh et al. (2024): Meta-Regression Analysis of Association Between Relative Risk of Hospitalization/Death and Viral Clearance Rate Ratio Across Randomized Treatment Comparisons

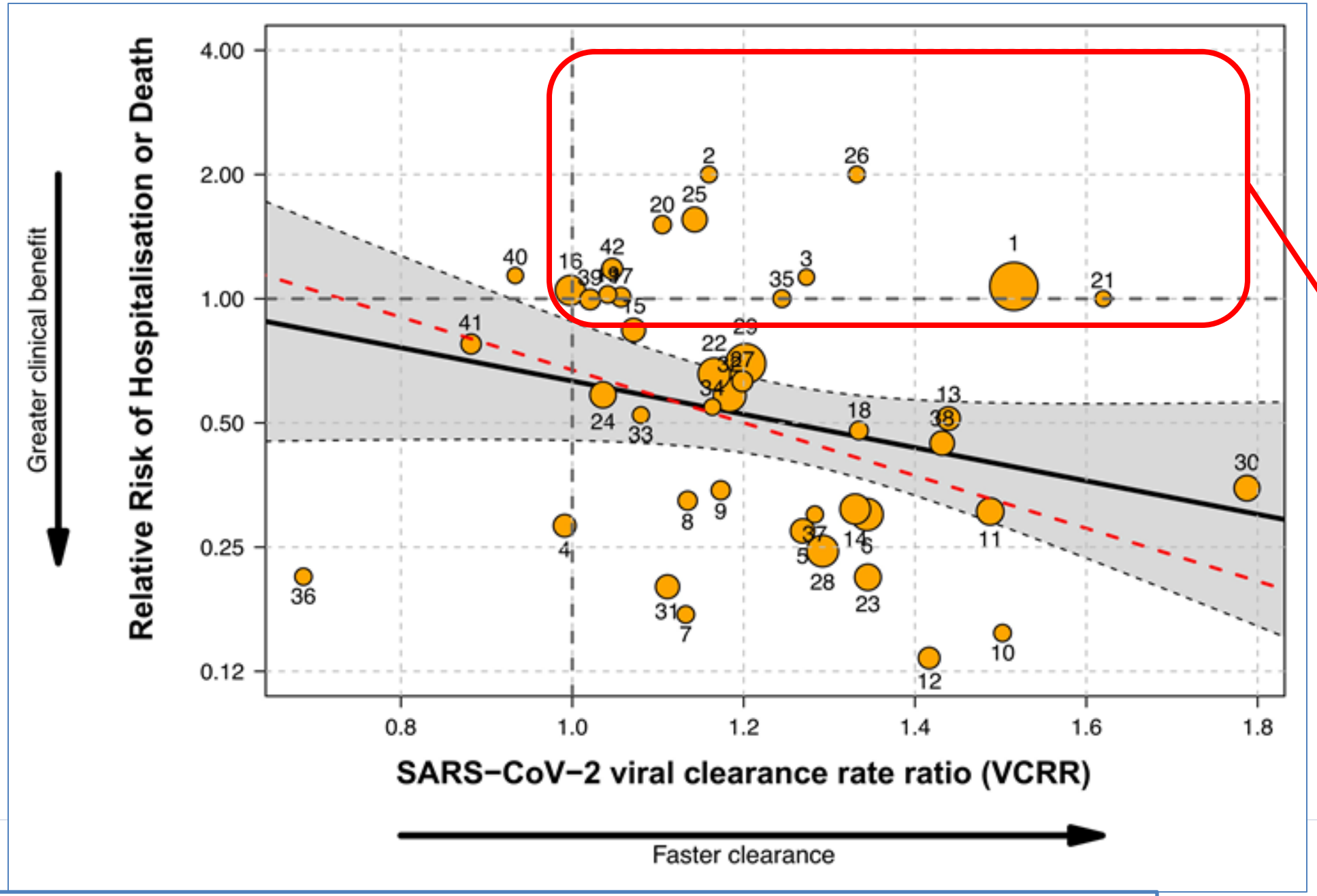


42 randomized comparisons of various antivirals to placebo/no treatment in 32 RCTs (novel and repurposed antivirals; nMabs; convalescent plasma; interferons)

Source: Singh et al. J Antimicrob Chemother, Volume 79, Issue 5, May 2024, Pages 935–945, https://doi.org/10.1093/jac/dkae045



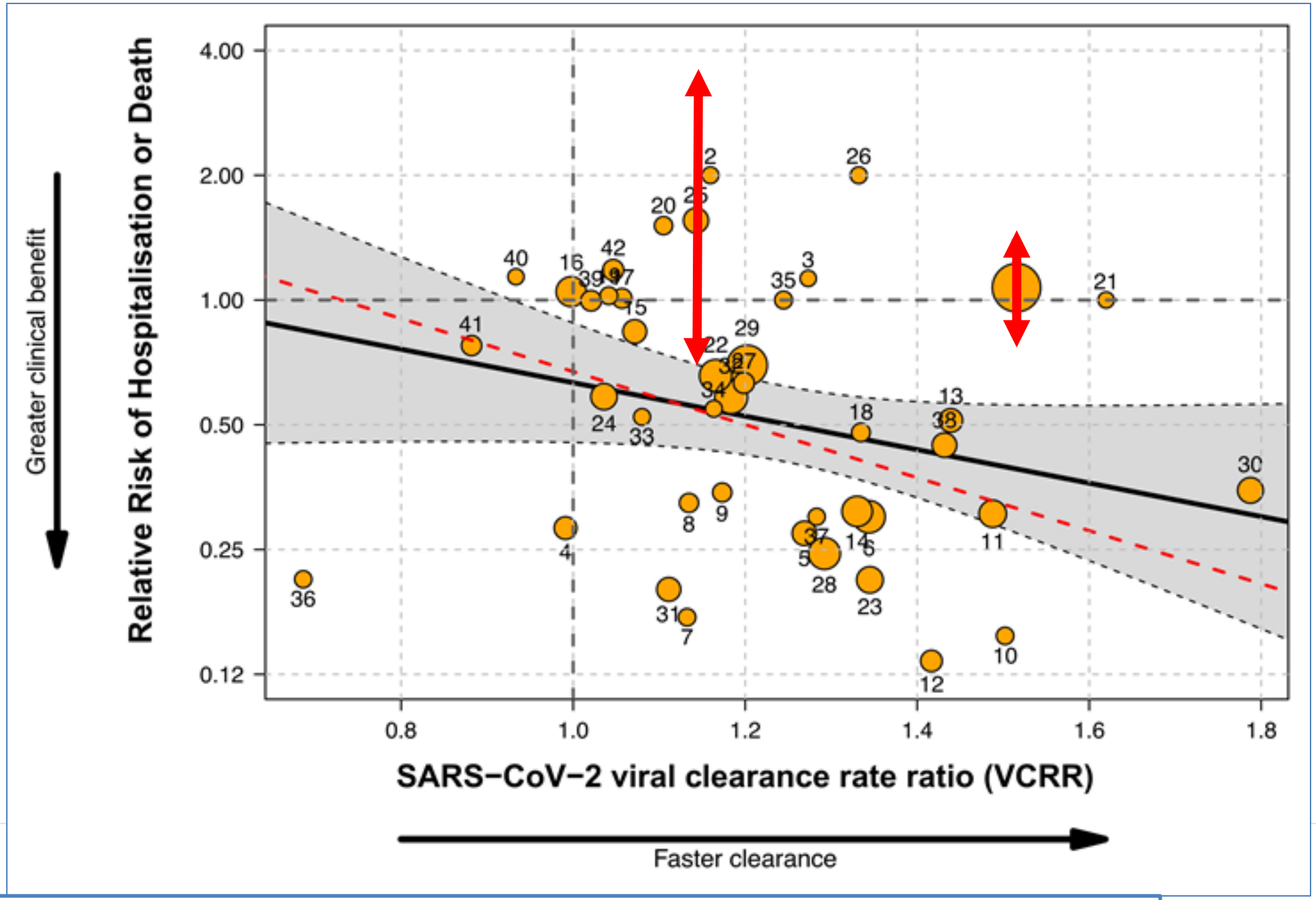
Source: Singh et al. *J Antimicrob Chemother*, Volume 79, Issue 5, May 2024, Pages 935–945, https://doi.org/10.1093/jac/dkae045



Effect on viral clearance beneficial but adverse effect on clinical outcome

Potentially undesirable from regulatory/public health perspective

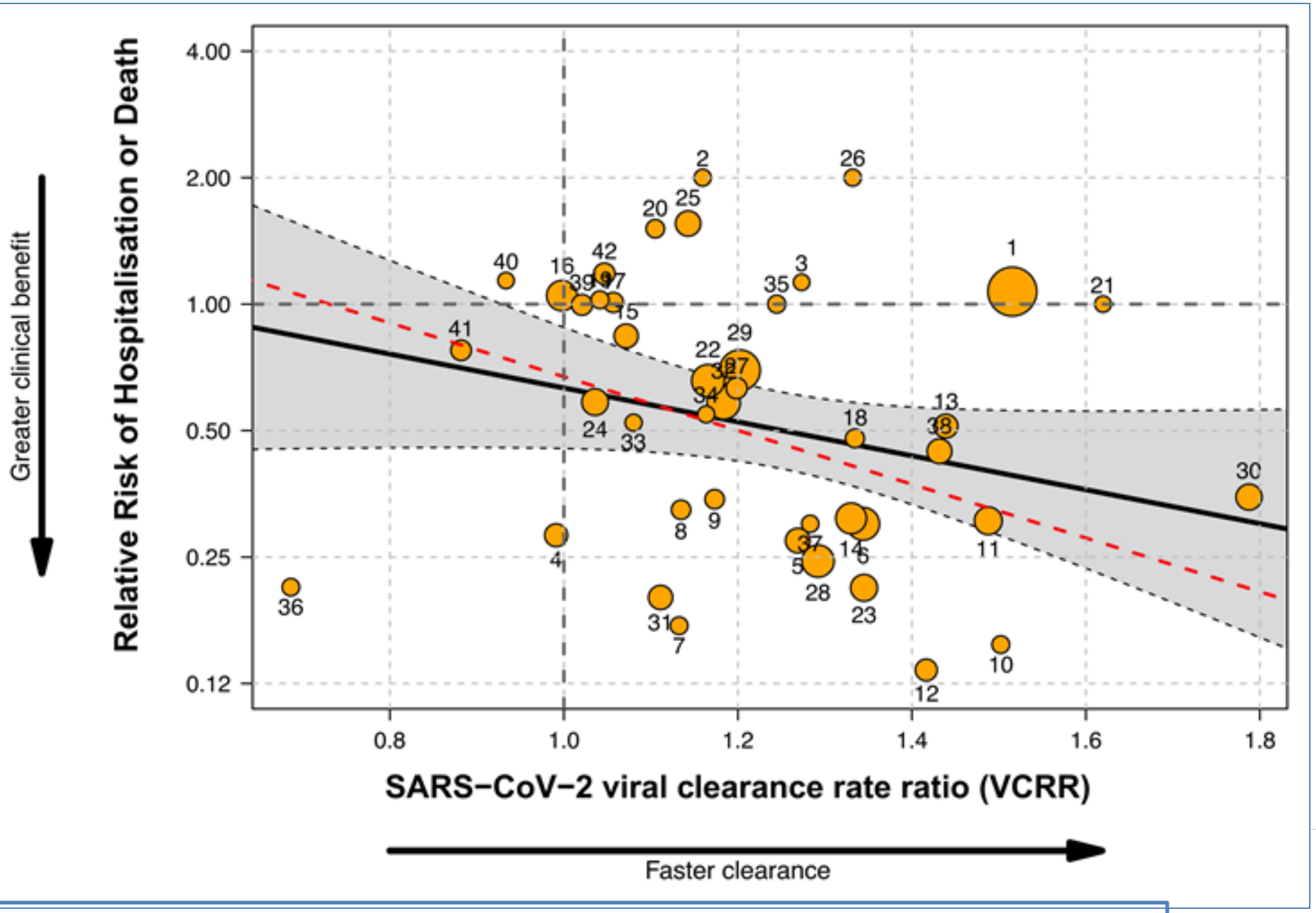
Source: Singh et al. *J Antimicrob Chemother*, Volume 79, Issue 5, May 2024, Pages 935–945, https://doi.org/10.1093/jac/dkae045



95% CIs quite wide and don't rule out a clinical benefit of treatment

Other treatment comparisons in this quadrant often involve 1 or 2 hosp/death per arm

Source: Singh et al. *J Antimicrob Chemother*, Volume 79, Issue 5, May 2024, Pages 935–945, https://doi.org/10.1093/jac/dkae045



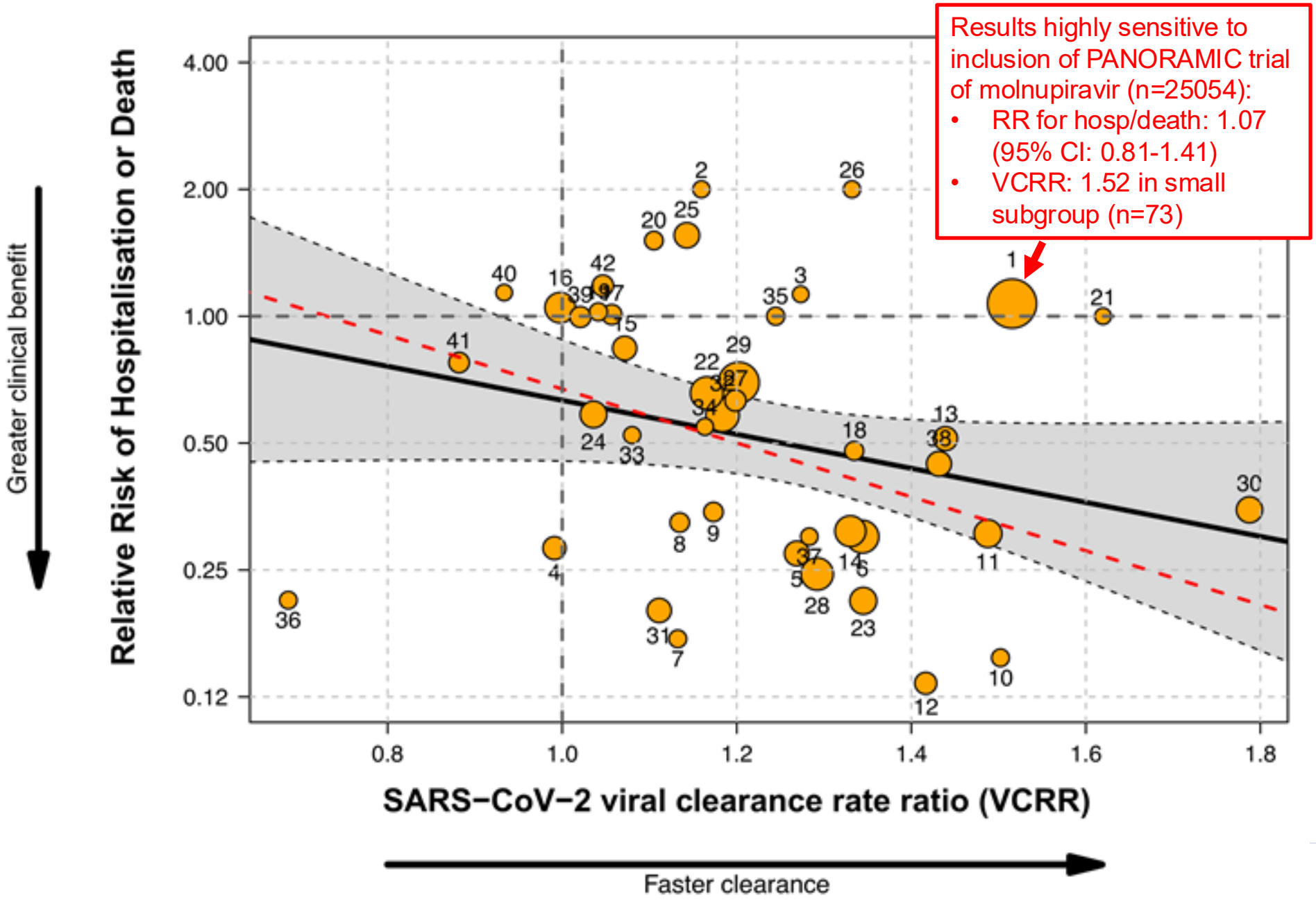
"Overall, 9.7% (R^2) of the variation in clinical benefit was explained by variation in VCRRs"

with

[**solid black line**]

an estimated slope for log RR of −0.92 (95% CI: −0.99 to 0.13; p=0.08)

Source: Singh et al. *J Antimicrob Chemother*, Volume 79, Issue 5, May 2024, Pages 935–945, https://doi.org/10.1093/jac/dkae045



Results highly sensitive to inclusion of PANORAMIC trial of molnupiravir (n=25054):

- RR for hosp/death: 1.07 (95% CI: 0.81-1.41)
- VCRR: 1.52 in small subgroup (n=73)

Excluding PANORAMIC:

"Half the variation in clinical benefit (R^2=50.4%) was explained by variation in VCRRs"

with

[dashed red line]

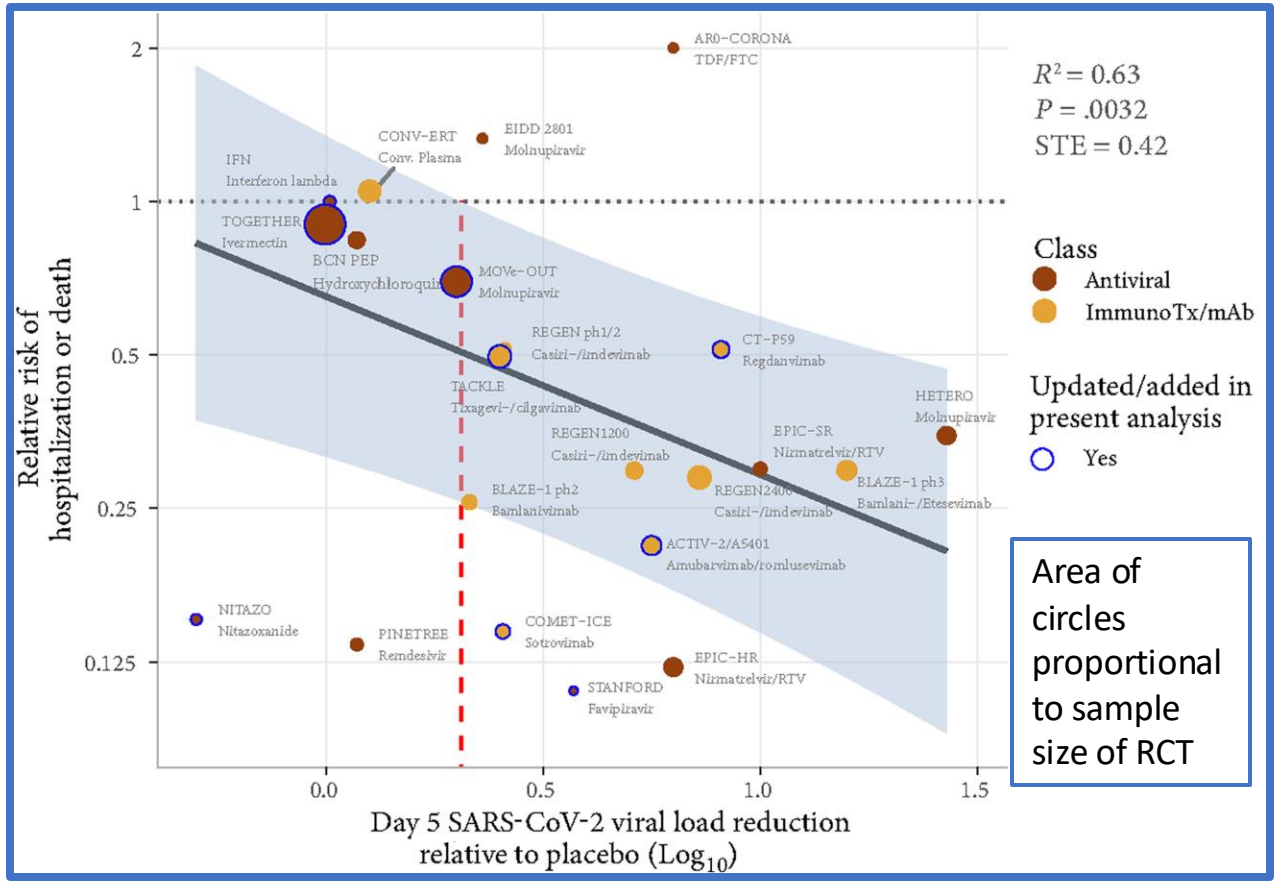
an estimated slope for log RR of −1.47

(95% CI: −2.43 to −0.51 p=0.003)

<u>Authors concluded:</u>
Viral clearance is a reasonable surrogate endpoint

Source: Singh et al. *J Antimicrob Chemother*, Volume 79, Issue 5, May 2024, Pages 935–945, https://doi.org/10.1093/jac/dkae045

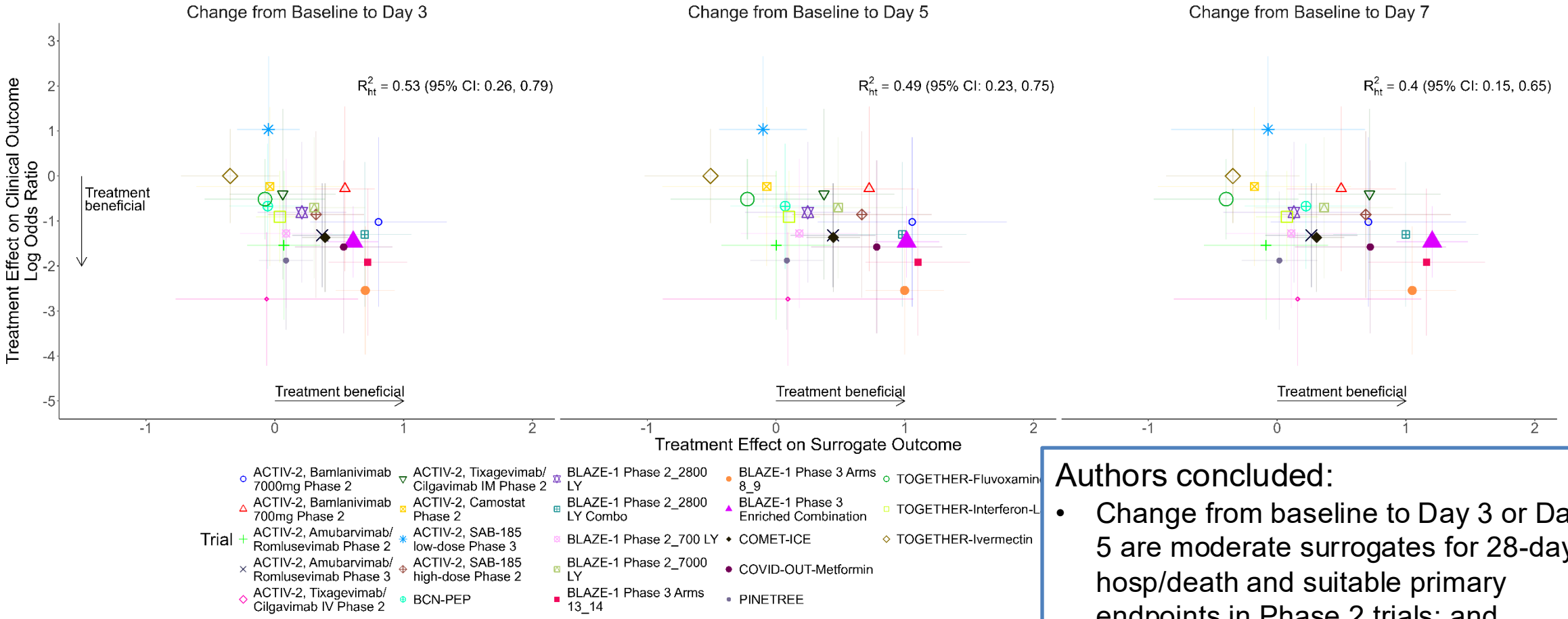
Parienti and de Grooth (2024): Meta-Regression Analysis of Association Between Relative Risk of Hospitalization/Death and Difference in Viral Load Reduction at Day 5 Across Randomized Treatment Comparisons



- Earlier analysis with fewer RCTs than Singh et al.
  - Considered treatment effects in terms of difference (treatment vs placebo) in viral load reduction (log_{10} copies/mL) in nasopharyngeal samples
- Similar strength of association as in Singh analysis without PANORAMIC
- The authors identified a surrogate threshold effect (STE; dashed red line) of 0.42 log_{10} copies/mL
  - ➢Value depends on linear model validity and extrapolation of results to new treatment and to evolving viral strain/ host population

Source: Parienti and de Grooth. J Infect Dis, Volume 229, Issue 4, 15 April 2024, Pages 1244–1245, https://doi.org/10.1093/infdis/jiae052

Mateja (2025): Individual Participant Data Meta-Regression Analysis of Association Between Odds of Hospitalization/Death and Difference in Viral Load Reduction at Days 3, 5 and 7 Across Randomized Treatment Comparisons



Source: Gail Potter (NIAID), from article forthcoming in J. Infect Dis. (2025)

Authors concluded:

- Change from baseline to Day 3 or Day 5 are moderate surrogates for 28-day hosp/death and suitable primary endpoints in Phase 2 trials; and preferred over change to Day 7
- Viral load slope over time and AUCMB didn't improve prediction

Concluding Remarks

- High (persistently) SARS-CoV-2 RNA levels predictive of higher risk of hospitalization/death in the natural history setting

- Reasonable evidence that treatment effects on risk of hospitalization/death were associated with treatment effects on viral clearance --- in RCTs largely conducted in the pre-omicron era

- Hence, reasonable evidence for viral load reduction as a surrogate for hosp/death with significant caveat that viral strains and host populations have evolved, and usual caveat that meta-regression results need to be extrapolated to new treatments
  - Useful for Phase 2 trials (potentially for Phase 3 in some populations??)
  - Field would benefit from more standardized approach to measurement, including time(s), and statistical analysis (e.g. handling of LLOQ; Moser et al. JID. 2023)

- Viral load reduction as a predictor (or surrogate) for symptom outcomes does not appear to have been explored in detail
  - Disconnect in some trials suggests evidence for surrogacy may be [much?] weaker than for hosp/death