Rapid Reviews COVID-19

Review 2: "Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

This large, multi-country, randomized evaluation of remdesivir, hydroxychloroquine, lopinavir, and interferon is highly important evidence. The trial comes with several strengths, including 1) randomized evaluation of treatment effects, 2) large sample size, 3) web-based randomization and concealed allocation, 4) assessment of patient-important outcomes in the ITT population, 5) primary analysis supplemented with subgroup analysis and sensitivity analyses, 6) trial design and reporting independent of funders, and 7) high external validity due to participation of both low- and high-income countries. The trial reporting is supplemented with a meta-analysis of all current trials. The mortality findings of the SOLIDARITY trial are in general in accordance with findings from other trials.

The trial also comes with some limitations, 1) open-labelled trial design, 2) no formal sample size calculation, 3) unstratified randomization (ideally stratified for age and mechanical ventilation), 4) unclear or at least not fully presented eligibility criteria (according to trial registration, exclusion criteria changed during course of trial), 5) full protocol not available online, only trial registration and protocol for DISCOVERY (not able to see what analyses were prespecified and post hoc), 6) only recording of SUSARs, these are not reported, no formal recording or reporting of SAR, which is highly relevant, 7) only short-term follow-up, ideally also follow-up on longer-term mortality (i.e. 90 days) and quality of life.

Suggested revisions include 1) full presentation of eligibility criteria, including changes during the trial, 2) link to full protocol, 3) applying which analysis were pre-specified and which were post hoc with reference to the protocol and statistical analysis plan, and 4) reporting of SUSARs (and SARs if recorded).

Based upon the above-mentioned strengths and limitations and considering the large sample size and multi-country design, my recommendation regarding strength of evidence in the preprint is 'reliable.'