Drug repurposing for COVID-19: the problem of excessive hypothesis testing

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Abstract

Rationale, aims, and objectives The current strategy of searching for an effective drug to treat COVID-19 relies mainly on repurposing existing therapies developed to target other diseases. There are currently more than four thousand active studies assessing the efficacy of existing drugs as therapies for COVID-19. The number of ongoing trials and the urgent need for a treatment poses the risk that false-positive results will be incorrectly interpreted as evidence for treatments' efficacy and a ground for drug approval. Our purpose is to assess the risk of false-positive outcomes by analyzing the mechanistic evidence for the efficacy of exemplary candidates for repurposing, estimate false discovery rate, and discuss solutions to the problem of excessive hypothesis testing. Methods We estimate the expected number of false-positive results and probability of at least one false-positive result under the assumption that all tested compounds have no effect on the course of the disease. Later, we relax this assumption and analyze the sensitivity of the expected number of true-positive results to changes in the prior probability (π) that tested compounds are effective. Finally, we calculate False Positive Report Probability and expected numbers of false-positive and true-positive results for different thresholds of statistical significance, power of studies, and ratios of effective to non-effective compounds. We also review mechanistic evidence for the efficacy of two exemplary repurposing candidates (hydroxychloroquine and ACE2 inhibitors) and assess its quality to choose the plausible values of the prior probability (π) that tested compounds are effective against COVID-19. Results Our analysis shows that, due to the excessive number of statistical tests in the field of drug repurposing for COVID-19 and low prior probability (π) of the efficacy of tested compounds, positive results are far more likely to result from type-I error than reflect the effects of pharmaceutical interventions.

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