Effect of steroids on Covid-19 mortality risk: a Bayesian interpretation

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Dear Editor:

In the Metcovid study, Jeronimo and colleagues conclude that methylprednisolone treatment of hospitalized patients with suspected SARS-Cov-2 infection did not reduce mortality risk[1]. This conclusion was inconsistent with the finding from the RECOVERY trial [2] which showed a 17% reduction of 28-day mortality risk associated with dexamethasone (risk ratio [RR] 0.83; 95% confidence interval [CI] 0.75 to 0.93). Here, we would like to offer an alternative interpretation of the efficacy of steroids in Covid-19 patients.

The Metcovid study was based on 393 patients, much smaller than the RECOVERY trial (n = 6425 patients). Thus, a more reliable effect size can be estimated from the two studies with appropriate weight for the difference in sample sizes. We used the random-effects model [3] to synthesize the data from the studies, and found that steroids reduced the risk of 28-day mortality by 10% (RR 0.90; 95% CI, 0.83 to 0.98).

A relevant question to ask is what is the probability that steroids reduce mortality risk among Covid-19 patients. This question can be addressed by a Bayesian analysis [4] which supplements the traditional inference based on P-values [5]. In the Bayesian analysis, data from an existing study are combined with prior data to derive the posterior probability of an effect, and this approach of inference has been applied in clinical trial interpretation [4, 6]. For binary outcome, prior data are often expressed in terms of a beta distribution, and likelihood of existing data is modeled as a binomial distribution, and the posterior result is a beta distribution (i.e., the beta-binomial model) [7]. Alternatively, the prior relative risk and likelihood are expressed by a normal distribution, then the resulting distribution is also a normal distribution (i.e., the normal - normal model) [8].

In the RECOVERY study, the investigators observed 428 deaths among 2104 patients on dexamethasone, and 1110 deaths among 4321 patients on usual care (control), and these data can be considered prior information. When the data from the Metcovid study (72 deaths in 194 patients on methylprednisolone, and 76 deaths in 1993 patients on usual care) were integrated with the prior information by a beta-binomial model, the posterior RR was 0.92 (95% CI, 0.84 to 0.99). Moreover, using the relative risk from the RECOVERY trial [2] as a prior information and Metcovid trial [1] as

likelihood, the probability that methylprednisolone reduced Covid-19 mortality risk by 5% and 10% or greater is 99% and 87%, respectively (**Figure 1**).

Based on the meta-analysis and Bayesian consideration, we propose an alternative interpretation: in patients hospitalized with SARS-Cov-2 infection, steroids reduces the risk of 28-day mortality, but the magnitude of reduction is likely modest.

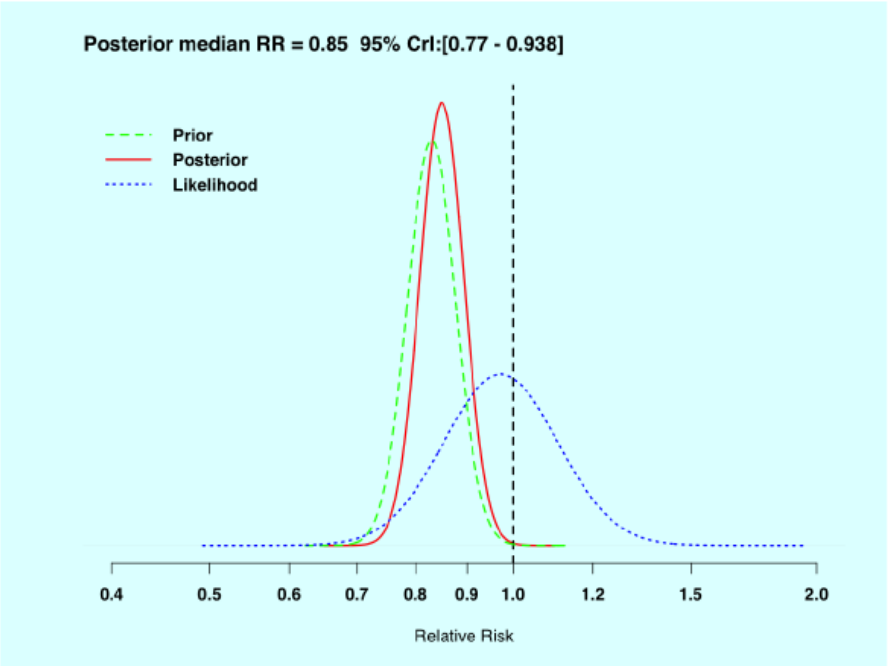
Neither author has any potential conflicts of interest

References

1. Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial. Clin Infect Dis. 2020. Epub 2020/08/14. doi: 10.1093/cid/ciaa1177. PubMed PMID: 32785710; PubMed Central PMCID: PMCPMC7454320.
2. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020. Epub 2020/07/18. doi: 10.1056/NEJMoa2021436. PubMed PMID: 32678530; PubMed Central PMCID: PMCPMC7383595.
3. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Statist Software 2010;36(3):1-48.
4. Bittl JA, He Y. Bayesian Analysis: A Practical Approach to Interpret Clinical Trials and Create Clinical Practice Guidelines. Circ Cardiovasc Qual Outcomes. 2017;10(8). Epub 2017/08/12. doi: 10.1161/CIRCOUTCOMES.117.003563. PubMed PMID: 28798016; PubMed Central PMCID: PMCPMC6421843.
5. Ferreira D, Barthoulot M, Pottecher J, Torp KD, Diemunsch P, Meyer N. Theory and practical use of Bayesian methods in interpreting clinical trial data: a narrative review. Br J Anaesth. 2020;125(2):201-7. Epub 2020/07/01. doi: 10.1016/j.bja.2020.04.092. PubMed PMID: 32600802.
6. Brophy JM. Bayesian Interpretation of the EXCEL Trial and Other Randomized Clinical Trials of Left Main Coronary Artery Revascularization. JAMA Intern Med. 2020;180(7):986-92. Epub 2020/06/02. doi: 10.1001/jamainternmed.2020.1647. PubMed PMID: 32478838; PubMed Central PMCID: PMCPMC7265123.
7. Brophy JM, Joseph L. Placing trials in context using Bayesian analysis. GUSTO revisited by Reverend Bayes. JAMA. 1995;273(11):871-5. Epub 1995/03/15. PubMed PMID: 7869558.
8. Diamond GA, Kaul S. Prior convictions: Bayesian approaches to the analysis and interpretation of clinical megatrials. J Am Coll Cardiol. 2004;43(11):1929-39. PubMed PMID: 15172393.

Figure 1: Posterior probability distribution (red solid line) of relative risk of 28-day mortality associated with steroid treatment of hospitalized patients with SARS-Cov-2 infection as a function of prior probability (green dotted line) and likelihood of data (blue dotted line). The prior probability was derived from the RECOVERY trial: relative risk of 0.83 with 95% CI ranging from 0.75 to 0.93. The likelihood of data was derived from the Metcovid study: 72 deaths in 194 patients on steroid treatment, and 76 in 199 patients on usual care. The posterior relative risk was 0.85 (95% credible interval: 0.77 to 0.94). The posterior probability that relative risk <0.90 and <0.95 was 0.987 and 0.873, respectively.

Figure 1


Posterior median RR = 0.85 95% CrI:[0.77 - 0.938]
Prior
Posterior
Likelihood
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.2
1.5
2.0
Relative Risk