ORCHID Analysis: Restricted Mean Days in State

Max Rohde
Department of Biostatistics
Vanderbilt University

July 15, 2021

Overview

ORCHID was a blinded, placebo-controlled, randomized trial conducted to assess the efficacy of hydroxychloroquine for the treatment of COVID-19.[1]

Data were collected for each patient on study days 1, 2, 3, 4, 7, 14, and 28. At each timepoint, the status of the patient was assessed using a 7-point ordinal scale:

1. death
2. hospitalized, receiving extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation
3. hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy
4. hospitalized, receiving supplemental oxygen without positive pressure or high flow
5. hospitalized, not receiving supplemental oxygen
6. not hospitalized and unable to perform normal activities
7. not hospitalized and able to perform normal activities

1: Self, W. H., Semler, M. W., Leither, L. M., Casey, J. D., Angus, D. C., Brower, R. G., ... & Brown, S. M. (2020). Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. Jama, 324(21), 2165-2176.

Statistical Modeling

The data were fit with a Bayesian proportional odds model[2], where the outcome y was predicted by

- `yprev` : the patient's state from the previous day
- `gap` : the number of days between this timepoint and the previous timepoint
- `day` : the current timepoint (using a 2nd degree polynomial)
- `age` : the age of the patient (using a restricted cubic spline)
- `sofa_nogcs` : sequential organ failure assessment score (SOFA score), not including the Glasgow Coma Scale

2: https://cran.r-project.org/web/packages/brms/

The posterior mean of the odds ratio for hydroxychloroquine treatment was 1.0199 with a 95% credible interval of [0.894, 1.175]. The posterior probability that the the odds ratio for hydroxychloroquine treatment was greater than 1 was 0.6058.

Restricted mean time in state

Method

Another way to assess the treatment difference between hydroxychloroquine and placebo is to calculate the restricted mean time a patient spends in a certain state or states – often chosen to be at home. This has the advantage of being more interpretable to some audiences than the odds ratio.

Last Observation Carried Forward

For example, assume we define "at home" to be an outcome of 6 or 7. One approach is to use Last Observation Carried Forward (LOCF). Recall the timepoints are $\{1, 2, 3, 4, 7, 14, 28\}$. Using LOCF, the observation on day 4 is carried forward for days 4, 5, and 6, so we should weight the observed outcome on day 4 by 3. Similarly, we should weight the observed outcome on day 7 by 7.

Using this method, we obtain the following weights for each study day: $\{w_1 = 1,\ w_2 = 1,\ w_3 = 1,\ w_4 = 4,\ w_7 = 7,\ w_{14} = 14,\ w_{28} = 1\}$.

Let the probability of being in state 6 on day 1 be $P_1(y = 6)$, and more generally, the probability of being in state y on day t is $P_t\ (Y = y)$ for $t \in \{1, 2, 3, 4, 7, 14, 28\}$ and $y \in \{1, 2, 3, 4, 5, 6, 7\}$. Then we can compute mean days in states 6 or 7 as

$$\sum_t P_t\ (Y = 6)\ w_t + \sum_t P_t\ (Y = 7)\ w_t$$

Linear Interpolation

Alternatively, instead of LOCF, we can use linear interpolation. For example, we estimate the probability of $P_5(y = 6)$ by linearly interpolating between $P_4(y = 6)$ and $P_7(y = 6)$, and so forth for all the days between 1 and 28. Then we can compute restricted mean days in states 6 or 7 as

$$\sum_t P_t\ (Y = 6) + \sum_t P_t\ (Y = 7) \quad \text{where } t \in \{1, 2, 3, 4, 5, \ldots, 27, 28\}$$

where we no longer need weights for each probability, since each probability now represents a single day after linear interpolation.

Results

We now apply the methods described above to the dataset. The following results were computed assuming representative covariates of `age` = 57 and `sofa_nogcs` = 3. Linear interpolation gave similar results to LOCF (results not shown here), so all the following results use linear interpolation.

The below plots show the estimated restricted mean days in state, where the states are defined using a range of cutoffs, as well as the difference in restricted mean days in state between hydroxychloroquine and placebo.

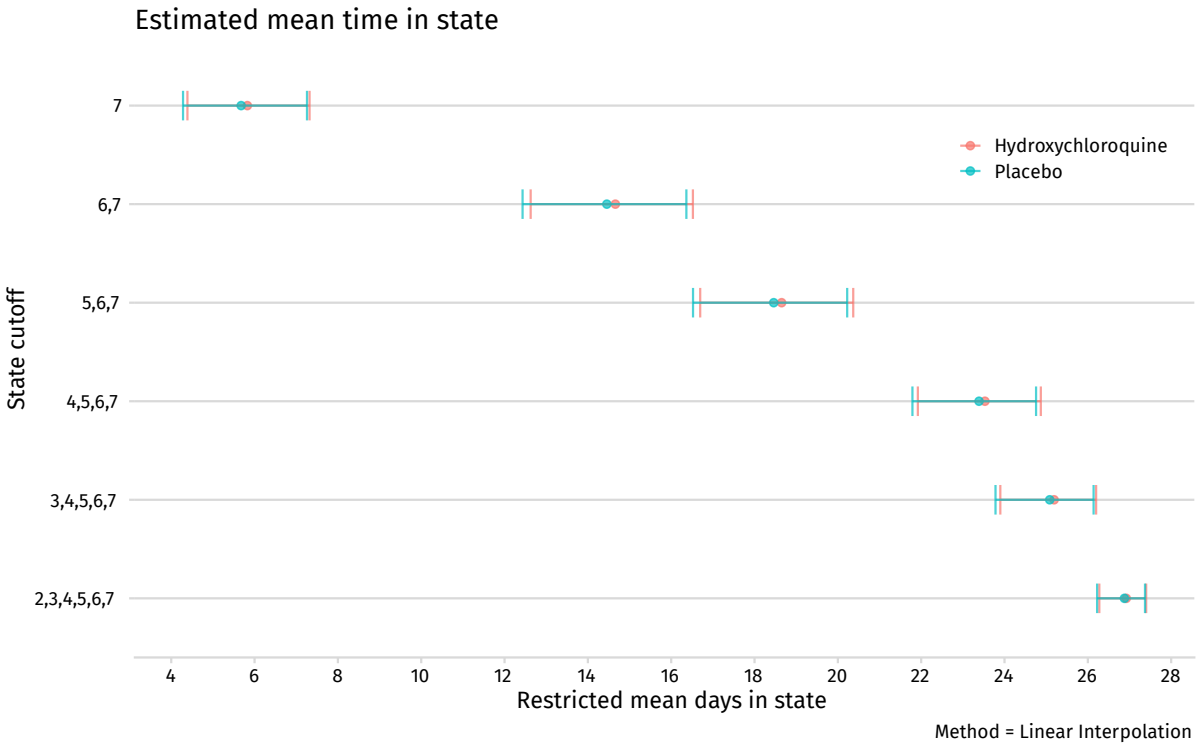

Figure 1: Estimated mean time in state, for a variety of state definitions. Linear interpolation was used to account for gaps between timepoints. The posterior mean in shown along with a 95% credible interval computed from the 0.025 and 0.975 quantiles of the posterior draws.

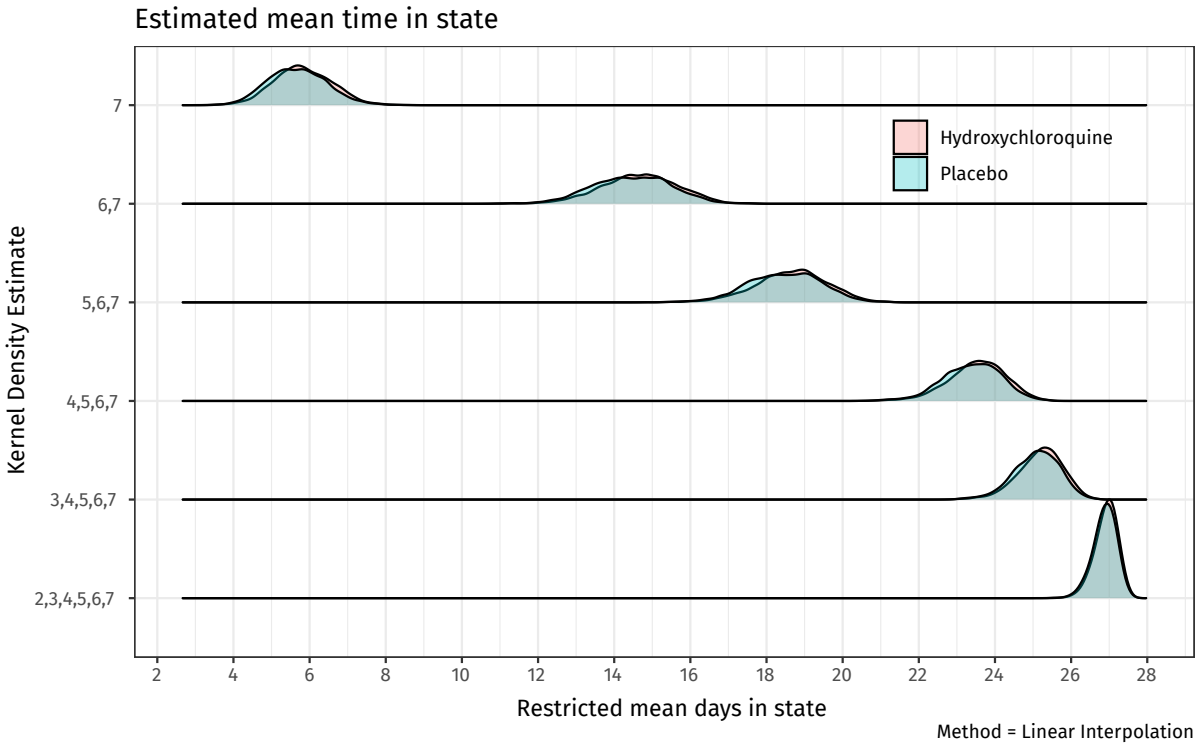

Figure 2: Estimated mean time in state, for a variety of state definitions. Linear interpolation was used to account for gaps between timepoints. The posterior distribution is shown using a kernel density estimate for smoothing.

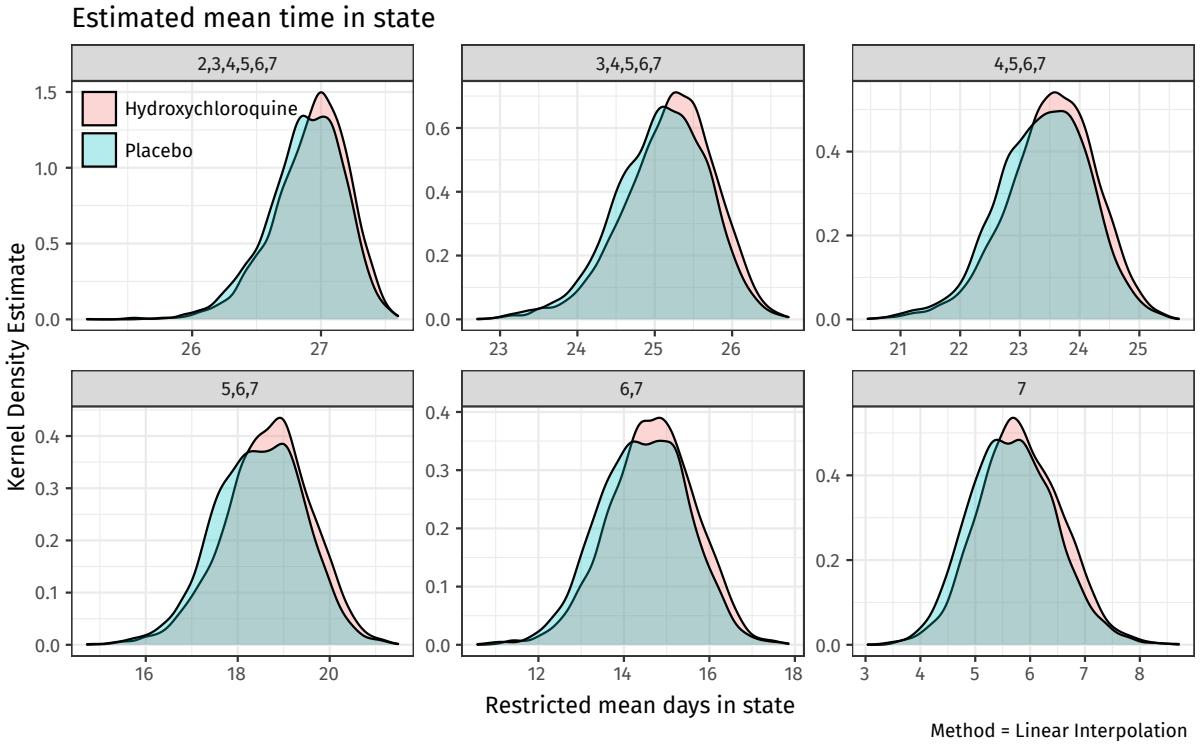

Figure 3: Estimated mean time in state, for a variety of state definitions. Linear interpolation was used to account for gaps between timepoints. The posterior distribution is shown using a kernel density estimate for smoothing. Note that the x and y scales are chosen freely for each panel, in order to focus on the differences between the treatments.

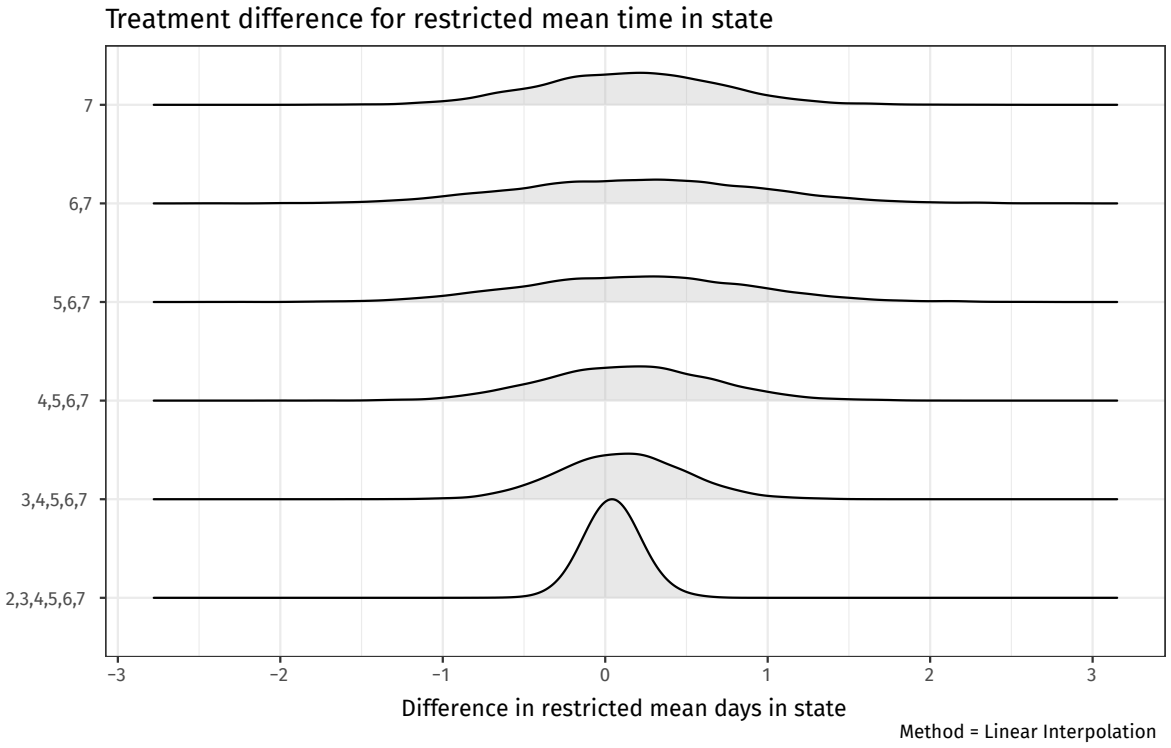

Figure 4: Estimated difference in mean time in state between hydroxychloroquine and placebo, for a variety of state definitions. Linear interpolation was used to account for gaps between timepoints. The posterior distribution is shown using a kernel density estimate for smoothing.