Evaluating Treatment Efficacy in Hospitalized COVID-19 Patients

Yu Gu

Department of Statistics & Actuarial Science
The University of Hong Kong

January 7, 2024

Outline

1. Introduction
2. Methods
   - Proportional odds model
   - Proportional hazards model
   - Transition model
3. Application to ACTT-1 Trial

Outline

1. Introduction
2. Methods
   - Proportional odds model
   - Proportional hazards model
   - Transition model
3. Application to ACTT-1 Trial

Introduction

- A number of COVID-19 phase 3 clinical trials have been conducted since the onset of the pandemic, such as ACTT, ACTIV, and RECOVERY.
- The primary objective is to reliably assess the efficacy of novel treatments for COVID-19, mostly in moderately or severely ill patients.
- Some trials have suggested clinical benefits of remdesivir, tocilizumab, baricitinib, etc.

WHO Ordinal Scale

The WHO ordinal scale has been widely used to measure the clinical status of patients hospitalized with COVID-19.

1	No activity limitation
2	Activity limitation
3	No oxygen therapy
4	Oxygen mask or nasal prongs
5	Noninvasive mechanical ventilation or high-flow nasal cannula
6	Intubation and invasive mechanical ventilation (IMV)
7	IMV + additional support such as pressors or extracorporeal membrane oxygenation
8	Death

Traditional Endpoints

- Traditional endpoints are the time to a specific change in clinical status or the clinical status on a particular day:
  - Time to recovery: first day of reaching categories 1, 2 or 3
  - Time to death
  - Clinical status at day 15 or day 28
- Limitations:
  - do not fully represent important clinical outcomes
  - do not make efficient use of all available data

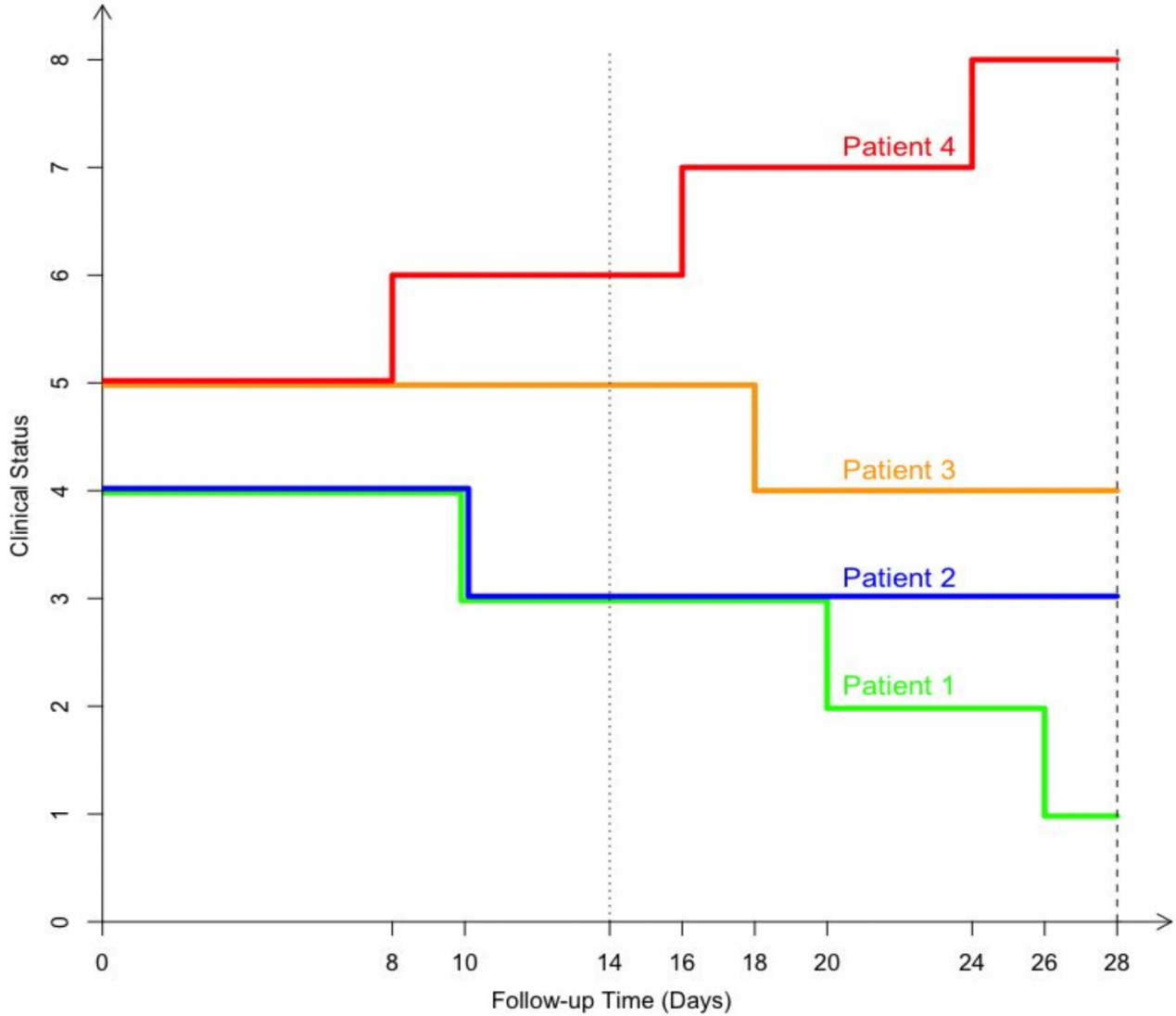


Figure 1: Clinical-status trajectories for four patients with COVID-19

New Methods

We propose three robust and powerful methods to assess the totality of evidence for treatment efficacy:

1. Proportional odds (PO) models for repeated measures of clinical status
2. Proportional hazards (PH) models for time to each level of improvement or deterioration
3. Multi-state transition model for the entire trajectory of clinical status

Outline

1. Introduction

2. Methods
   - Proportional odds model
   - Proportional hazards model
   - Transition model

3. Application to ACTT-1 Trial

Outline

1. Introduction

2. Methods
   - Proportional odds model
   - Proportional hazards model
   - Transition model

3. Application to ACTT-1 Trial

PO Models

We specify a series of PO models:

$$\log \frac{\Pr(S_t \leqslant j)}{\Pr(S_t > j)} = \alpha_{tj} + \beta_t^{\mathrm{T}} A + \gamma^{\mathrm{T}} X, \quad j = 1, \ldots, J-1 \tag{1}$$

- S_t: clinical status at day t, $t = 1, \ldots, T$
- $A = 0, 1$: binary treatment indicator
- X: baseline covariates
- β_t: log odds ratio of lower severity

Parameterization of β_t

- $\beta_t \equiv \beta$:
  - To test the null hypothesis of no treatment effect at any time
  - To estimate the overall treatment effect
- To estimate the time-varying treatment effect, we let β_t be a piecewise linear function, with change points placed at every week.

Log-Likelihood

- The pseudo log-likelihood takes the form

$$\ell_n(\theta) = \sum_{i=1}^{n} \sum_{t=1}^{T} \sum_{j=1}^{J} \xi_{itj} g_{itj}(\theta),$$

where $\xi_{itj} = I(S_{it} = j)$, $\delta_{t1} = \alpha_{t1}$, $\delta_{tj} = \log(e^{\alpha_{tj}} - e^{\alpha_{t,j-1}})$ $(j = 2, \ldots, J-1)$, and

$$g_{itj}(\theta) = I(j \leqslant J-1) \left[\delta_{tj} + \eta^{\mathrm{T}} W_{it} - \log \left\{ 1 + \sum_{l \leqslant j} e^{\delta_{tl} + \eta^{\mathrm{T}} W_{it}} \right\} \right]$$
$$- I(j \geqslant 2) \log \left\{ 1 + \sum_{l \leqslant j-1} e^{\delta_{tl} + \eta^{\mathrm{T}} W_{it}} \right\}.$$

Estimation

- We compute the MLE $\widehat{\theta}$ through the natural gradient descent algorithm.
- To account for the correlations of the repeated measures, we compute the robust covariance estimator $\mathcal{I}^{-1}(\widehat{\theta})\Sigma(\widehat{\theta})\mathcal{I}^{-1}(\widehat{\theta})$, where

$$\mathcal{I}(\theta) = -\sum_{i=1}^{n}\sum_{t=1}^{T}\sum_{j=1}^{J}\xi_{itj}\partial^2 g_{itj}(\theta)/\partial\theta^2,$$

$$\Sigma(\theta) = \sum_{i=1}^{n}\left\{\sum_{t=1}^{T}\sum_{j=1}^{J}\xi_{itj}\partial g_{itj}(\theta)/\partial\theta\right\}^{\otimes 2}.$$

- Final estimator of treatment effect: $\widehat{\beta}_t$

Outline

1. Introduction
2. Methods
   - Proportional odds model
   - Proportional hazards model
   - Transition model
3. Application to ACTT-1 Trial

Multiple Events

- We view all levels of improvement or deterioration from the initial clinical status as multiple events.
- For example, if the intial status is 5, there are a total of seven events: improvement by 1–4 categories and deterioration by 1–3 categories.
- For $k = 1, \ldots, 6$, let T_k denote the time to the first occurrence of improvement by k categories.
- For $k = 7, \ldots, 10$, let T_k denote the time to the first occurrence of deterioration by $(k - 6)$ categories.

Multiple Events (Cont.)

- Although there are ten types of events, each patient can only experience up to seven events.
- If a patient improves (or deteriorates) by multiple categories on a single day, then we assume that all intervening levels of improvement (or deterioration) also occur on that day.
- If a patient dies before a particular improvement, then we censor the time to that improvement at the last day of follow-up, such that the hazard function pertains to the cumulative incidence of improvement.

PH Models

For each event, we specify a Cox PH model, stratified by the initial status s:

$$\lambda_{ks}(t \mid A, X) = \lambda_{ks,0}(t) e^{\beta_k A + \gamma_k X}, \quad k = 1, \ldots, 10 \tag{2}$$

- $\lambda_{ks,0}(\cdot)$: arbitrary baseline hazard function
- β_k: log hazard ratio for the kth event

Estimation of β_k

- We fit the ten models separately to obtain the maximum partial likelihood estimators $\widehat{\beta}_k$ $(k = 1, \ldots, 10)$.
- To account for the correlations of multiple events, we adopt the WLW method (Wei, Lin and Weissfeld, JASA, 1989) to estimate the covariance matrix $\{\widehat{\sigma}_{kl};\ k, l = 1, \ldots, 10\}$.
- We test the null hypothesis that $\beta_k = 0$ using the Z-score $Z_k = \widehat{\beta}_k \widehat{\sigma}_{kk}^{-1/2}$.

Overall Treatment Effects

- We can estimate the overall treatment effect on improvement by

$$\widehat{\beta}_{\text{imp}} = \frac{\sum_{k=1}^{6} Z_k}{\sum_{k=1}^{6} \widehat{\sigma}_{kk}^{-1/2}},$$

and estimate the overall treatment effect on deterioration by

$$\widehat{\beta}_{\text{det}} = \frac{\sum_{k=7}^{10} Z_k}{\sum_{k=7}^{10} \widehat{\sigma}_{kk}^{-1/2}}.$$

- We can further estimate an overall treatment benefit of accelerating improvement and preventing deterioration by

$$\widehat{\beta}_{\text{ben}} = \frac{\sum_{k=1}^{10} d_k Z_k}{\sum_{k=1}^{10} d_k \widehat{\sigma}_{kk}^{-1/2}},$$

where $d_k = 1$ for $k = 1, \ldots, 6$, and $d_k = -1$ for $k = 7, \ldots, 10$.

Combined Z-Score Test

- We test the global null hypothesis of no treatment effect on improvement, i.e., $\beta_1 = \cdots = \beta_6 = 0$ by the combined Z-score test statistic

$$Z_{\text{imp}} = \frac{\sum_{k=1}^{6} Z_k}{\left\{\sum_{k=1}^{6}\sum_{l=1}^{6} \widehat{\sigma}_{kl} / \left(\widehat{\sigma}_{kk}^{1/2}\widehat{\sigma}_{ll}^{1/2}\right)\right\}^{1/2}},$$

  and test the global null hypothesis of no treatment effect on deterioration, i.e., $\beta_7 = \cdots = \beta_{10} = 0$ by the test statistic

$$Z_{\text{det}} = \frac{\sum_{k=7}^{10} Z_k}{\left\{\sum_{k=7}^{10}\sum_{l=7}^{10} \widehat{\sigma}_{kl} / \left(\widehat{\sigma}_{kk}^{1/2}\widehat{\sigma}_{ll}^{1/2}\right)\right\}^{1/2}}.$$

- In addition, we test the global null hypothesis that $\beta_1 = \cdots = \beta_{10} = 0$ by the test statistic

$$Z_{\text{ben}} = \frac{\sum_{k=1}^{10} d_k Z_k}{\left\{\sum_{k=1}^{10}\sum_{l=1}^{10} d_k d_l \widehat{\sigma}_{kl} / \left(\widehat{\sigma}_{kk}^{1/2}\widehat{\sigma}_{ll}^{1/2}\right)\right\}^{1/2}}.$$

Outline

1. Introduction

2. Methods
   - Proportional odds model
   - Proportional hazards model
   - Transition model

3. Application to ACTT-1 Trial

Transition Model

Let p_{tjk} denote the one-step transition probability of transitioning from category j on day $t-1$ to category k on day t. We relate p_{tjk} to treatment and baseline covariates through the transition model:

$$\log \frac{p_{tjk}}{p_{tjj}} = \alpha_{tjk} + \beta_{tjk} A + \gamma_{tjk}^{\mathsf{T}} X + b \tag{3}$$

- LHS: log odds of transition from j to k relative to no transition
- β_{tjk}: log odds ratio of transition from j to k at day t
- b: Gaussian random effect

Parameterization

- For each transition (j, k), we assume α_{tjk} to be a piecewise linear function of t.
- In addition, we specify that $\beta_{tjk} = \beta_t \operatorname{sign}(j - k)$, such that β_t reflects the overall treatment effects in increasing the odds of improvement and reducing the odds of deterioration.
- We can further assume β_t to be a constant or piecewise linear function of t, depending on specific purposes.

Likelihood

Under the conditional Markov assumption, the likelihood given the initial status is

$$\prod_{i=1}^{n} \int_{b_i} \sum_{\mathcal{R}_i \in \Xi_i} \prod_{t=1}^{U_{iM_i}} \prod_{j=1}^{J} \left(p_{itjj}^{R_{itjj}} \prod_{k \in \mathcal{D}_j} p_{itjk}^{R_{itjk}} \right) \phi(b_i; \lambda) db_i$$

- R_{itjk}: binary transition indicator for j to k at day t
- For fixed (i, t, j), $\{R_{itjk} : k \in \{j, \mathcal{D}_j\}\}$ follow a multinomial distribution with $\sum_k R_{itjk} = 1$ and probabilities p_{itjk}.

The biggest advantage of the transition model is that it can handle missing clinical status data automatically, without the need for imputation.

Estimation

- We compute the MLE $\widehat{\theta}$ via an EM algorithm by treating R_{itjk}'s and b_i's as complete data.

- The limiting covariance matrix of $\widehat{\theta}$ can be consistently estimated by the inverse of the matrix

$$\sum_{i=1}^{n} \left[E\{\partial \ell_c^{(i)} / \partial \theta \mid \mathcal{O}_i\} \right]^{\otimes 2} \Big|_{\theta=\widehat{\theta}}$$

Outline

1. Introduction

2. Methods
   - Proportional odds model
   - Proportional hazards model
   - Transition model

3. Application to ACTT-1 Trial

ACTT-1 Trial

- The Adaptive COVID-19 Treatment Trial-1 (ACTT-1) is a double-blind, randomized, placebo-controlled trial that evaluated the effectiveness of remdesivir in treating hospitalized adults.
- 541 patients received remdesivir and 521 received placebo.
- Patients were assessed daily while hospitalized and at days 15, 22, and 29 after discharge.
- At enrollment, 285 patients were in category 7, 193 were in category 6, 435 were in category 5, and 138 were in category 4.
- By the end of follow-up, $\sim$ 60% patients were discharged and 13% died.

Existing Methods

Time to recovery: hazard ratio 1.30 (95% CI, 1.13 to 1.50; P<0.001)

Time to death: hazard ratio 0.73 (95% CI, 0.52 to 1.02; P=0.064)

Clinical status at day 15: odds ratio 1.47 (95% CI, 1.18 to 1.82; P<0.001)

Results from PO Models

- The common odds ratio over days 1–28 was estimated at 1.48 (95% CI, 1.23 to 1.79; P$<$0.001).
- Conclusion: remdesivir significantly reduced disease severity compared to placebo.
- The confidence interval for the common odds ratio is narrower than that of the odds ratio at day 15.

Results from PO Models (Cont.)

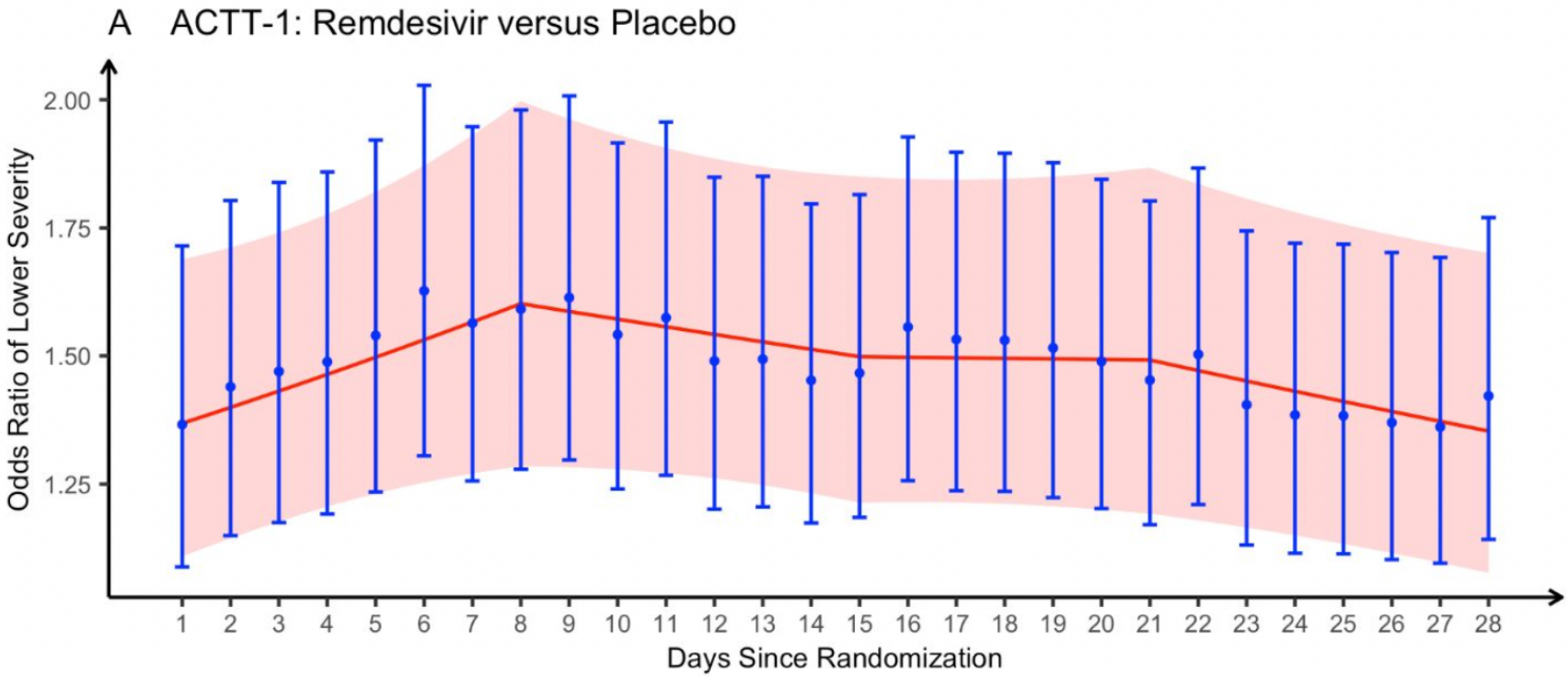


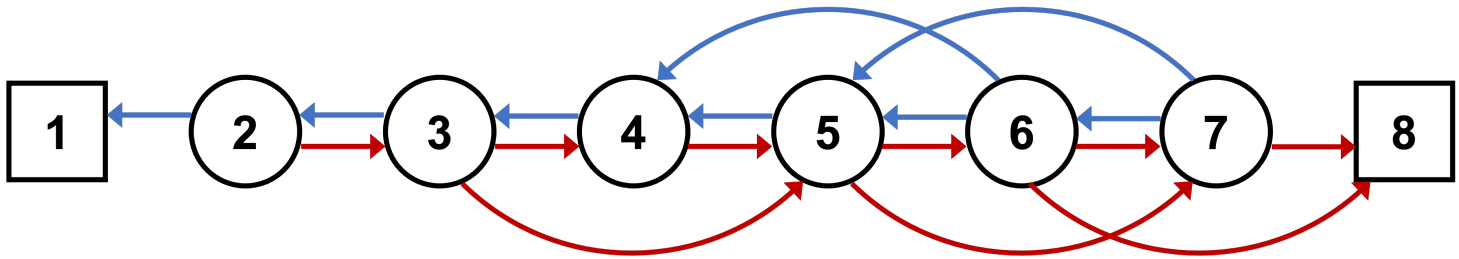
Figure 2: Time-varying odds ratios of lower severity for remdesivir versus placebo

Results from PH Models

Table 1: Treatment Effects on Times to Occurrences of Clinical Events

Endpoint	HR	95% CI	P
Recovery	1.30	(1.13, 1.50)	<0.001
Death	0.73	(0.52, 1.02)	0.064
Improvement by			
1 category	1.16	(1.02, 1.32)	0.025
2 categories	1.21	(1.06, 1.38)	0.004
3 categories	1.17	(1.02, 1.35)	0.023
4 categories	1.17	(0.99, 1.39)	0.061
5 categories	1.03	(0.78, 1.36)	0.835
6 categories	1.50	(0.92, 2.44)	0.105
any categories	1.18	(1.03, 1.35)	0.017
Deterioration by			
1 category	0.75	(0.61, 0.92)	0.006
2 categories	0.58	(0.41, 0.81)	0.002
3 categories	0.35	(0.18, 0.66)	0.001
4 categories	0.82	(0.17, 4.00)	0.803
any categories	0.62	(0.46, 0.82)	0.001
Overall benefit	1.27	(1.09, 1.47)	0.002

Results from Transition Model



The overall treatment effect of remdesivir versus placebo in increasing the odds of improvement and reducing the odds of deterioration was estimated at 0.09 (95% CI, 0.03 to 0.16; P=0.004).

Results from Transition Model (Cont.)

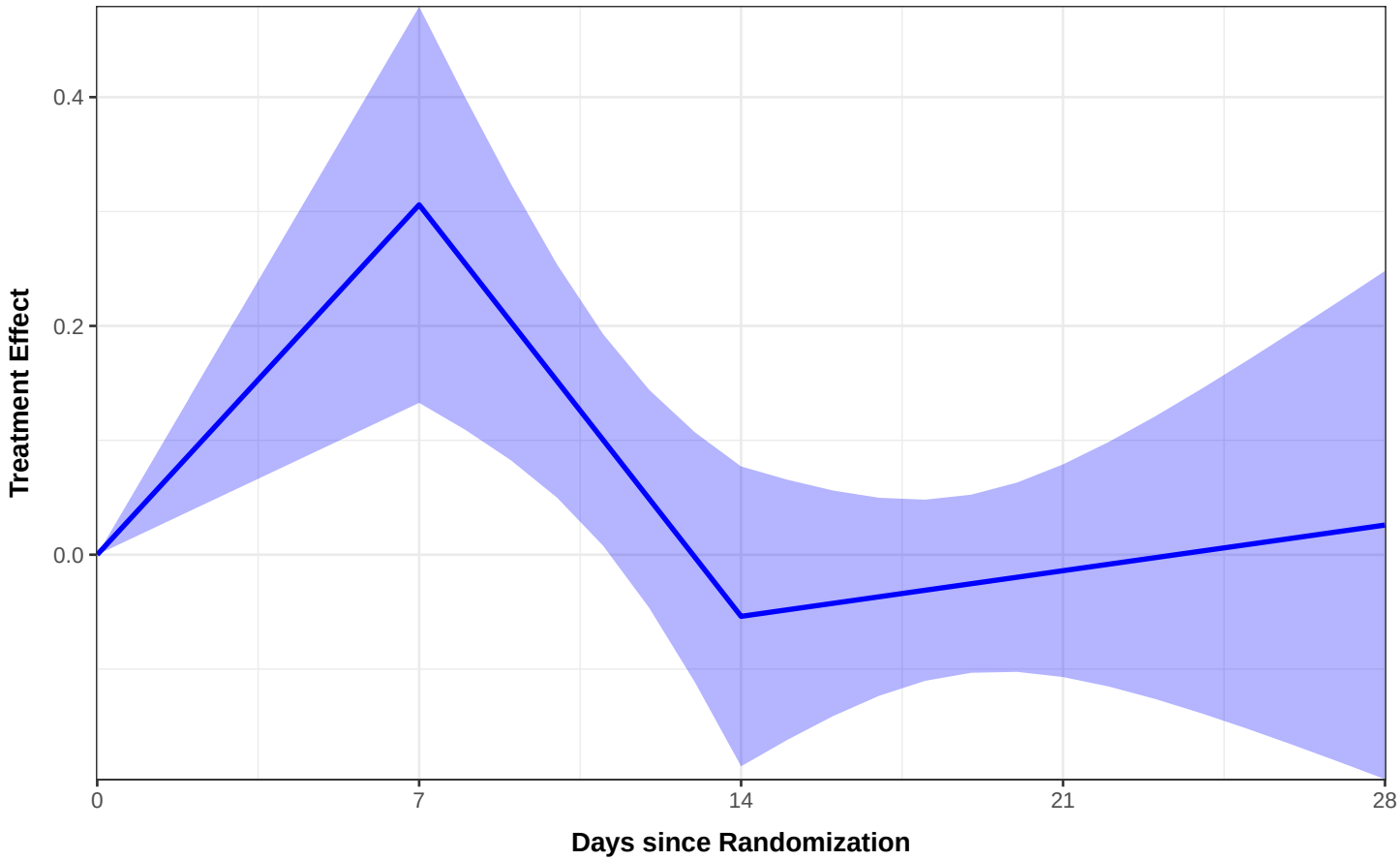


Figure 3: Estimated time-varying treatment effect from transition model

References


Lin, D. Y., Wang, J., Gu, Y., Zeng, D. (2024+). Evaluating Treatment Efficacy in Hospitalized COVID-19 Patients. *Clinical Trials: Journal of the Society for Clinical Trials*. Minor revision submitted.


Gu, Y., Zeng, D., Lin, D. Y. (2024+). A Powerful Transition Model to Assess Treatment Effect with Potentially Missing Ordinal Outcomes in COVID-19 Clinical Trials. In preparation.

Thank you!