Patient Cloning for Assessing Dynamic Treatment Protocols: A Novel Approach for Observational Data Analysis Using Real-World Data (RWD)

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Background and Objectives

Traditional approaches for analyzing real-world data are often ill-equipped to handle complex clinical decision-making.

Methods such as propensity score matching were designed to mimic static treatments at a single timepoint; they cannot tackle **dynamic treatments** in which treatment decisions are made over time in response to changing patient characteristics (**Figure 1**).

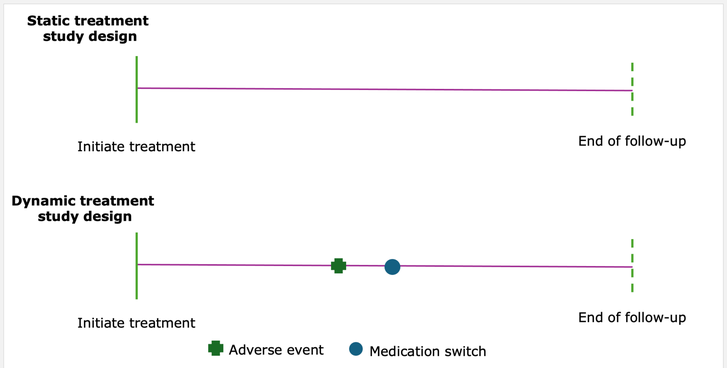

Figure 1. Illustration of a static treatment assignment compared with a treatment protocol responding to time-varying patient characteristics.

Examples of dynamic treatment regimes:

- Doses adjusted to achieve desired biomarker levels
- Treatment stopped when adverse events occur
- Switch or add medications to improve treatment response

We provide a step-by-step review of the clone-censor-weighting approach for studying dynamic treatment protocols (Hernán, 2018). The approach is illustrated using hospital chargemaster data to investigate the effect of remdesivir for preventing in-hospital mortality.

Methods

Design and Setting:
Retrospective observational cohort study of COVID-19-related hospitalizations. Hospital chargemaster data from 333 US hospitals located in 40 states from 1 May 2020 to 31 December 2021.

Treatments:
1. Early remdesivir: Initiate on day of or day following hospital admission
2. No early remdesivir: Do not initiate remdesivir on day of or day following hospital admission
3. No remdesivir: Never initiate remdesivir

Outcome:
In-hospital mortality (including discharge to hospice)

Covariates:
Age, sex, region, hospital, select baseline medications and comorbidities. See Breskin et al., 2023 for full list.

This hypothetical data will be used to demonstrate the clone-censor-weight methodology in an analysis of the real-world comparative effectiveness of remdesivir in treating COVID-19.

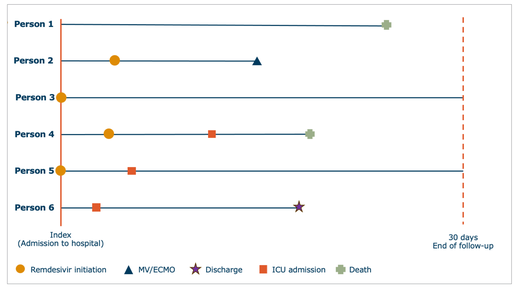

Figure 2. Hypothetical cohort data for patients admitted to hospital with COVID-19 infections.

Step 1: In the **clone-censor-weight** design, patients are "cloned" into one cohort per treatment protocol, allowing for comparison of specific treatment sequences observed in the real world.

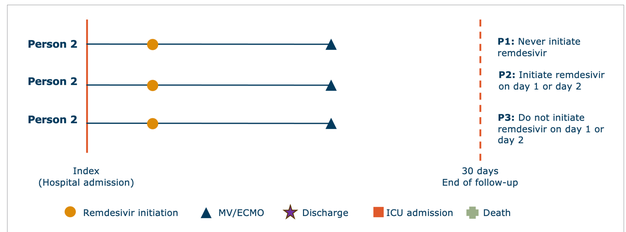

Figure 3. Each participant's data is copied once for each protocol specified in the study design. In this example there are 3 remdesivir protocols: never initiate remdesivir, initiate remdesivir on day of or day after hospital admission, or do no initiate remdesivir on day of or day after hospital admission.

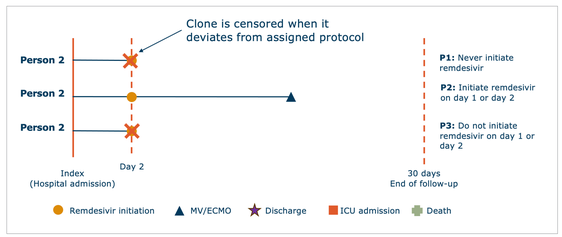

Figure 4. Each clone is censored at the point which they deviate from their assigned protocol or reach the end of the follow-up period.

Step 2: In each cloned cohort, patients are artificially censored upon deviation from the treatment sequence associated with that cohort.

Step 3: To account for the informative nature of the artificial censoring, patients are reweighted using inverse probability of censoring weights (IPCW) to reflect the original target population.

Results

Of 370,181 patients admitted to the hospital with COVID-19 present at admission between 1 May 2020 and 31 December 2021, **274,319 patients** met the inclusion criteria and were included in the study.

- Comorbidities: hypertension (64%), diabetes (38%), obesity (30%), cardiovascular disease (27%), smoking (27%), or chronic kidney disease (15%).
- At admission, 55% had acute respiratory failure and 8% had SIRS.
- By day 30 of admission, 117,926 patients (43%) initiated remdesivir, with a median treatment duration of 6 days. Of these, 96,103 (81%) initiated on the first day of hospitalization, 14,318 (12%) initiated on the second day, and 7,505 (6%)initiated after the second day.

We demonstrated that failure to account for complex, time-varying patient characteristics underestimated the real-world effectiveness of remdesivir.

- After adjustment, the 30-day risks of in-hospital mortality for each protocol were:
  - Early remdesivir: 13.2% (95% CI = 13.0%, 13.4)
  - No early remdesivir: 16% (95% CI = 16%, 17%)
  - Never remdesivir: 16.9% (95% CI = 16.5%, 17.4%)

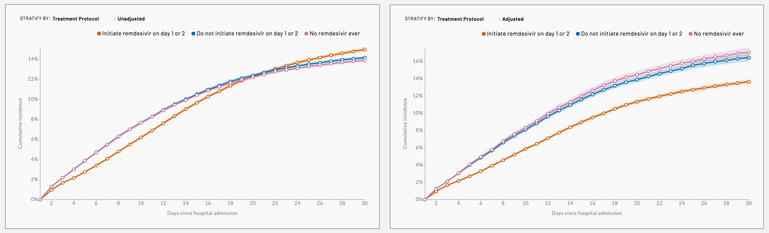

Figure 5. Unadjusted and adjusted cumulative incidence of in-hospital mortality under remdesivir-based treatment protocols among patients hospitalized with COVID-19.

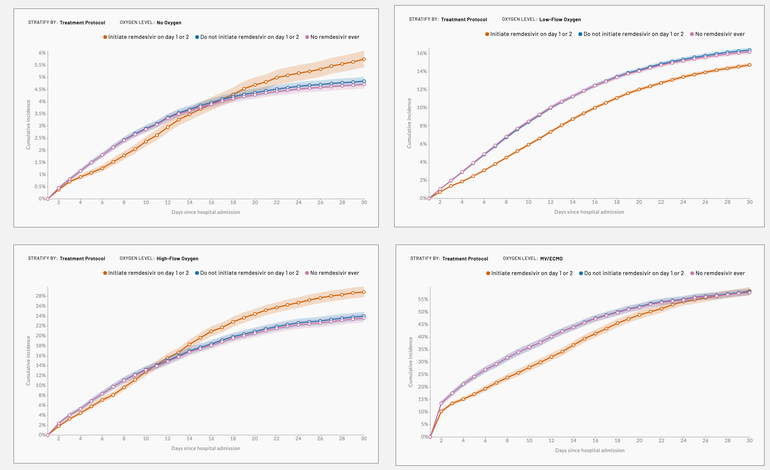

Figure 6. Cumulative incidence of in-hospital mortality under remdesivir-based treatment protocols among patients hospitalized with COVID-19 by level of oxygen supplementation at admission.

Conclusions

As pharmaceutical therapies advance, and as access to data about real-world use of those therapies grows, we must update our analytic methods accordingly.

Randomized controlled trials are too costly and time-consuming to answer every treatment question.

The clone-censor-weight approach bridges this evidence gap between clinical trials and real-world practice.

View our public report here for additional methods and results!