Estimating the Causal Effect of Early Use of Erythropoietic Stimulating Agents in Intermediate-1 to Low-risk MDS Patients: An Application of the Longitudinal Targeted Maximum Likelihood Estimation

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Introduction

- The paper uses the European Myelodysplastic Syndromes Registry and estimates average treatment effects (ATE) of using erythropoiesis-stimulating agents (ESA).
- We compare patients having initiated/received ESA for certain time periods with patients having never ever received ESA for the same amount of time.
- We account for time-varying confounding that affect both the treatment decisions and patient outcomes

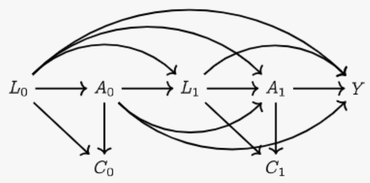
Longitudinal TMLE

- **Double Robust**
  only one of outcome (Q) or intervention mechanism (g) is needed for consistency of the final estimate
- **Machine Learning**
  super learner algorithm can be used to estimate components of Q and g while retaining valid statistical inference.
- **Uncertainty**
  SEs are correct asymptotically when estimates of Q and g are both consistent, and are conservative when only g is estimated consistently.
- **Various Outputs**
  mean outcomes for treatment and control groups; ATE, ATT, causal risk ratio/ causal odds ratio

Data and Variables

One observation O is coded as

$O = (L_0, A_0, C_0, Y_1, .., L_T, A_T, C_T, Y_{T+1})$, where



L nodes are confounders (baseline and time-varying)

A nodes are treatment nodes, 1 if being in the ESA group and 0 not

C nodes are censoring nodes, 1 if being uncensored and 0 not

Y nodes are outcomes including EQ-5D scores and cumulative survival probabilities.

Baseline confounders: Age at baseline, MDS co-morbidity index

time-varying confounders: haemoglobin levels

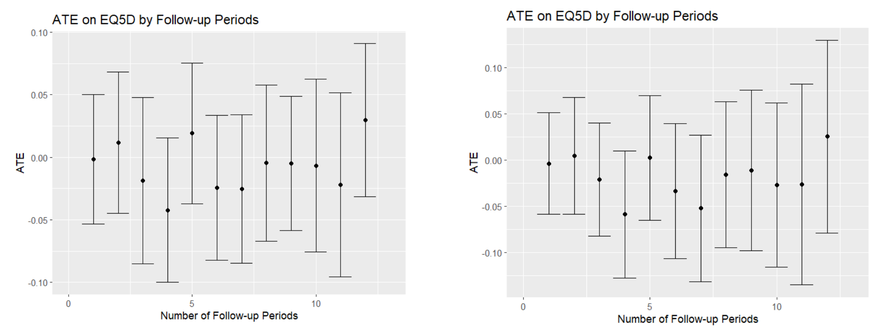
time-varying covariates: haemoglobin levels, bone marrow blasts greater than or equal to 5%, Karnofsky performance status, platelets count categories, absolute neutrophil count (not confounders so for simplicity not presented on the DAG, but are used to predict Y)

Super Learner

- SL algorithm uses cross-validation to find the optimal weighted convex combination of multiple candidate prediction algorithms.
- Machine learning algorithms can improve the specifications of Q and f functions.
- The algorithms we use include generalized linear model, Stepwise regression, neural network, generalized additive models, Elastic net

ESA Initiation Analysis

- Samples: 440 individuals for the QoL analysis, 519 individuals for survival analysis
- We assume patients who have started ESA would not stop taking ESA before they are censored, and compare them with patients having never ever taken ESA for the same amount of time.
- We account for time-varying confounding that affect both the treatment decisions and patient outcomes



(1) with super learner (2) with GLM

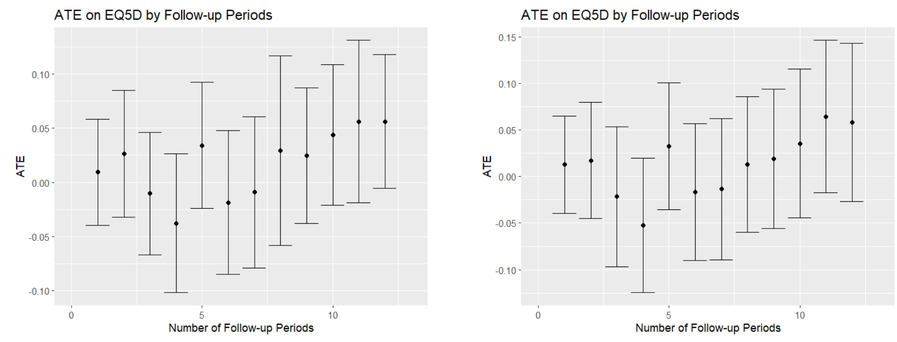
Figure 1: SL Estimations of ATEs of Initiating ESA for QoL Analysis

(1) with super learner (2) with GLM

Figure 2: SL Estimations of ATEs of Initiating ESA for Survival Analysis

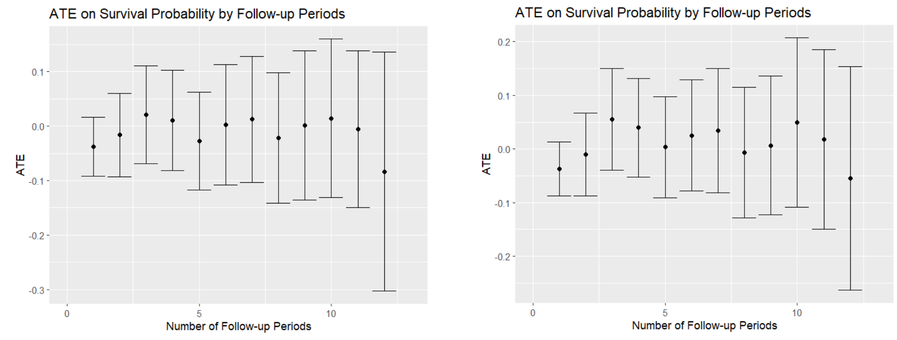
ESA Receipt Analysis

- Samples: 425 individuals for the QoL analysis, 519 individuals for survival analysis
- We identify the time periods that patients having actually taken ESA based on the start date and stop date they report, and compare them with patients having never ever taken ESA for the same amount of time.
- We account for time-varying confounding that affect both the treatment decisions and patient outcomes



(1) with super learner (2) with GLM

Figure 3: SL Estimations of ATEs of Receiving ESA for QoL Analysis



(1) with super learner (2) with GLM

Figure 4: SL Estimations of ATEs of Receiving ESA for Survival Analysis

Findings

- Using ESA appears not to have very significant effect on patients' EQ5D or on their cumulative survival probabilities across varying treatment time periods.
- Super learner algorithms may help reduce the bias of the predicted ATEs and intervention-specific mean outcomes.

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