Does SSRI use reduce COVID-19 mortality? A Study of EHR data in N3C Enclave using Targeted Learning for Causal Inference

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OBJECTIVE

- To understand disparate findings from previous research showing mixed efficacy of SSRI use in COVID-19 patients[1] through the evaluation of the feasibility of targeted maximum likelihood estimation (TMLE) as an effective approach
- This retrospective database study compares risk of mortality in chronic SSRI vs. naive patients among a large COVID-19 population

STUDY DESIGN

- Using data from the National COVID Cohort Collaborative (N3C) Enclave, which includes rich phenotype EHR data shared across collaborators
- The index date for patients in this study was the first record of a positive PCR or antigen test, or ICD-10 diagnosis code indicating COVID-19 positivity
- The chronic SSRI cohort consisted of COVID-positive patients exposed at least 4 times to ≥1 SSRIs (fluvoxamine, fluoxetine, sertraline) within 1 year prior to the index date; naive patients were defined as COVID-positive patients who were not exposed to any of the SSRIs at any time prior to the index date
- The primary outcome measure was mortality, evaluated within 180 days post-index

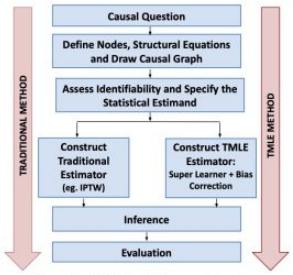

Figure 1. Statistical Process Overview

The image represents statistical process comparing the Traditional IPTW and TMLE method

ANALYSIS

- Directed Acyclic Graphs (DAGs) captured causal assumptions about variables related to COVID-19 treatment and outcome. A minimally-sufficient set of confounders were established from the DAG to estimate the effect of SSRI exposure on mortality
- To better address potential confounding, propensity scores were computed using ensemble super learners to predict treatment from potential confounders and also used to inversely-weight observations (IPTW). Each of the given SSRI treated patients were matched to an untreated subject using Nearest Neighbor propensity score matching (package *'MatchIt'*). Packages *'WeightIt', 'cobalt'* were used for propensity score (PS) weighting and package *'Survey'* was used for the estimation of treatment effect on the outcome
- The initial estimate, called g-computation, is a maximum likelihood substitution estimator and considers the binary outcome of mortality using an ensemble of super-learners (packages for g estimation *(Propensity Scores)* - *'SL.glm', 'SL.ranger', 'SL.gam', 'SL.xgboost'*)
- The estimation of Q included packages *'SL.glm', 'SL.glmnet', 'SL.ranger', 'SL.xgboost'*
- TMLE was used to incorporate ensemble super learning to estimate the average treatment effect (ATE) using the R TMLE package (*'tmle'*)[2]. This tmle package retains estimates of g(treatment) and Q(outcome) estimation used in deriving unconfounded estimates. The traditional analysis (IPTW) involved '*survey glm*' to estimate the effect of treatment on outcome. Crude and conditional odds ratios (ORs) were calculated using traditional (multivariable linear) methods
- Results from the TMLE, traditional IPTW, and the crude unadjusted approaches were compared

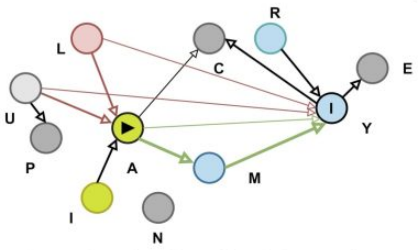

Figure 2. Directed Acyclic Graph to Display Causal Relationships Between Variables[2]

Variable roles: A = exposure or treatment: Y = outcome; L= confounder, R= risk factor for Y, M= mediator; C = collider; E = effect of Y; I = instrument; u = unmeasured confounder, P = proxy of U: N = noise variable

The DAG provides a simplistic and transparent way to evaluate causal relationships between variables. In this study a complex DAG was constructed to evaluate variables *L, R, E, M, C, U, P* that relate to propensity of fluvoxamine, fluoxetine or sertraline treatment (A) and all-cause mortality (Y) in patients diagnosed with COVID-19

RESULTS

- There were 34,473 patients in the chronic SSRI and 523,301 patients in the naive cohort
- Unadjusted (crude) results indicated an elevated mortality risk among the patients treated with chronic SSRIs (OR: 2.40, 95% CI [2.28 - 2.53]). However, much of this risk was likely due to confounding and largely attenuated by PS-matching (IPTW-OR: 1.35, 95% CI [1.22 - 1.51]) and TMLE (TMLE-OR: 1.29, 95% CI [1.19 - 1.39]) to estimate risk
- A slightly elevated mortality risk was observed in SSRI patients. Chronic SSRI users had greater comorbidities than the naive cohort
- The lack of treatment effect is consistent with prior studies, but could be due to limitations in our study, such as missing data on dosage of SSRI medications and vaccination status

CONCLUSION

- This study demonstrates the feasibility of implementing TMLE in the N3C Enclave to evaluate causal effects in very large population-based observational studies with a binary outcome
- The stable and reasonable finite-sample performance, and use of machine learning for efficient modeling of high-dimensional and complex data sources offers clear benefits in these settings

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