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Using ODA in the Evaluation of Randomized Controlled Trials: Application to Survival Outcomes

Ariel Linden, Dr.P.H. and Paul R. Yarnold, Ph.D.
Linden Consulting Group, LLC Optimal Data Analysis LLC

In a recent series of papers, ODA has been applied to observational data to draw causal inferences about treatment effects. Presently, ODA is applied to survival outcomes from a randomized controlled trial, with a reanalysis of a study by Linden and Butterworth [2014] that investigated (as a secondary outcome) the effect of a comprehensive hospital-based intervention in reducing mortality at 90 days for chronically ill patients. In the original analysis, differences in mortality rates between treatment and control groups were estimated using logistic regression and calculated as both risk differences and risk ratios, and a treatment effect was found in the subgroup of patients with chronic obstructive pulmonary disease (COPD), but not in the other subgroup of patients with congestive heart failure (CHF). In the present study, we reanalyze these results using both Cox regression, and weighted ODA, wherein the weight of every subject is their follow-up time (i.e., number of days of follow-up).

In a comprehensive series of papers, ODA and CTA frameworks have been applied to observational data to draw causal inferences about treatment effects.[1-17] In the present paper, however, we follow up on our previous reanalysis[18] of data from a randomized controlled trial (RCT), with the focus on survival outcomes.

Linden and Butterworth[19] conducted an RCT to study whether a comprehensive hospital-based intervention could reduce mortality at 90 days (as a secondary outcome after readmissions) for chronically ill patients versus regular care. In the original analysis, differences in mortality rates between treatment and control groups were estimated using logistic regression and calculated as both risk differences and risk ratios, and a treatment effect was found in the subgroup of patients with chronic obstructive pulmonary disease (COPD), but not in the other subgroup of patients with congestive heart failure (CHF). Presently we reanalyze the results of this clinical trial using both Cox regression and weighted ODA.

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Methods

Cox regression

Cox regression models[20] were estimated separately for CHF and COPD subgroups, and for the entire sample. The time variable represents the number of days from patient enrollment in the study until either death or 90 days (last day of study follow-up). Correspondingly, the censoring variable was coded as 1 if a patient died and as 0 otherwise. In each model, the outcome was regressed on the treatment indicator variable to estimate hazard ratios (HR), and 2000 bootstrap samples were used to compute 95% confidence intervals.[21]

ODA

ODA models[22,23] were generated separately for CHF and COPD subgroups, and well as for the entire sample. The binary indicator for death was specified as the class variable, the treatment indicator was set as the attribute, and the time variable was specified as the weight. 25,000 Monte Carlo simulations were used to compute *P* values, and leave-one-out (LOO) analysis was conducted to assess cross-generalizability.

Results

Cox regression

The HR in the CHF subgroup was 0.90 (95% CI: 0.38, 2.12) which was not statistically significant (*P*=0.81). The HR in the COPD subgroup was 0.27 (95% CI: 0.09, 0.81) which was statistically significant (*P* = 0.02). For the overall sample, the HR was 0.54 (95% CI: 0.28, 1.03) which was not statistically significant (*P*=0.06).

ODA

The CHF subgroup ODA model was: if treatment = 0 (control) then predict the observation is dead, otherwise if treatment = 1 (intervention) then predict the observation is alive. This model correctly classified 119 of 236 (50.4%) patients as alive, and 11 of 21 (52.4%) patients as dead (50% accuracy is expected by chance for each condition): this level of classification accuracy corresponds to weighted ESS = 3.86, a very weak effect[22,23] which was not statistically significant (*P*=0.76).

The COPD subgroup ODA model was also: if treatment = 0 (control) then predict the observation is dead, otherwise if treatment = 1 (intervention) then predict the observation is alive. This model correctly classified 120 of 236 (50.9%) patients as alive, and 15 of 19 (79.0%) patients as dead, yielding a weighted ESS = 34.08, a moderate effect[22,23] which was statistically significant (*P*=0.037). This finding was stable in LOO validity analysis suggesting this result is cross-generalizable.

In the overall sample, the ODA model was also: if treatment = 0 (control) then predict the observation is dead, otherwise if treatment = 1 (intervention) then predict the observation is alive. This model correctly classified 239 of 472 (50.6%) patients as alive, and 26 of 40 (65.0%) patients as dead, eliciting a weighted ESS = 15.70, a relatively weak effect [22,23] which was not statistically significant (*P*=0.128).

Discussion

In this paper we have demonstrated how ODA can be used to assess treatment effects in an RCT when the outcome is survival. Presently, ODA results corresponded to those of Cox regression, that is, in the COPD subgroup there appeared to be a treatment effect, whereas in the CHF subgroup there was no treatment effect.

ODA should be considered the preferred approach over commonly-used parametric models because ODA avoids the assumptions required of parametric models (e.g. linearity, sufficient sample size, independence, etc.), while by being insensitive to skewed data or outliers, and in its ability to handle any variable metric including categorical, Likert-type integer, and real number measurement scales.[23]

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Finally, ODA has the capability to use cross-validation methods such as LOO which was employed presently, in addition to hold-out, multiple-sample, test-retest, and bootstrap[22,23] cross-validation methods to assess the generalizability of the model to other states with similar characteristics planning to implement a similar set of initiatives [24]. Again, there is no equivalent in the regression-based framework, failing to provide insight into the likelihood that any observed intervention effect would generalize.

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Author Notes

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