ELSEVIER

Journal of Clinical Epidemiology 66 (2013) S51−S56

Journal of Clinical Epidemiology

Approaches to inverse-probability-of-treatment−weighted estimation with concurrent treatments

Alan R. Ellis[a], M. Alan Brookhart[a,b,*]

[a]*Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, CB# 7590, Chapel Hill, NC 27599-7590, USA*
[b]*Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 2105F McGavran-Greenberg, CB# 7435, Chapel Hill, NC 27599-7435, USA*

Accepted 13 March 2013

Abstract

Objectives: In a setting with two concurrent treatments, inverse-probability-of-treatment weights can be used to estimate the joint treatment effects or the marginal effect of one treatment while taking the other to be a confounder. We explore these two approaches in a study of intravenous iron use in hemodialysis patients treated concurrently with epoetin alfa (EPO).

Study Design and Setting: We linked US Renal Data System data with electronic health records (2004−2008) from a large dialysis provider. Using a retrospective cohort design with 776,203 records from 117,050 regular hemodialysis patients, we examined a composite outcome: mortality, myocardial infarction, or stroke.

Results: With EPO as a joint treatment, inverse-probability-of-treatment weights were unstable, confidence intervals for treatment effects were wide, covariate balance was unsatisfactory, and the treatment and outcome models were sensitive to omission of the baseline EPO covariate. By handling EPO exposure as a confounder instead of a joint treatment, we derived stable weights and balanced treatment groups on measured covariates.

Conclusions: In settings with concurrent treatments, if only one treatment is of interest, then including the other in the treatment model as a confounder may result in more stable treatment effect estimates. Otherwise, extreme weights may necessitate additional analysis steps.

Keywords: Propensity score; Statistics as topic; Models; Statistical; Epidemiologic methods; Estimation

1. Introduction

Inverse-probability-of-treatment−weighted (IPTW) estimation is now commonly used to control for confounding in nonexperimental studies of medical interventions [1−3]. IPTW estimation requires that the analyst specify a model of the treatment rather than the outcome. The fitted treatment model is then used to estimate inverse-probability-of-treatment weights that are applied to each subject. If the treatment model is correctly specified, the reweighting results in a population of patients in whom treatment assignment is unrelated to the baseline variables that are included in the treatment model. Under the assumptions of exchangeability, positivity, consistency, and a correctly specified treatment model [1,4,5], IPTW estimation results in estimates that can be interpreted as the average treatment effect (ATE) in the population being studied. (Informally, exchangeability refers to the absence of unmeasured confounders, positivity requires that each subject have a nonzero probability of receiving each of the treatments being compared, and consistency means that the observed outcome equals the counterfactual outcome of the treatment actually received.) The IPTW approach is attempting to mimic a situation in which treatment is randomly allocated to individuals.

IPTW estimation can be extended to settings with concurrently administered treatments. Herein, one is attempting to estimate the average joint effect of the treatments. Thus, IPTW estimation is attempting to mimic a situation in which each concurrent treatment is randomized individually. This requires that one construct a model of the probability that a patient would receive any particular combination of the treatments being studied.

Conflicts of interest: In the past 5 years, A.R.E. has received research funding from the University of North Carolina Center for Pharmacoepidemiology, which receives industry support, and from Merck. M.A.B. has received research support from Amgen, Rockwell Medical, and Pfizer. M.A.B. has sat on advisory boards for Amgen and Pfizer but has not accepted honoraria for these activities.

* Corresponding author. Tel.: +919-843-2639; fax: +919-966-2089.
E-mail address: abrookhart@unc.edu (M.A. Brookhart).

0895-4356/$ - see front matter
http://dx.doi.org/10.1016/j.jclinepi.2013.03.020

What is new?

- Inverse-probability-of-treatment−weighted (IPTW) estimation can be applied to two or more concurrently administered treatments.
- In this setting, IPTW estimation may be more likely to result in large weights and estimates that are very sensitive to model specification.
- If only one treatment is of interest, then including the other treatment in the treatment model as a confounder may result in more stable estimates of the effect of interest.
- In studies of concurrent treatments, analysts using IPTW methods should be vigilant for problems arising from large weights. In some settings, it may be more feasible to estimate the marginal effect of a single treatment.
- If a joint treatment effect is of interest, extreme inverse probability of treatment weights may need to be addressed by excluding observations whose covariate values are rare in any treatment group, by limiting the analysis to common treatment regimes, or through other means.

IPTW estimates can be highly unstable in the presence of large weights because the estimates may be driven by outcomes occurring in a small number of patients [6−8]. This can happen if patients are treated contrary to indication, the population is poorly defined (i.e., includes patient subgroups that rarely receive treatment), or the treatment model is misspecified (i.e., predicted probabilities of treatment are incorrect). Large weights may be particularly likely in settings with concurrent treatments, where there may be many treatment categories, some treatment combinations may be uncommon, and correct specification of the treatment model may be more difficult.

In a setting with concurrent treatments, if interest focuses primarily on the effect of one treatment, IPTW estimation can be used to estimate the marginal effect of the treatment of interest, taking the concurrently used treatments to be confounders. This simplifies the estimation of the treatment model. It also imposes fewer assumptions on the analysis because exchangeablility, positivity, and consistency need to hold for only one treatment.

We explore these issues in a study of iron treatment outcomes in hemodialysis patients, a setting in which concurrent use of erythropoiesis-stimulating agents (ESAs) must be addressed and extreme weights are known to be problematic [9]. Specifically, our study examines the effect of iron treatment administered at a point in time, as measured during a 1-month exposure period, on a composite cardiovascular outcome.

2. Background

2.1. Anemia management in hemodialysis patients

Anemia affects about 10% of patients in the early stages of chronic kidney disease and more than 70% of patients with end-stage renal disease (ESRD) [10]. The anemia of ESRD is primarily caused by impaired production of renal erythropoietin. It is worsened by dialysis-related blood loss, which depletes iron reserves [11]. The anemia of ESRD involves treatment with ESAs to stimulate the production of red blood cells and administration of intravenous iron to address iron deficiency [12].

Several biological mechanisms suggest potential risks associated with the use of iron [13]. For example, frequent iron administration may lead to oversaturation of transferrin and the release of free, catalytically active iron into the plasma [14]. Free iron is also known to catalyze the formation of highly reactive oxygen species [15,16]. These could give rise to lipid radicals, which may damage the vasculature [17] and lead to atherogenesis [18], possibly increasing the long-term risk of cardiovascular events [13,19]. However, little is known about the relation between iron dose and cardiovascular outcomes.

We recently undertook a study in which we used data from the US Renal Data System linked with data from dialysis providers to assess the relative safety and effectiveness of different iron formulations and dosing strategies. We used multivariable models to examine multiple outcomes, including cardiovascular events and mortality. To minimize bias owing to confounding factors, we sought to implement IPTW estimation. Because joint treatment with ESAs and iron complicated the IPTW analysis, we conducted sensitivity analyses to identify the best way to model treatment. To demonstrate the sensitivity of treatment effect estimates to the treatment model, we used as an example a composite outcome: mortality, myocardial infarction, or stroke. In this article, we report the results of our sensitivity analyses and comment briefly on the handling of concurrent treatments in IPTW analyses.

3. Methods

3.1. Data, study design, and sample

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, the US Renal Data System collects, analyzes, and distributes information about ESRD treatment in the United States, including data from the Medical Evidence Report Form, the Medicare Enrollment Database, the ESRD Death Notification Form, and the standard analytic files, which contain final action claims data [20]. We linked US. Renal Data System data with 5 years of electronic health record data (2004−2008) from a large US dialysis provider that owns and manages more than 1,500 outpatient dialysis facilities throughout the United