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ORIGINAL ARTICLE

Instrumental variable methods for a binary outcome were used to informatively address noncompliance in a randomized trial in surgery

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Abstract

Objectives: Randomization can be used as an instrumental variable (IV) to account for unmeasured confounding when seeking to assess the impact of noncompliance with treatment allocation in a randomized trial. We present and compare different methods to calculate the treatment effect on a binary outcome as a rate ratio in a randomized surgical trial.

Study Design and Setting: The effectiveness of peeling versus not peeling the internal limiting membrane of the retina as part of the surgery for a full thickness macular hole. We compared the IV-based estimates (nonparametric causal bound and two-stage residual inclusion approach [2SRI]) with standard treatment effect measures (intention to treat, per protocol and treatment received [TR]). Compliance was defined in two ways (initial and up to the time point of interest). Poisson regression was used for the model-based approaches with robust standard errors to calculate the risk ratio (RR) with 95% confidence intervals.

Results: Results were similar for 1-month macular hole status across methods. For 3- and 6-month macular hole status, nonparametric causal bounds provided a narrower range of uncertainty than other methods, though still had substantial imprecision. For 3-month macular hole status, the TR estimate was substantially different from the other point estimates.

Conclusion: Nonparametric causal bound approaches are a useful addition to an IV estimation approach, which tend to have large levels of uncertainty. Methods which allow RRs to be calculated when addressing noncompliance in randomized trials exist and may be superior to standard estimates. Further research is needed to explore the properties of different IV methods in a broad range of randomized controlled trial scenarios.

Keywords: Instrumental variable; RCT; Noncompliance; Binary; Causal modeling; Risk ratio

1. Introduction

Randomized controlled trials (RCTs) are widely seen as the optimal way to evaluate the effect of treatments. However, the design, conduct, and analysis of an RCT can undermine the purpose of randomization and introduce bias in the estimation of treatment effects. Departures from random allocation (often referred to as noncompliance or nonadherence) create uncertainty in the interpretation of findings with regard to the causal effect of treatment. Although an intention-to-treat (ITT)−based analysis remains the default analysis [1−3], in the presence of substantial noncompliance, it is natural to ask the question ‘‘what is the effect of actually receiving the treatment?’’

Two common approaches used to address noncompliance are per-protocol (PP) and treatment-received (TR) analyses. Under a PP analysis, only data from those participants deemed to have complied with the (treatment) protocol are included. In a TR analysis, the analysis groups are formed on the basis of the actual TR, irrespective of the randomized treatment. The shortcomings of these

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What is new?

Key findings

- Across the different time points and noncompliance definitions for the case study, the point estimates of the various methods were generally similar.
- The nonparametric casual bound approach produced a narrow range of uncertainty than the risk ratio confidence interval of the two-stage residual inclusion instrumental variable (IV) method and standard intention to treat, per protocol and treatment received estimates.

What this adds to what was known?

- This article compared conventional analyses for dealing with noncompliance in a randomized controlled trial with two IV approaches for a binary outcome.
- The assumptions, advantages, and disadvantages of the approaches are considered using a surgical trial with substantial receipt of the nonallocated treatment over the follow-up period (''noncompliance'').

What is the implication and what should change now?

- The nonparametric causal bounds approach for binary outcome may be more informative than the standard method to address noncompliance in a trial in some situations.
- The generalizability of the finding should be explored across a range of settings and levels of treatment effect and noncompliance.

conventional approaches to dealing with noncompliance are well recognized [1,3]. Those who do not comply with treatment allocation (e.g. did not get surgery as allocated) tend to be different from the typical participant (they are often sicker and poorer in health, though in some situations the reverse can be true). A PP analysis excludes the subset of participants who do not comply from the analysis risk potentially introducing selection bias, as those who comply may reflect different patient characteristics between the groups. The TR analysis is carried out on the basis of transferring individuals who ''crossed over'' to the other group, and so also introduces bias into the comparison.

More recently, causal methods which address noncompliance while maintaining the integrity of randomization and avoiding exclusions of participants have been proposed [3−5], which vary in complexity and the underlying assumptions. Focus has mainly been on continuous outcomes [2,4,6−8] partly through the more ready application of methods, although approaches for binary outcomes do exist [1,4,5,9,10]. Their use has been limited, and when used, the focus has been on calculating the risk difference and in the setting of an observational study [11,12]. In particular, causal bound instrumental variable (IV) methods have received little attention but can be readily calculated when the instrument, exposure variable, and the outcome are binary [9]. Surgery is considered an example of a scenario where compliance issues are ''simple'' (i.e., surgery is or is not received) as opposed to drug treatment or complex interventions which are delivered over time [5]. However, the recent work has highlighted the potential complexity of surgical interventions [13−15]. The use of compliance-based trial analyses in the area of surgery has been very limited to date, and methodological considerations have focused on surgery versus medicine and for a continuous outcome [16]. The aim of the work presented herein is to explore the compliance in a surgical randomized trial, where the treatment effect for a binary primary outcome is expressed as a risk ratio (RR). Through the case study, we seek to illustrate the use of randomization respecting compliance analyses versus conventional methods and to consider issues relating to compliance in this setting.

1.1. Case study−FILMS trial

The Full Thickness Macular Hole and Internal Limiting Membrane Peeling Study (FILMS) trial compared macular hole surgery with or without peeling (removal) of the internal limiting membrane (ILM) of the retina for idiopathic full thickness macular holes (FTMH) [17,18]. Macular hole surgery, which seeks to close the hole and improve patient visual outcome, involves a number of steps with peeling an optional additional step. Patients with stage 2 or 3 FTMH were randomized to receive macular hole surgery with or without ILM peeling or not at nine centers. Of the 141 participants randomized, 138 were included in the statistical analysis (three were discovered not to meet the eligibility criteria after being randomized). The status of the macular hole (open or closed), the main surgical outcome, was assessed at 1, 3, and 6 months after surgery. Other outcomes collected included visual function (EDTRS visual acuity in the study eye [the primary outcome] and the fellow eye) and quality of life (Visual Function Questionnaire-25 and EuroQol 5 Dimensions 3 Levels). Principal (ITT based) study analyses found evidence of decreased occurrence of an open hole at 1 month but no statistical evidence of difference at 3 and 6 months [17]. However, interpretation of these findings was complicated by the occurrence of further surgery with 29 (43%) of the nonpeeling group received peeling within the 6-month follow-up period (Table 1). Some occurrences of peeling within this group were as per the initial treatment and some as a further surgical intervention, which was allowed in FILMS according to standard clinical care. Although a number of factors could