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Q1 Estimating time-varying treatment switching effects via local linear smoothing and quasi-likelihood☆

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ABSTRACT

Vascular access complications have been the major cause of excessive morbidity and mortality in the dialysis population. They also account for a large portion of hospitalization for dialysis patients and are a main contributor to the high dialysis care cost. Despite the Fistula First Initiative, the majority of patients initiate dialysis with a central venous catheter which is associated with poor outcomes. In this paper we investigate whether switching from a central venous catheter to an arteriovenous fistula sooner is associated with smaller hospitalization rate. We propose a flexible model for time-varying switching effect while accounting for trend over calendar time, trend over time on dialysis and time-varying effects of covariates. We model all unknown functions nonparametrically using local linear smoothers and estimate them using weighted local quasi-likelihood. We show that the proposed estimators have the desirable large-sample properties and excellent performance in simulations. Application of the proposed method to a real data set indicates that hospitalization rate is smaller when patients switch from a central venous catheter to an arteriovenous fistula sooner. The proposed methods are general which are applicable to other situations with treatment switching.

1. Introduction

In many medical studies patients enter an initial treatment at different time points. Some patients subsequently switch to a different treatment and some stayed with the original treatment. An outcome such as hospital admissions and some covariates are recorded over time since the initial treatment for each patient. One of the goals is to investigate potential treatment switching effect on the outcome adjusting for covariates. We use the term treatment in a broad sense to indicate an event such as intervention, onset of a certain disease, and exposure to a risk factor.

Our research was motivated by the need of improvement of vascular access for dialysis patients. More than 408,000 adults in the United States were on dialysis and these patients had much higher hospitalization and mortality rates than those of the general population (USRDS, 2014). One of the major causes of high morbidity and mortality is vascular access complications

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such as infection and thrombosis. Vascular access complications account for nearly 30% of hospital admissions (Moist and Al-Jaishi, 2013). Dialysis treatments require access to blood vessels capable of providing rapid extracorporeal blood flow. There are three types of vascular access in order of preference: arteriovenous fistula (AVF), arteriovenous grafts (AVG), and central venous catheter (CVC) (Kumwenda et al., 2015). In spite of the association with poor outcomes, CVC is used as acute vascular access by majority of patients at the initiation of dialysis since AVF and AVG need time to develop and mature (Shingarev et al., 2013; Lacson et al., 2009). Studies have demonstrated that switching from CVC to AVF is associated with decreased mortality (Allon et al., 2006; Bradbury et al., 2009). However, no research has been conducted to study the timing of switch and the dynamic effect of vascular access change.

In this paper we will investigate whether switching from CVC to AVF sooner is associated with smaller hospitalization rate. In addition to the switching time, hospitalization rate may depend on calendar time and time on dialysis. Furthermore, it may depend on time-varying and time-independent covariates such as albumin and gender. To account for these important factors, we will consider a model that consists of trends over calendar time and time on dialysis, time-varying switching effect and covariate effects with varying coefficients. This model is new and flexible. Silverman and Wood (1987), Kohn and Ansley (1991) and Ma and Zhong (2008) considered branching curve models where a curve branches out smoothly at the switching time. Their methods cannot be used to investigate time-varying switching effect of vascular access change since, in addition to the Gaussian assumption, these methods assume a single switching time for all patients and do not include covariates effects. To deal with multiple time indices, Estes et al. (2014) considered a generalized varying coefficient model where a linear model was assumed for switching time. We will use a bivariate nonparametric function to model the effect of switching time and time since switching jointly. Although motivated by the vascular access switch in dialysis patients, the proposed generalized time-varying treatment switching effect models are sufficiently general for a variety of other potential applications.

The article is organized as follows. Sections 2 and 3 introduce our model and estimation procedure. Sections 4 and 5 present asymptotic properties and simulation results. We apply our methods in Section 6 to investigate the effect of dialysis vascular access change from CVC to AVF on hospitalization rate. Technical proofs are given in an Appendix.

2. The time-varying treatment switching effect model

We consider a general model for treatment switching effect in this section. We will adopt generic terms such as treatments A and B. A specific model for the effect of switching from CVC to AVF on hospitalization rate in dialysis patients will be presented in Section 6. We adopt the partly conditional approach where the analysis is conditional on being alive (Kurland et al., 2009; Estes et al., 2014).

Suppose that each subject in a cohort starts with treatment A and is then followed over a period of time. During this period of time the subject may switch to treatment B. For the dialysis vascular access problem, each patient starts with CVC (treatment A) at the initiation of dialysis and may switch to AVF (treatment B) later. Another example is that each subject is free of a potential risk factor at the beginning and may be exposed to this risk factor later.

Let c_A and c_B be the calendar times when a subject starts treatment A and switches to treatment B respectively. We set $c_B = \infty$ when a subject does not switch to treatment B. We consider three time indices: calendar time c, time on treatment A $t = c - c_A$, and time on treatment B $u = c - c_B$. Let $\boldsymbol{x}(t) = (x_1(t), \ldots, x_p(t))^T$ be a vector of covariates at time t. Note that some covariates may be time-independent even though all of them are represented as functions of t. Let $y(t)$ be the outcome at time t.

For subject i, let c_{iA} and c_{iB} be the calendar times when subject i starts treatment A and switches to treatment B respectively. Let $c_{i1} < c_{i2} < \cdots < c_{in_i}$ be calendar time points where observations are made. Let $t_{ij} = c_{ij} - c_{iA}$ be the time points on treatment A where observations are made, $s_i = c_{iB} - c_{iA}$ be the switching time of subject i, and $u_{ij} = t_{ij} - s_i$ be the time on treatment B. Let $\boldsymbol{x}_{ij} = \boldsymbol{x}(t_{ij})$ and $y_{ij} = y(t_{ij})$ be observations of the covariates and outcome at time t_{ij}. Let $\mu_{ij} = \mathrm{E}(y_{ij})$ and $g(\cdot)$ be a given link function. We consider the following model

$$g(\mu_{ij}) = f(t_{ij}) + l(c_{ij}) + b(s_i, u_{ij}) + \boldsymbol{x}_{ij}^T \boldsymbol{\beta}(t_{ij}), \quad i = 1, \ldots, m,\ j = 1, \ldots, n_i, \tag{1}$$

where $f(\cdot)$ models the trajectory over time index of treatment A, $l(\cdot)$ models the trajectory over calendar time, $b(\cdot, \cdot)$ models the change associated with treatment switching, and $\boldsymbol{\beta}(\cdot) = (\beta_1(\cdot), \ldots, \beta_p(\cdot))^T$ is vector of p varying coefficient functions. We assume that f, l and $\beta_1(\cdot), \ldots, \beta_p(\cdot)$ are univariate smooth functions, and b is a bivariate smooth function such that $b(\cdot, u) = 0$ when $u < 0$. We allow the effect of switching to depend on both the time of switching s and time since switching u. For identifiability, we assume that $\mathrm{E}(l(c)) = 0$ and $b(0, 0) = 0$. Furthermore, we assume that not all subjects start treatment A at the same time.

For generality we will not assume a specific distribution for y. Instead, we assume that the variance function $V(\mu)$ is known and use the quasi-likelihood

$$Q(\mu, y) = \int_y^\mu (y - u)/\sigma^2 V(\mu) \mathrm{d}u \tag{2}$$

for estimation.

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