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Instrumental Variable Additive Hazards Models with Exposure-dependent Censoring

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Summary

Li, Fine and Brookhart (2015) presented an extension of the two-stage least squares (2SLS) method for additive hazards models which requires an assumption that the censoring distribution is unrelated to the endogenous exposure variable. We present another extension of 2SLS that can address this limitation.

Keywords

Two stage residual inclusion; unmeasured confounding

1. Introduction

Instrumental variable regression methods have been widely used for addressing the problem of unmeasured confounding when a valid instrument is available for analysis. Two-stage least squares (2SLS) has been used when the outcome of interest is uncensored. Li, Fine and Brookhart (2015) recently proposed a simple but powerful extension of 2SLS to additive hazards models for censored survival outcomes. As acknowledged in that paper, a limitation of their method is that the censoring distribution is assumed to be unrelated to the endogenous exposure variable given exogenous variables. The purpose of this paper is to discuss a different extension of 2SLS that can address this limitation.

2. Two-stage predictor substitution and residual inclusion

We employ the same notations as Li, Fine and Brookhart (2015). Let T be the failure time of interest and C be the censoring time. The observed survival data are $Y = \min(T, C)$ and $\delta = I(T \leq C)$. Let X_e be an endogenous exposure variable of interest, X_o be observed exogenous variables, X_u be unobserved confounders and X_I be an instrumental variable. The conditional hazard function of the survival outcome follows an additive hazards model

$h_0(t) + \beta_e X_e + \beta_o^T X_o + \eta$ and the endogenous exposure model follows $X_e = a_c + a_I X_I + a_o X_o + v$, where η and v are dependent on X_u but not (X_I, X_o) .

Li, Fine and Brookhart (2015) first obtain the least-square estimates $(\hat{a}_c, \hat{a}_I, \hat{a}_o^T)$ and predict the exposure $\hat{X}_e = \hat{a}_c + \hat{a}_I X_I + \hat{a}_o^T X_o$. Then, they fit the additive hazards model using $\hat{X}_e$ and X_o as the covariates. This procedure is often called two-stage predictor substitution (2SPS)

in the literature. An alternative two-stage residual inclusion (2SRI) method can be formulated as follows: Using the same exposure model to obtain least-square estimates $(\hat{\alpha}_c, \hat{\alpha}_1, \hat{\alpha}_0^T)$, we predict the residuals $\hat{\nu} = X_e - \hat{\alpha}_c - \hat{\alpha}_1 X_1 - \hat{\alpha}_0^T X_o$. The second-stage model uses $(X_e, X_o^T, \hat{\nu})$ as predictors.

Intuitive rationales of the instrumental variable methods are given as follows: Note that the major complication of unmeasured confounding is that X_e and η are dependent but η is unobserved. In order to correct for the bias, one needs to redefine the predictors in such a way that they are independent of the unobserved effective error term. Two different decompositions are possible and form the bases for 2SPS and 2SRI. For 2SPS, the endogenous exposure is decomposed into the predicted exposure which is a function of (X_1, X_o) and a remainder ν that is independent of (X_1, X_o) . The predicted exposure in the second stage is then independent of the effective error term, which is $\nu + \eta$. For 2SRI, the error term η is decomposed into a part that depends on (X_e, X_1, X_o) and a remainder term that is independent of (X_e, X_1, X_o) . By including the first term in the second stage as a predictor, the effective predictors are independent of the effective error term.

When the outcome T is uncensored and follows a linear model, the coefficients for (X_e, X_o^T) in 2SRI are identical to coefficients of $(\hat{X}_e, X_o^T)$ in 2SPS. However, for censored outcomes they are different in general. In fact, they are valid under different censoring assumptions. For 2SPS, since $\tilde{X}_e = \alpha_c + \alpha_1 X_1 + \alpha_o^T X_o$ depends solely on (X_1, X_o) , risk-set arguments are valid under Assumption (C6) given below:

$$C \text{ is conditionally independent of } T \text{ given } (X_1, X_o). \quad (C6)$$

For 2SRI, the predictor of the second-stage model depends on (X_e, X_1, X_o) and risk-set arguments are valid under the relaxed assumption

$$C \text{ is conditionally independent of } T \text{ given } (X_e, X_1, X_o). \quad (C6'a)$$

To see that (C6) is necessary for 2SPS, we consider the compensated process

$$M^*(t) = I(Y \leq t, \Delta=1) - \int_0^t I(Y \geq s) [h_0^*(s) + \beta_e \tilde{X}_e + \beta_o^T X_o] ds$$

where $h_0^*(t)$ is the marginal hazard function of a random variable T^* for which the conditional hazard function of T^* given η is $h_0(t) + \eta$ and T^* is conditionally independent of (X_1, X_o, X_u) given η . It follows that $E(M^*(t) | X_1, X_o) = 0$, but $E(M^*(t) | X_e, X_1, X_o) \neq 0$ in general because η and X_e are dependent. Therefore, (C.6) is needed for the consistency of 2SPS.

While the assumption (C6' a) is weaker than (C6) in general, the validity of 2SRI requires an additional assumption on the relationship between η and ν :

$$\eta = \gamma_\nu \nu + \varepsilon' \quad (\text{C6' b})$$

where ε' is independent of (X_I, X_O, X_U) . Note that Assumption (C6' b) is substantially more relaxed than a similar assumption in a prominent paper by Terza, Basu and Rathouz (2008), in which their equation (3) requires $\varepsilon' \equiv 0$. When $\varepsilon' \equiv 0$, the unobserved confounder can be fully identified by the observable exposures and instruments, which is unrealistic in practice. Assumption (C6' b) is substantially more general but is needed in 2SRI because one needs to decompose η into a part that is dependent on X_e and a part that is independent of X_e . It is not needed in 2SPS because $\tilde{X}_e$ solely depends on (X_I, X_O) , which are independent of η . However, including X_e as a predictor of 2SRI allows C to be dependent on X_e in (C6' a). The assumptions (C6' a) and (C6' b) imply unbiasedness of the following compensated process:

$$M^\dagger(t) = I(Y \leq t, \Delta = 1) = \int_0^t I(Y \geq s) [h_0^\dagger(s) + \beta_e X_e + \beta_o^T X_o + \gamma_\nu \nu] ds$$

where $h_0^\dagger(t)$ is the marginal hazard function of a random variable $T^\dagger$ for which the conditional hazard function of $T^\dagger$ given ε' is $h_0(t) + \varepsilon'$, and $T^\dagger$ is conditionally independent of (X_e, X_I, X_O, X_U) given ε' . It follows that $E(M^\dagger(t) | X_e, X_I, X_O) = 0$ because ε' and X_e are independent.

3. Numerical studies

We follow simulation settings I–III in Li, Fine and Brookhart (2015) to simulate data without exposure-dependent censoring. In Scenario I, survival times are generated from an exponential distribution and $\beta_e = 1$. In Scenario II, survival times are generated from a Weibull distribution and $\beta_e = 0.15$. In Scenario III, survival times are generated from a gamma frailty model with a linear conditional hazard function and $\beta_e = 0.2$. For each of the settings, we consider three scenarios corresponding to (a) independence between X_e and C , (b) weak dependence between X_e and C and (c) moderate dependence between X_e and C . Dependence in cases (b) and (c) follow a Clayton copula with $\theta = 1$ and 2 , and the corresponding Kendall's rank correlations are of 0.3 and 0.5 . Table 1 shows the simulation results. When censoring is not exposure-dependent, the performance of two methods are almost identical. When censoring is exposure-dependent, the 2SPS of Li, Fine and Brookhart (2015) can have substantial relative biases of the true effect, while the two-stage residual inclusion method has negligible relative biases. The empirical standard error of the two estimators has negligible differences.

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Table 1

Simulation results comparing two-stage predictor substitution (2SPS) of Li, Fine and Brookhart (2015) and the proposed two-stage residual inclusion (2SRI); (a) independence between X_c and C, (b) weak dependence between X_c and C and (c) moderate dependence between X_c and C. Results are based on 5000 simulations. Truth represents true parameter values ($\times 100$). AB represents absolute sampling bias ($\times 100$). PB represents percentage bias ($\times 100\%$) and SE represents sampling standard deviation ($\times 100$).

Scenario	n	Truth	(a)				(b)				(c)									
			2SPS		2SRI		2SPS		2SRI		2SPS		2SRI							
			AB	PB	SE	AB	PB	SE	AB	PB	SE	AB	PB	SE	AB	PB	SE			
I	100	100	-6	-6	(262)	-5	-5	(269)	-32	-32	(273)	6	6	(281)	-53	-53	(276)	4	4	(285)
	200	100	-6	-6	(167)	-4	-4	(170)	-43	-43	(175)	-2	-2	(179)	-59	-59	(178)	1	1	(182)
	400	100	-2	-2	(111)	-2	-2	(114)	-38	-38	(118)	2	2	(120)	-54	-54	(121)	4	4	(123)
	800	100	-4	-4	(78)	-4	-4	(79)	-42	-42	(82)	-2	-2	(83)	-60	-60	(84)	-2	-2	(86)
	1200	100	2	2	(64)	-2	-2	(65)	-42	-42	(66)	-2	-2	(67)	-60	-60	(68)	-1	-1	(68)
II	100	15	-2	-13	(41)	-2	-11	(42)	-8	-54	(44)	-1	-7	(44)	-12	-79	(45)	-1	-9	(46)
	200	15	-2	-10	(28)	-1	-9	(29)	-8	-51	(31)	-1	-4	(31)	-11	-75	(31)	-1	-5	(32)
	400	15	-1	-4	(19)	<1	-3	(19)	-7	-49	(21)	<1	-2	(22)	-11	-74	(22)	-1	-4	(22)
	800	15	<1	-2	(14)	<1	-1	(14)	-8	-52	(15)	-1	-5	(15)	-11	-76	(16)	-1	-6	(16)
	1200	15	<1	-2	(11)	<1	-1	(11)	-8	-50	(12)	<1	-3	(12)	-11	-75	(13)	-1	-5	(13)
III	100	20	-2	-11	(40)	-2	-9	(41)	-10	-50	(44)	-1	-8	(45)	-14	-68	(46)	-2	-10	(47)
	200	20	-2	-8	(27)	-1	-7	(28)	-10	-50	(30)	-1	-8	(31)	-14	-71	(31)	-1	-9	(32)
	400	20	-1	-5	(19)	-1	-4	(19)	-10	-48	(21)	-1	-6	(21)	-14	-68	(22)	-1	-7	(22)
	800	20	-1	-7	(13)	-1	-6	(13)	-10	-45	(15)	-1	-4	(15)	-13	-66	(15)	-1	-5	(15)
	1200	20	-1	-6	(11)	-1	-4	(11)	-9	-47	(12)	-1	-5	(12)	-14	-68	(12)	-1	-6	(12)