Comparing survival functions with interval-censored data in the presence of an intermediate clinical event

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Background

- In clinical trials and longitudinal studies, a subject under investigation may experience an intermediate clinical event (IE) before the event of interest. The occurrence of the IE may induce changes in survival functionns
- To resolve length-biased problems due to the IE, the time-dependent Cox regression and landmark studies were conducted (Mantel et al., 1974;Anderson et al., 1983). The score tests based on counterfactual variables were derived by Lefkopoulou & Zelen(1995) and Nam & Zelen(2001)
- Moreover, when the primary outcome is interval-censored, the situation is more complicated

Methods

- Nam and Zelen(2001) studied a length-biased problem with right-censored data in the presence of the IE
- They derived the score test using a proportional hazards model for comparing two survival functions
- Multiple imputation converts interval-censored data to right-censored data so that standard methods can be applied. This method can simplify complicated situations
- We propose two methods: 1) uniform weight method and 2) weighted weight method
- The uniform method follows the method of Kim et al.(2006) and the weighted method followed that of Huang et al.(2008) to accommodate for left truncation
- The score statistics were used after imputation

Simulation setup

- Generate the true failure time T_0 and waiting time W from the survival function, respectively, $Q_{0g}(t_0) = e^{-\lambda_{0g} t_0}, G_g(w) = e^{-\mu_g w}$ for $g = A, B$
- If $W > T_0$, then $T = T_0$. If $W \leq T_0$, T_1 is generated from the truncated probability density function $q_{1g}(t_1)/Q_{1g}(w)$, where $Q_{1g}(t) = e^{-\lambda_{1g} t}$. Set $T = T_1$
- Define a censoring indicator δ that follows a Bernoulli distribution with a censoring probability c_p. c_p is set as 0 or 0.3
- Set $\theta_A = 0.5, \theta_B = \{0.3, 0.4, 0.5\}, \lambda_{0A} = \lambda_{0B} = 1, m_{1A} = 1$ and $2, m_{1B} = \{1, 1.25, 1.5, 2\}$
    - $\theta_g = \mu_g/(\mu_g + \lambda_{0g})$: the probability of experiencing the IE
    - $m_{1g}(= 1/\lambda_{1g})$: the mean time to failure of the subjects who experience the IE

Simulation setup

- To generate interval-censored data, the first scheduled visit time E_1 is generated from $U(0, \psi)$. For a subject having the IE, E_1 is generated from $U(W, W + \psi)$ to ensure $E_1 \geq W$
- The length of the time interval between two follow-up visits was assumed as a constant, $\psi = 0.5$. $E_k = E_{k-1} + \psi, k = 2, 3, \ldots$
- At each of these time points, it is assumed that a subject could miss the scheduled visit
- L_i is defined as the largest E_k among scheduled visit points less than T_i and R_i as the smallest E_k among scheduled visit points greater than T_i
- If $\delta_i = 0$, T_i is right-censored. If $\delta_i = 1$, T_i is observed on $(L_i, R_i]$
- For comparison, we included the log-rank test and the stratified log-rank test (the stratum is experiencing the IE or not) along with our proposed tests

Simulation results

Table: Empirical 5%-level tests by varying θ_B, m_{1A}, and m_{1B} with $\theta_A = 0.5$ when all events are observed in some intervals and there are some missed visits with a probability of 0.1 for the first year and then of 0.2 thereafter

$n = 200$

(θ_A, θ_B)	(m_{0A}, m_{0B})	(m_{1A}, m_{1B})	I	II	III	IV
(0.5, 0.5)	(1, 1)	(2, 2)	0.059	0.057	0.054	0.056
(0.5, 0.5)	(1, 1)	(1, 1)	0.055	0.042	0.042	0.043
(0.5, 0.4)	(1, 1)	(2, 2)	0.096	0.221	0.054	0.054
(0.5, 0.4)	(1, 1)	(1, 1)	0.061	0.282	0.045	0.044
(0.5, 0.3)	(1, 1)	(2, 2)	0.232	0.621	0.051	0.050
(0.5, 0.3)	(1, 1)	(1, 1)	0.053	0.747	0.045	0.043

I = log-rank, II = Stratified log-rank, III = Uniform weight method, IV = Weighted weight method

Simulation results

Table: Empirical 5%-level tests by varying θ_B, m_{1A}, and m_{1B} with $\theta_A = 0.5$ when censoring fraction is 0.3 and there are some missed visits with a probability of 0.1 for the first year and then of 0.2 thereafter

$n = 200$

(θ_A, θ_B)	(m_{0A}, m_{0B})	(m_{1A}, m_{1B})	I	II	III	IV
(0.5, 0.5)	(1, 1)	(2, 2)	0.059	0.059	0.042	0.045
(0.5, 0.5)	(1, 1)	(1, 1)	0.050	0.054	0.052	0.050
(0.5, 0.4)	(1, 1)	(2, 2)	0.078	0.180	0.048	0.050
(0.5, 0.4)	(1, 1)	(1, 1)	0.057	0.219	0.044	0.043
(0.5, 0.3)	(1, 1)	(2, 2)	0.168	0.485	0.047	0.050
(0.5, 0.3)	(1, 1)	(1, 1)	0.060	0.582	0.040	0.043

I = log-rank, II = Stratified log-rank, III = Uniform weight method, IV = Weighted weight method

Simulation results

Table: Empirical power of tests by varying m_{1B} when censoring fraction is 0 and 0.3 and when there are some missed visits with a probability of 0.1 for the first year and then of 0.2 thereafter

$n = 200$						
(θ_A, θ_B)	(m_{0A}, m_{0B})	(m_{1A}, m_{1B})	I	II	III	IV
Censoring fraction = 0						
(0.5, 0.5)	(1, 1)	(2, 1.5)	0.310	0.289	0.364	0.360
(0.5, 0.5)	(1, 1)	(2, 1.25)	0.652	0.575	0.808	0.812
(0.5, 0.5)	(1, 1)	(2, 1.0)	0.925	0.860	0.991	0.990
Censoring fraction = 0.3						
(0.5, 0.5)	(1, 1)	(2, 1.5)	0.248	0.202	0.297	0.301
(0.5, 0.5)	(1, 1)	(2, 1.25)	0.507	0.432	0.695	0.695
(0.5, 0.5)	(1, 1)	(2, 1.0)	0.802	0.720	0.957	0.956

I = log-rank, II = Stratified log-rank, III = Uniform weight method, IV = Weighted weight method

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Thank you!