AN ANALYSIS OF EXPECTED SURVIVAL DIFFERENTIAL IN A LUNG CANCER TRIAL: AN ITERATIVE PROCEDURE WITH A CENSORED REGRESSION MODEL

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INTRODUCTION

- An alternative look at the analysis of expected survival differential
- A latent variable framework with a differential threshold of survival time with or without disease
- to maximize the probability of survival differential
- A standard censored regression model
- Two regimes are considered in the model with a switching criterion for above and below a pre-assigned threshold level of the expected survival differential
- EM algorithm
- Lung cancer data (publicly available) from a randomized Phase III clinical trial
- Treatment of locally advanced non-small cell lung cancer
- Comparison between the stand-alone use of radiotherapy and a combination therapy

MODEL

Cohen (1957) Biometrika 44
Blight (1970) Biometrika 57(2)
Amemiya (1973) Econometrica 41

A standard censored regression model

Assumptions:

d_i^* : the expected time difference for a treatment group between the disease-free survival and survival with disease for the ith patient

d_i^* follows a normal distribution with mean μ and variance σ^2.

A sample of size of *n* patients ($d_1^*, d_2^*, \ldots, d_n^*$)

A threshold value t_0 for which

$$d_i^* > t_0 \text{ , or } d_i^* \le t_0 \text{ , for all i = 1, 2, ...n}$$

Survival difference model:

In the present study, we consider

$$\left.\begin{array}{l} d_i = \beta' x_i + u_i \\ d_i = 0 \end{array}\right\} \quad \begin{array}{l} \text{If RHS} > 0, \\ \text{otherwise} \end{array}$$

(1)

where,

--d_i is the observed survival difference;

--β is a $k \times 1$ vector of unknown parameters;

--x_i is a $k \times 1$ vector of known constants;

--u_i are random errors that are independently and normally distributed, with mean zero and a common variance σ^2.

--N_0 : the number of observations for which $d_i = 0$;

--N_1 : the number of observations for which $d_i > 0$.

DEFINITIONS

Definitions, estimation, and iteration procedure follow Maddala (1987), Amemiya (1973). and Fair (1977)

Let,

$$\Phi_i = \int_{-\infty}^{\beta' x_i/\sigma} \frac{1}{(2\Pi)^{1/2}} e^{-t^2/2} dt \qquad (2)$$

$$\phi_i = \frac{1}{(2\Pi)^{1/2}} e^{-(\beta' x_i)^2/2\sigma^2} \qquad (3)$$

where ϕ_i and Φ_i are, respectively, the density function and distribution function of the standard normal evaluated at $\beta' x_i/\sigma$.

$$\gamma_i = \frac{\phi_i}{1-\Phi_i} \qquad (4)$$

ESTIMATION

$$D_1' = (d_i, d_2, \ldots, d_{N_i}) \text{ is a } 1 \times N_1 \text{ vector of } N_1 \text{ nonzero observations on } d_i$$
$$X_1' = (x_i, x_2, \ldots, x_{N_i}) \text{ is a } k \times N_1 \text{ matrix of values of } x_i \text{ for nonzero } d_i$$
$$X_0' = (x_{N_1+1}, \ldots, x_N) \text{is a } k \times N_0 \text{ matrix of values of } x_i \text{ for } d_i = 0$$
$$\gamma_0' = (\gamma_{N_1+1}, \ldots, \gamma_N) \text{ is a } 1 \times N_0 \text{ vector of values of } \gamma_i \text{ for } d_i = 0 \qquad (5)$$

For the observations d_i that are zero, *u* has a symmetric distribution,

$$\text{Prob}(u_i < -\beta' x_i) = \int_{-\infty}^{-\beta' x_i} f(u)du = \int_{\beta' x_i}^{\infty} f(u)du = 1 - F(\beta' x_i) = 1 - F_i$$

$$\text{Prob}(d_i = 0) = \text{Prob}(u_i < -\beta' x_i) = (1 - F_i)$$ For the observations d_i that are greater than zero,

$$\text{Prob}(d_i > 0) \cdot f(d_i \mid d_i > 0) = \frac{1}{(2\Pi\sigma^2)^{1/2}} e^{-(1/2\sigma^2)(d_i - \beta' x_i)^2}$$

Maximum Likelihood Approach

Likelihood function:

$$L = \prod_0 (1 - F_i) \prod_1 \frac{1}{(2\Pi\sigma^2)^{1/2}} e^{-(1/2\sigma^2)(d_i - \beta' x_i)^2}$$

where the first product is over the N_0 observations for which $d_i = 0$

and the second product is over the N_1 observations for which $d_i > 0$.

$$\sum \log(1 - F_i) + \sum_1 \log\left(\frac{1}{(2\Pi\sigma^2)^{1/2}}\right) - \sum_1 \frac{1}{2\sigma^2}(d_i - \beta' x_i)^2 \quad (6)$$

From first order conditions,

$$\sigma^2 = \frac{1}{N_1}\sum_1 (d_i - \beta' x_i) d_i = \frac{D_1'(D_1 - X_1\beta)}{N_1} \quad (7)$$

$$\beta = (X_1' X_1)^{-1} X_1' D_1 - \sigma (X_1' X_1)^{-1} X_0' \gamma_0' \quad (8)$$

$$= \beta_{LS} - \sigma\left(X_1'X_1\right)^{-1} X_0'\gamma_0'$$

where β_{LS} is the least-squares estimator for β obtained from the N_1 nonzero observations on d.

ITERATION PROCEDURE FOR COMPUTATION

1. Fair (1977)
2. Dempster et al. (1977)
3. Blight (1970)
4. Cohen (1957)

Step 1: Compute β_{LS}, and calculate $(X'_1X_1)^{-1}X_0$.

Step 2: Choose a value of β, sat $\beta^{(1)}$, and compute σ^2 from equation (7). If this value of σ^2 is less than or equal to zero, take for the value of σ^2 some small positive number. Let $\sigma^{(1)}$ denote the square root of this chosen value of σ^2.

Step 3: Compute the vector γ_0 using $\beta^{(1)}$ and $\sigma^{(1)}$. Denote this by $\gamma_0^{(1)}$.

Step 4: Compute β from equation (8) using $\sigma^{(1)}$ and $\gamma_0^{(1)}$. Denote this value by $\tilde{\beta}^{(1)}$.

Let

$$\beta^{(2)} = \beta^{(1)} + \lambda\left(\tilde{\beta}^{(1)} - \beta^{(1)}\right) \quad \left(0 < \lambda \leq 1\right)$$

λ is just a damping factor used in procedures of this sort.

Step 5: Using $\beta^{(2)}$, go to step 2, and repeat the process until the iteration converge.

DATA

- A lung cancer trial (Lung Cancer Study Group (1988), Piantadosi (1997))
- Data for 164 cancer patients
- 86 of the cancer patient population were treated with stand-alone radio- therapy
- 78 with combination therapy
- Predictors: treatment type, recurrence of cancer, tumor status, weight loss, and age as predictors for survival difference.

ANALYSIS

- The above iteration procedure was used for computation of parameters in the model
- SAS IML
- λ= 0.4 ; tolerance limit from .0001 to .01 (recommended);
- convergence issues: λ = .8, .9.
- The model was estimated for each treatment group.

RESULTS

Table 1.
Recurrence of disease and death between two treatment groups

	Combination therapy	Stand alone therapy	* p-value
	n = 78	n = 86	
No of recurrence of disease	50	66	.004
No of death	44	57	.066
Recurrence rate within 1 year	33	55	<.001
Death rate within one year	21	38	.02

* Mantel-Haenszel test; source: LCSG(1988)

Table 2.
Effect on difference in survival days with and without disease
Estimated parameters (p-values)

	Radio-therapy	**Combination therapy**	**Overall**
n	*86*	*78*	*164*
Cell type	22.44 (.822)	8.26 (.906)	31.24 (.881)
Tumor status	-43.48 (.435)	-1.23 (/319)	-4.37 (.512)
Recurrence	24.12 (.082)	126.52 (.105)	31.21 (.162)
Therapy type	-	-	103.42* (.026)
Weight loss	-	-	-
Age	-1.21 (.821)	-2.01 (.532)	1.31 (.631)

* significant at 3% level of significance

Results from LCSG (1988):

- There is statistically significant difference for recurrence of disease and recurrence rate between radiotherapy and combination therapy within one year ($p < .001$).

- Death rate within one year was significantly different between the therapies ($p = .02$).

- Log rank test also showed statistically significant difference in time to recurrence of the disease.

Current findings:

- It is interesting to note that in this paper survival difference does not have statistically significant effect of recurrence rate.

- The results shown in Table 2 show that cell type, tumor status, recurrence, weight loss or age have no statistical impact on the survival difference of the each and overall treatment groups.

- Only the therapy type in the overall model shows statistical significance ($p = .026$) on the survival difference (d_i).

- It is well known that such models need comparatively larger observations. Also, sometimes to achieve convergence was difficult or not possible. Thus, it is imperative that the results of the overall model as depicted in Table 2 should be cautiously interpreted.

CONCLUSIONS

- It facilitates the applications of such censored regression models for survival analyses.

- Empirically, the results of the overall model show that the type of therapy (radiotherapy, or combination therapy) as used on cancer patients can have a statistically significant effect on the survival time differential. But it needs cautious interpretations of the results.

- This model needs comparatively larger patient population to draw valid inference from the results. For small samples size, it is also computationally difficult. However, it provides an alternative look at survival analysis.

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