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ESTIMATION OF RELATIVE RISK AND STOPPING TIME OF A CLINICAL TRIAL USING MARTINGALE TECHNIQUE

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Abstract: Using Kalbfleisch and Prentice (1980) clinical trial survival data on cancer patients, the relative risk and the stopping time have been estimated using Martingale approach. Further, a comparison has been made between a group of patients diagnosed with second primary cancer and a group of patients with no history of cancer in the past. These two groups of patients were treated with a new treatment and were compared with a control group receiving the usual treatment. Patients with history of prior therapy supposed to have elevated relative risk is endorsed by the findings.

Keywords: Counting process, Martingale technique, Relative risk, Stopping time.

1. INTRODUCTION

For some of the diseases, it is difficult to predict the correct prognosis. In such a situation, treatments to the patients are given to get some respite from the ailment resulting in extension of remission duration. The relative risk in no way gives the details of happening of risk of an event. In fact, it gives an idea of likelihood of the event of an exposed group with respect to unexposed group or likelihood of an event between two exposed groups of varying exposures. Studies on defined population was carried out to obtain relative risk by Kupper et. al. (1975). Greenland (1986) suggested modifications in the methodology of obtaining risk ratio to eliminate the bias of case- cohort design proposed by Kupper et. al (1975). Thomas (1981, 1983) also developed relative risk models for case-control studies and dose-response relations. Jegu et. al. (2014) and Keegan et. al. (2017) studies show that there is very high relative risk of second time prime cancer among the people gone through cancer therapy earlier. Islam et.al. (2012) studies have similar findings of high relative risk of renal failure among HIV infected people than HIV uninfected people. Breslow (1987) assumed that the incidence of primary cancer among cancer survivors follows Poisson distribution. For estimating relative risk of second primary cancer in comparison to first time diagnosed cancer patients Boyle and Perkin (1991) calculated standardized incidence ratios. Becker (1989, 1993) analyzed epidemiological data and justified the role of Martingale techniques in the study of parametric epidemic models and proved that Martingale methods lead

to estimates of survival times and their standard errors. Biswas et. al. (1992) used Martingale technique and obtained relative risk and stopping time using Gehan (1965) clinical trial data of leukemia patients. The Present study is an attempt to develop methods using Martingale stochastic process concept to study the relative risk and the stopping time to compare a group of cancer patients with no previous history of the disease and another group of cancer patients with pre-history (both these groups were given a new treatment) with a control group of patients receiving standard treatment. Patients with second primary cancer, treatments are generally given to lengthen the duration of remission.

2. METHODOLOGY

Suppose T_0 is the standard treatment and two treatments to be tested are T_1 and T_2. Further, suppose that the corresponding hazard rates of reaching remission from the complexities of the ailment at time t are

$H_0(t) = h_0\lambda(t)$,

$H_1(t) = h_1\lambda(t)$ and

$H_2(t) = h_2\lambda(t)$ respectively.

Therefore, the relative risks of treatment 1 and treatment 2 on the standard treatment can be estimated as

$\widehat{R_1}(t) = \frac{H_1(t)}{H_0(t)} = \frac{h_1}{h_0} = \widehat{\beta_1}$ (say), when T_1 is the test treatment. (1)

$\widehat{R_2}(t) = \frac{H_2(t)}{H_0(t)} = \frac{h_2}{h_0} = \widehat{\beta_2}$ (say), when T_2 is the test treatment (2)

Let, $n_0(t), n_1(t)\ and\ n_2(t)$ are counting process of three groups of patients under treatments T_0, T_1 and T_2 respectively such that $n_0(0) = 0, n_1(0) = 0\ and\ n_2(0) = 0$. This means that $n_i(t)$ (i = 0, 1, 2; t ≥ 0) is the number of incidents taking place in the time interval (0, t] and is continuous on the right. One of the purpose of this investigation is to find τ (the stopping time), when remission has come to an end. Where, τ = min [t such that $\lambda(t) = 0$].

Suppose, $[\eta_i(t)$; i = 0,1,2] denotes the past information of counting process $[n_i(t)$;i = 0,1,2]. Further, assume that $[dn_i(t)$;i = 0,1,2] denotes the number of patients getting remission during the minuscule interval (t, t+dt).

⇒ P $[dn_0(t) = 1 \mid \eta_0(t)] = h_0\lambda(t)$dt,

P $[dn_1(t) = 1 \mid \eta_1(t)] = h_1\lambda(t)$dt

and P $[dn_2(t) = 1 \mid \eta_2(t)] = h_2\lambda(t)$dt

⇒ P $[dn_0(t) = 0 \mid \eta_0(t)] = 1 - h_0\lambda(t)$dt,

P $[dn_1(t) = 0 \mid \eta_1(t)] = 1 - h_1\lambda(t)\mathrm{d}t$

and P $[dn_2(t) = 0 \mid \eta_2(t)] = 1 - h_2\lambda(t)\mathrm{d}t$

Since, $n_0(t), n_1(t)\ and\ n_2(t)$ are counting processes, therefore,

$$n_0(t) - h_0 \int_0^t \lambda(x)\mathrm{d}x = m_0(t) \tag{3}$$

$$n_1(t) - h_1 \int_0^t \lambda(x)\mathrm{d}x = m_1(t) \tag{4}$$

and $n_2(t) - h_2 \int_0^t \lambda(x)\mathrm{d}x = m_2(t)$ (5)

are Martingales with zero mean over σ field $\mathcal{F}\{n(t)\}$.

Let $P_0(t) = \frac{\mathfrak{k}(t-)}{h_0\lambda(t-)}$, (7)

$$P_1(t) = \frac{\mathfrak{k}(t-)}{h_1\lambda(t-)} \text{ and} \tag{8}$$

$$P_2(t) = \frac{\mathfrak{k}(t-)}{h_2\lambda(t-)} \tag{9}$$

are functions of predictable variations (t- is used to indicate $P_i(t)$ predictable). Further, $h_i\lambda(t-)$ is the hazard rate at transition point from non-respite to respite and for computing $\int P_i(t)\mathrm{d}m_i(t)$, values of $h_i\lambda(t-)$ should be used prior to transition point.

Where, $\mathfrak{k}(t-) = 0$ if $\lambda(t-) = 0$,

= 1 otherwise.

$$\Rightarrow \overline{m_0}(t) = \int_0^t P_0(x)\ \mathrm{d}m_0(x), \tag{10}$$

$$\overline{m_1}(t) = \int_0^t P_1(x)\ \mathrm{d}m_1(x) \text{ and} \tag{11}$$

$$\overline{m_0}(t) = \int_0^t P_2(x)\ \mathrm{d}m_2(x) \tag{12}$$

are also Martingales with zero mean over σ field $\mathcal{F}\{n_i(t); i=0,1,2\}$.

$\Rightarrow \overline{m_0}(t) - \widehat{\beta_1}\overline{m_1}(t)$ and $\overline{m_0}(t) - \widehat{\beta_2}\overline{m_2}(t)$ are also Martingales over σ field $\mathcal{F}\{n_i(t); i=0,1,2\}$.

2.1 Estimation of Stopping Time

Let $t = \tau_1$ (stopping time for comparing the efficacy of test treatment 1 with respect to standard treatment).

$E[\overline{m_0}(\tau_1) - \widehat{\beta_1}\overline{m_1}(\tau_1)] = E[\overline{m_0}(0) - \widehat{\beta_1}\overline{m_1}(0)] = 0$ and

$E[\overline{m_0}(\tau_1) - \widehat{\beta_1}\overline{m_2}(\tau_1)] = E[\overline{m_0}(0) - \widehat{\beta_1}\overline{m_2}(0)] = 0.$

$\Rightarrow \int_0^{\tau_1} \frac{k(t-)}{h_0\lambda(t-)} dn_0(t) - \int_0^{\tau_1} k(t-)\, d(t) - \widehat{\beta_1} \int_0^{\tau_1} \frac{k(t-)}{h_1\lambda(t-)} dn_0(t) - \widehat{\beta_1} \int_0^{\tau_1} k(t-)\, d(t) = 0.$ [using equations (7), (8), (10) and (11)]

$\Rightarrow \sum_i \frac{1}{\alpha_i^{(0)}} - \tau_1 - \widehat{\beta_1} \sum_j \frac{1}{\alpha_j^{(1)}} + \widehat{\beta_1}\tau_1 = 0$, where $\alpha_i^{(0)} and\ \alpha_j^{(1)}$ are hazard rates of remission noticed on patients given standard treatment and test treatment 1 respectively.

$$\Rightarrow \hat{\tau}_1 = \frac{\widehat{\beta_1} \sum_j \frac{1}{\alpha_j^{(1)}} - \sum_i \frac{1}{\alpha_i^{(0)}}}{\widehat{\beta_1} - 1} \tag{13}$$

Similarly, if τ_2 is the stopping time while comparing the efficacy of test treatment 2 with respect to standard treatment then [using equations (7), (9), (10) and (12)]

$$\hat{\tau}_2 = \frac{\widehat{\beta_2} \sum_j \frac{1}{\alpha_j^{(2)}} - \sum_i \frac{1}{\alpha_i^{(0)}}}{\widehat{\beta_2} - 1} \tag{14}$$

2.2 Estimation of Relative Risks

Replacing t by stopping time τ_1 and using equations (3) and (4), we get;

$m_0(\tau_1) = n_0(\tau_1) - h_0 \int_0^{\tau_1} \lambda(x)\mathrm{dx}$ and

$m_1(\tau_1) = n_1(\tau_1) - h_1 \int_0^{\tau_1} \lambda(x)\mathrm{dx}$

$\Rightarrow E[m_0(\tau_1)] = m_0(0) = n_0(0) = 0$ and $E[m_1(\tau_1)] = m_1(0) = n_1(0) = 0$

(Using optimum stopping rule)

$\Rightarrow E[m_0(\tau_1)] = E[n_0(\tau_1)] - h_0 \int_0^{\tau_1} \lambda(x)\mathrm{dx} = 0$ and

$E[m_1(\tau_1)] = E[n_1(\tau_1)] - h_1 \int_0^{\tau_1} \lambda(x)\mathrm{dx} = 0$

$$\Rightarrow E[n_0(\tau_1)] = h_0 \int_0^{\tau_1} \lambda(x)\mathrm{dx} \tag{15}$$

$$\text{and } E[n_1(\tau_1)] = h_1 \int_0^{\tau_1} \lambda(x)\mathrm{dx} \tag{16}$$

Similarly, replacing t by stopping time τ_2 and using equations (3) and (5), we get;

$$E[n_0(\tau_2)] = h_0 \int_0^{\tau_2} \lambda(x)\mathrm{dx} \tag{17}$$

$$\text{and } E[n_2(\tau_2)] = h_2 \int_0^{\tau_2} \lambda(x)\mathrm{dx} \tag{18}$$

Substituting (15) and (16) in (1), we get;

$$\widehat{R_1}(t) = \frac{h_1}{h_0} = \widehat{\beta_1} = \frac{E[n_1(\tau_1)]}{E[n_0(\tau_1)]} \tag{19}$$

Similarly, substituting (17) and (18) in (2), we get;

$$\widehat{R_2}(t) = \frac{h_2}{h_0} = \widehat{\beta_2} = \frac{E[n_2(\tau_2)]}{E[n_0(\tau_2)]} \tag{20}$$

3. NUMERICAL ILLUSTRATION

Veteran's administration lung cancer clinical trial data (Kalbfleisch and Prentice,1980) providing the duration of remission has been used to compare the relative efficacy of two treatments (Test treatment A and Test treatment B) with respect to the standard treatment. The group of patients receiving standard treatment is called control group. The group of patients receiving test treatment with no history of prior therapy is test group A. Test group B consists of those patients who have gone through prior therapy earlier. Days of remission of these three sets of patients are given in table 1.

Table 1 (Lung Cancer Trial)

Control group (duration of remission in days)	Test group A (duration of remission in days)	Test group B (duration of remission in days)
72, 228, 10, 110, 314, 42, 144, 30, 384, 4, 13, 59, 117, 151, 22, 18, 139, 20, 31, 52, 18, 51, 122, 27, 54, 7, 63, 392, 92, 35, 117, 132, 162, 3, 95, 112, 216, 278, 260, 156, 143, 105, 103	112, 242, 111, 389, 33, 25, 357, 1, 30, 283, 25, 21, 13, 87, 7, 24, 99, 8, 99, 61, 25, 95, 80, 29, 24, 31, 51, 52, 73, 8, 36, 48, 7, 140, 186, 19, 45, 80, 52, 53, 15, 133, 111, 378, 49	1, 201, 44, 15, 2, 20, 51, 18, 90, 84, 164, 19, 43, 340, 231
Total no. of patients: 43	Total no. of patients: 45	Total no. of patients: 15

Suppose, mean and variance of duration of remission of 88 patients after combining control group and test group A are denoted by μ'_{1A} and μ_{2A} respectively. Similarly, suppose that mean and variance of duration of remission of 58 patients after combining control group and test group B are denoted by μ'_{1B} and μ_{2B} respectively.

Therefore, $\mu'_{1A} = 97.7273$

$\mu_{2A} = 9846.476$

$\mu'_{1B} = 104.7586$

$\mu_{2B} = 9915.625$

Let, n'_{01} and n'_{11} are the number of patients whose remission time is on the right of

$\mu'_{1A} + \theta\sqrt{\mu_{2A}}$ under standard and treatment A respectively. Similarly, let n'_{01} and n'_{22} are the number of patients whose remission time is on the right of $\mu'_{1B} + \theta\sqrt{\mu_{2B}}$ under standard and treatment B respectively.

i.e. $n'_{01} = \mathrm{E}[n_0(\tau_1)]$, $n'_{11} = \mathrm{E}[n_1(\tau_1)]$, $n'_{02} = \mathrm{E}[n_0(\tau_2)]$ and $n'_{22} = \mathrm{E}[n_2(\tau_2)]$ are expected number of people getting remission because of different treatments administered to them.

Let $p_i^{(0)}$, $p_j^{(1)}$ *and* $p_k^{(2)}$ denote the survival probabilities of different patients on standard treatment, test A and test B respectively and corresponding hazard rates of relief are denoted by $\alpha_i^{(0)}$, $\alpha_j^{(1)}$ *and* $\alpha_k^{(2)}$.

Therefore, $p_i^{(0)} = e^{\int_0^t \alpha_i^{(0)}} \Rightarrow \alpha_i^{(0)} = -\frac{1}{t} log_e(p_i^{(0)})$, (21)

$$p_j^{(1)} = e^{\int_0^t \alpha_j^{(1)}} \Rightarrow \alpha_i^{(0)} = -\frac{1}{t} log_e(p_j^{(1)}) \quad (22)$$

and $p_k^{(2)} = e^{\int_0^t \alpha_k^{(2)}} \Rightarrow \alpha_i^{(0)} = -\frac{1}{t} log_e(p_k^{(2)})$. (23)

Estimated probabilities of survival, hazard rates for remission of patients under standard treatment (control group), under treatment A (test group A) and under treatment B (test group B) are exhibited in **table 2, table 3** and **table 4** respectively.

Table 2 (Hazard Rates of Control Group Patients)

Duration of remission	Average duration t_i	Number of patients	$p_i^{(0)}$	$\alpha_i^{(0)}$	$\frac{1}{\alpha_i^{(0)}}$	$(\frac{1}{\alpha_i^{(0)}})^2$
0-50	25	14	0.67442	0.01576	63.45178	4026.128
50-100	75	8	0.48837	0.00956	104.60251	10941.685
100-150	125	10	0.25581	0.01091	91.65903	8401.378
150-200	175	4	0.16279	0.01037	96.43202	9299.134
200-250	225	2	0.11628	0.00956	104.60251	10941.685
250-300	275	2	0.06977	0.00968	103.30579	10672.085
300-400	350	3	-	-	-	-
Total		43			564.05364	54282.095

Table 3 (Hazard Rates of Test Group A Patients)

Duration of remission	Average duration t_i	Number of patients	$p_i^{(0)}$	$\alpha_i^{(0)}$	$\frac{1}{\alpha_i^{(0)}}$	$(\frac{1}{\alpha_i^{(0)}})^2$
0-50	25	22	0.51111	0.02685	37.24395	1387.112
50-100	75	12	0.24444	0.01878	53.24814	2835.364
100-150	125	5	0.13333	0.01612	62.03474	3848.309
150-200	175	1	0.11111	0.01256	79.61783	6338.999
200-250	225	1	0.08889	0.01076	92.93680	8637.249
250-300	275	1	0.06667	0.00985	101.52284	10306.888
300-400	350	3	-	-	-	-
Total		45			426.6043	33353.921

Table 4 (Hazard Rates of Test Group B Patients)

Duration of remission	Average duration t_i	Number of patients	$p_i^{(0)}$	$\alpha_i^{(0)}$	$\frac{1}{\alpha_i^{(0)}}$	$(\frac{1}{\alpha_i^{(0)}})^2$
0-50	25	8	0.46667	0.03049	32.79764	1075.685
50-100	75	3	0.26667	0.01762	56.75369	3220.981
100-150	125	0	0.26667	0.01057	94.60738	8950.556
150-200	175	1	0.20000	0.00920	108.69565	11814.745
200-250	225	2	0.06667	0.01204	83.05648	6898.379
250-300	275	0	0.06667	0.00985	101.52284	10306.888
300-400	350	1	-	-	-	-
Total		15			477.43368	42267.234

3.1 Estimation of Relative Risk and Stopping time

Case 1: Comparing the efficacy of test treatment A with standard treatment for different values of θ

In case of θ more than 1, the number of patients with duration of remission lying right side of $\mu'_{1A}+ \theta\sqrt{\mu_{2A}}$ tends to zero. Therefore, we assume that $0 \leq \theta \leq 1$.

For θ =1, $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 196.9567$

No. of patients of control group with duration of remission lying right side of $\mu'_{1A}+ \theta\sqrt{\mu_{2A}} = 7$

No. of patients of test group A with duration of remission lying right side of $\mu'_{1A}+ \theta\sqrt{\mu_{2A}} = 5$

$\Rightarrow \widehat{R_1}(t) = \widehat{\beta_1} = 0.7143$ [using (19)]

and the stopping time $\hat{\tau}_1 = 907.701$ [using (13) and (19)

For θ = 0.75, $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 172.149$

No. of patients of control group with duration of remission lying right side of $\mu'_{1A}+ \theta\sqrt{\mu_{2A}} = 7$

No. of patients of test group A with duration of remission lying right side of $\mu'_{1A}+ \theta\sqrt{\mu_{2A}} = 6$

$\Rightarrow \widehat{R_1}(t) = \widehat{\beta_1} = 0.8571$ and $\hat{\tau}_1 = 1388.461$

For θ = 0.5, $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 147.342$

No. of patients of control group with duration of relief lying right side of $\mu'_{1A}+ \theta\sqrt{\mu_{2A}} = 11$

No. of patients of test group A with duration of relief lying right side of $\mu'_{1A}+ \theta\sqrt{\mu_{2A}} = 6$

$\Rightarrow \widehat{R_1}(t) = \widehat{\beta_1} = 0.5455$ and $\hat{\tau}_1 = 729.07$

For θ = 0.25, $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 122.535$

No. of patients of control group with duration of relief lying right side of $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 15$

No. of patients of test group A with duration of relief lying right side of $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 8$

$\Rightarrow \widehat{R_1}(t) = \widehat{\beta_1} = 0.5333$ and $\hat{\tau}_1 = 721.087$

For θ = 0.00, $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 97.7273$

No. of patients of control group with duration of relief lying right side of $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 20$

No. of patients of test group A with duration of relief lying right side of $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 13$

$\Rightarrow \widehat{R_1}(t) = \widehat{\beta_1} = 0.65$ and $\hat{\tau}_1 = 819.317$

Case 2: Comparing the efficacy of test treatment B with standard treatment for different values of θ

In case of θ more than 1, the number of patients with duration of remission lying right side of $\mu'_{1B} + \theta\sqrt{\mu_{2B}}$ tends to zero. Therefore, we assume that $0 \leq \theta \leq 1$.

For θ =1, $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 204.3358$

No. of patients of control group with duration of remission lying right of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 7$

No. of patients of test group A with duration of remission lying right of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 6$

$\Rightarrow \widehat{R_2}(t) = \widehat{\beta_2} = 0.8571$ [using (20)]

and the stopping time $\hat{\tau}_2 = 1083.448$ [using (14) and (20)]

For θ = 0.75, $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 179.4329$

No. of patients of control group with duration of remission lying right of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 7$

No. of patients of test group A with duration of remission lying right side of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 9$

$\Rightarrow \widehat{R_2}(t) = \widehat{\beta_2} = 1.2857$ and $\hat{\tau}_2 = 174.27$

For θ = 0.5, $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 154.539$

No. of patients of control group with duration of relief lying right side of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 10$

No. of patients of test group A with duration of relief lying right side of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 12$

$\Rightarrow \widehat{R_2}(t) = \widehat{\beta_2} = 1.2$ and $\hat{\tau}_2 = 44.334$

For θ = 0.25, $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 129.644$

No. of patients of control group with duration of relief lying right side of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 15$

No. of patients of test group A with duration of relief lying right side of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 12$

$\Rightarrow \widehat{R_2}(t) = \widehat{\beta_2} = 0.8$ and $\hat{\tau}_2 = 910$

For θ = 0.00, $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 104.75$

No. of patients of control group with duration of relief lying right side of $\mu'_{1B} + \theta\sqrt{\mu_{2B}} = 19$

No. of patients of test group A with duration of relief lying right side of $\mu'_{1A} + \theta\sqrt{\mu_{2A}} = 12$

$\Rightarrow \widehat{R_2}(t) = \widehat{\beta_2} = 0.6316$ and $\hat{\tau}_2 = 712.58$

Estimated Relative risk and stopping time for different values of θ are summarized in **table 5.**

Table 5 (Estimates of Relative Risk and Stopping Time)

θ	$\widehat{\beta_1}$	$\widehat{\beta_2}$	$\hat{\tau}_1$	$\hat{\tau}_2$
1.00	0.7143	0.8571	907.701	1083.448
0.75	0.8571	1.2857	1388.461	174.27
0.50	0.5455	1.2000	729.070	44.334
0.25	0.5333	0.8000	721.087	910.00
0.00	0.6500	0.6316	819.317	712.58

4. CONCLUSION

Findings of the investigation clearly proves that patients with prior history of disease have higher relative risk in comparison to the group of patients with no history of prior therapy, irrespective of the values of θ. Further, with smaller values of θ, the Relative Risk decreases in both the test groups of patients in comparison to the control group. Results as described in table 5 indicates that with lowering the value of θ, the stopping time in both the cases get stabilized. It is concluded that it is better to take lower values of θ so that the stopping time is not extended beyond a limit.

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