BSTT536: Survival Data Analysis

Instructor: Hua Yun Chen, PhD

Division of Epidemiology and Biostatistics
School of Public Health
University of Illinois at Chicago

Model used for the power and sample size determination

1. Setting: Two sample comparison. For example: To compare the effects of two treatments on the survival time distributions.
2. The null hypothesis: No difference in the effects of the two treatments.
3. The alternative hypothesis: The difference in the effects of the two treatments follow the proportional hazards regression model. That is,
$$h_2(t) = h_1(t)\exp(\theta).$$
4. Under the model, the null hypothesis is $H_0 : \theta = 0$ and the alternative hypothesis is $H_A : \theta = \theta_0 \neq 0$.

Log-rank test

The log-rank test is used for testing the hypothesis.

$$U = \sum_{k=1}^{K} (d_{1k} - e_{1k}), \text{ and } V = \sum_{k=1}^{K} \frac{n_{1k} n_{2k} d_k (n_{+k} - d_{+k})}{n_k^2 (n_k - 1)}$$

where d_{1k} is the number of deaths in group 1 observed at time T_k and e_{1k} is the expected number of deaths in group 1 at time T_k under the null hypothesis.

$$e_{1k} = n_{1k} \frac{d_{1k} + d_{2k}}{n_{1k} + n_{2k}},$$

where n_{1k}, n_{2k} are respectively the numbers at risk at time T_k in groups 1 and 2.

Statistics for the power and sample size determination

1. The test has the level α, *i.e.*,

$$P\left(\frac{|U|}{\sqrt{V}} > z_{1-\alpha/2} \middle| H_0\right) = \alpha.$$

2. The test has at least the power $1-\gamma$, *i.e.*,

$$P\left(\frac{|U|}{\sqrt{V}} > z_{1-\alpha/2} \middle| H_A\right) \geq 1-\gamma.$$

3. We have already known that, under the null hypothesis H_0,

$$\frac{U}{\sqrt{V}} \sim N(0,1).$$

   We also need to know the distribution of $U/\sqrt{V}$ under the alternative hypothesis H_A to carry out the calculation.

The distribution of the statistic under H_A

1. Under the alternative hypothesis, Sellke and Siegmund (1983) showed that

$$\frac{U}{\sqrt{V}} \sim N(\theta\sqrt{V}, 1) \text{ or } U \sim N(\theta V, V).$$

2. Use the approximate distribution of the test statistic under the alternative hypothesis, we can calculate

$$\begin{aligned}
& P\left(\frac{|U|}{\sqrt{V}} > z_{1-\alpha/2}\middle| H_A\right) \\
= \quad & P(U > \sqrt{V} z_{1-\alpha/2} | H_A) + P(U < -\sqrt{V} z_{1-\alpha/2} | H_A) \\
= \quad & P\left(\frac{U-\theta V}{\sqrt{V}} > z_{1-\alpha/2} - \theta\sqrt{V} | H_A\right) \\
& + P\left(\frac{U-\theta V}{\sqrt{V}} < -z_{1-\alpha/2} - \theta\sqrt{V} | H_A\right) \\
= \quad & 1 - \Phi(z_{1-\alpha/2} - \theta\sqrt{V}) + \Phi(-z_{1-\alpha/2} - \theta\sqrt{V})
\end{aligned}$$

Sample size determination

1. To allow the test to be at the level of α under H_0 and to have at least power $1-\gamma$ under H_A, we need

$$1-\Phi(z_{1-\alpha/2}-\theta\sqrt{V})+\Phi(-z_{1-\alpha/2}-\theta\sqrt{V})\geq 1-\gamma.$$

   If $\theta \leq 0$, then

$$1-\Phi(z_{1-\alpha/2}-\theta\sqrt{V})+\Phi(-z_{1-\alpha/2}-\theta\sqrt{V})\approx\Phi(-z_{1-\alpha/2}-\theta\sqrt{V}).$$

2. From the above inequality,

$$-z_{1-\alpha/2}-\theta\sqrt{V}\geq z_{1-\gamma}.$$

3. Equivalently,

$$V\geq\left(\frac{z_{1-\alpha/2}+z_{1-\gamma}}{\theta}\right)^2.$$

Sample size determination (continuing 1)

1. First,

$$V = \sum_{k=1}^{K} \frac{n_{1k} n_{2k} d_k (n_{+k} - d_{+k})}{n_k^2 (n_k - 1)} \approx \sum_{k=1}^{K} \frac{n_{1k} n_{2k}}{n_k^2} d_k.$$

2. If we assume the numbers of subjects at risk at each failure time are approximately the same, then

$$V \approx \frac{1}{4} \sum_{k=1}^{K} d_k = \frac{d}{4},$$

where d is the total number of deaths in **both groups**. The sample sizes should be planned such that

$$d \geq 4 \left(\frac{z_{1-\alpha/2} + z_{1-\gamma}}{\theta} \right)^2.$$

Sample size determination (continuing 2)

1. If we assume the number of subjects at risk at each of the failure in group one is R times of that of group two, then

$$V \approx \frac{Rd}{(1+R)^2},$$

The sample sizes should be planned such that

$$d \geq \frac{(1+R)^2}{R} \left(\frac{z_{1-\alpha/2} + z_{1-\gamma}}{\theta} \right)^2.$$

2. The sample size n satisfies

$$n = \frac{d}{P(\delta = 1)},$$

where d is the required number of events.

Calculate the required sample size from the total number of deaths

1. A simple approximation assumes that censoring can only occur at the end of the study and $P(\delta = 1)$ is approximated by the average probability of death

   $$P(\delta = 1) \approx P(T \leq \tau) \approx 1 - \frac{S(\tau|\text{group 1}) + S(\tau|\text{group 2})}{2},$$

   where $\tau (= f + a/2)$ is the average length at risk.

2. A more involved approximation has

   $$P(\delta = 1) \approx 1 - \frac{1}{6}\left\{\bar{S}(f) + 4\bar{S}(f + 0.5a) + \bar{S}(f + a)\right\},$$

   where

   $$\bar{S}(t) = \frac{S(t|\text{group 1}) + S(t|\text{group 2})}{2},$$

   a is the accrual period and f is the follow-up period.

Compute $P(\delta = 1)$ based on accrual rate and follow-up time*

1. The study design has a period of patient accruement (duration a) followed by a period of follow-up time (duration f) after the completion of the accruement period. The study is terminated after the follow-up period.
2. Assuming constant recruitment rate
$$P(\delta = 1) = \int_0^a P(\delta = 1|\text{entry at t})\frac{1}{a}dt.$$
3. A patient entering at time t and still alive at the end of the study has a survival time $a + f - t$.
$$\begin{aligned} P(\delta = 1) &= 1 - \int_0^a P(T \geq a + f - t)\frac{1}{a}dt \\ &= 1 - \int_0^a S(a + f - t)\frac{1}{a}dt \\ &= 1 - \int_f^{a+f} S(u)\frac{1}{a}dt. \end{aligned}$$

Compute $P(\delta = 1)$ based on accrual rate and follow-up time*(continuing)

1. From numeric approximation to integration,

$$\int_f^{a+f} S(u)dt \approx \frac{a}{6}\left\{S(f) + 4S(f+0.5a) + S(f+a)\right\}.$$

   The Simpson's rule for approximation by polynomial interpolation **

$$\int_a^b g(u)du \approx \frac{b-a}{6}\left\{g(a) + 4g\left(\frac{a+b}{2}\right) + g(b)\right\}.$$

2. This leads to

$$P(\delta = 1) \approx 1 - \frac{1}{6}\left\{S(f) + 4S(f+0.5a) + S(f+a)\right\}.$$

3. Finally,

$$\begin{aligned} S(t) &= S(t|z=1)p(z=1) + S(t|z=0)P(z=0) \\ &= \frac{S(t|Z=1) + S(t|Z=0)}{2}. \end{aligned}$$

Example: Chronic active hepatitis

Computing the required number of events

1. Effect size: Ratio of the relative risks between the two treatments (Standard treatment:$Z = 0$; New treatment: $Z = 1$).

$$\psi = \frac{\log S(t|Z=1)}{\log S(t|Z=0)}.$$

   The new treatment is expected to increase five year survival rate from 41% to 60%.

$$\psi = \log(0.6)/\log(0.41) = 0.573.$$

2. Type I error (5%) and power (80%)
3. The required number of events

$$d = 4 * \frac{(1.96 + 0.84)^2}{(\log 0.573)^2} = 101.$$

   Note that $\theta = \log \psi$.

Example: Chronic active hepatitis (continuing)

Computing the required sample size from the required number of deaths.

1. Assume a five year study with the patient recruitment in the first three years and follow-up in the last two years. This means that
$$a = 3 \text{ and } f = 2.$$
2. We now need to calculate
$$S(2), S(0.5 * 3 + 2), S(5).$$
3. We read from Figure 10.1 on page 305 of the textbook that
$$\begin{aligned} S(2|Z=0) &= 0.70, \\ S(3.5|Z=0) &= 0.58, \\ S(5|Z=0) &= 0.41. \end{aligned}$$

Example: Chronic active hepatitis (continuing)

1. From that

$$\frac{\log S(t|Z=1)}{\log S(t|Z=0)} = \psi = 0.573,$$

   we can find

$$\begin{aligned} S(2|Z=1) &= 0.70^{0.573} = 0.82, \\ S(3.5|Z=1) &= 0.58^{0.573} = 0.73, \\ S(5|Z=1) &= 0.41^{0.573} = 0.60. \end{aligned}$$

2. Compute

$$\begin{aligned} P(\delta=1) &= 1 - \frac{1}{6}\left\{\frac{0.70+0.82}{2} + 4 * \frac{0.58+0.73}{2} + \frac{0.41+0.60}{2}\right\} \\ &= 0.35 \end{aligned}$$

3. The required sample size is

$$n = \frac{101}{0.35} = 289.$$

Compute power for a fixed sample size

1. Recall that

$$\begin{aligned} Power &= 1 - \Phi(z_{1-\alpha/2} - \theta\sqrt{V}) + \Phi(-z_{1-\alpha/2} - \theta\sqrt{V}) \\ &\approx \Phi(-z_{1-\alpha/2} - \theta\sqrt{V}) \end{aligned}$$

   when$\theta < 0$.

2. For balanced assignments to new and standard treatments,

$$V \approx d/4.$$

3. From a given sample size n, the number of observed events

$$d = n * P(\delta = 1).$$

4. These mean

$$Power \approx \Phi\left(-z_{1-\alpha/2} - \frac{\theta}{2}\sqrt{n * P(\delta = 1)}\right).$$

Power:Chronic active hepatitis

1. Effect size: The new treatment is expected to increase five year survival rate from 41% to 60%.

$$\psi = \log(0.6)/\log(0.41) = 0.573.$$

$$\theta = \log\psi = -0.557.$$

2. Assume a five year study with the patient recruitment in the first three years and follow-up in the last two years. This means that

$$a = 3 \text{ and } f = 2.$$

3. From the previous calculation

$$P(\delta = 1) \approx 0.35$$

Power:Chronic active hepatitis (continuing)

1. For a sample size 100 and type I error 5%,

$$Power \approx \Phi\left(-1.96 - \frac{-0.557}{2}\sqrt{100 * 0.35}\right) = 0.377.$$

2. For a sample size 150 and type I error 5%,

$$Power \approx \Phi\left(-1.96 - \frac{-0.557}{2}\sqrt{150 * 0.35}\right) = 0.523.$$

3. For a sample size 200 and type I error 5%,

$$Power \approx \Phi\left(-1.96 - \frac{-0.557}{2}\sqrt{200 * 0.35}\right) = 0.644.$$

4. To compute the power for a different effect size, $P(\delta = 1)$ need to be recalculated.