KM

This procedure estimates the survival function for time to occurrence of an event. Some of the times may be “censored” in that the event does not occur during the observation period, or contact is lost with participants (loss to follow-up).

If the subjects are divided into treatment groups, KM produces a survival function for each treatment group (factor level) and a test of equality of the survival functions across treatment groups. The survival functions across treatment groups can also be compared while controlling for categories of a stratification variable.

Notation

The following notation is used throughout this chapter unless otherwise stated:

p	Number of levels (strata) for the stratification variable
g	Number of levels (treatment groups) for the factor variable

Estimation and SE for Survival Distribution

Suppose that for a given combination of the stratification and factor variables, a random sample of n individuals yields a sample with k distinct observed failure times (uncensored). Let $t_1 < \ldots < t_k$ represent the observed life times and T_L be the largest observation in the sample. (Note that $T_L = t_k$ if the largest observation is uncensored.) Define

n_i = Number of subjects who are at risk at time t_i.

d_i = Number of failures (deaths) at t_i.

λ_i = Number of censorings in interval $[t_i, t_{i+1})$.

Note that

$$n_0 = n$$
$$n_{i+1} = n_i - d_i - \lambda_i, \quad i = 0, 1, \ldots, k-1$$
$$t_0 = 0$$
$$t_{k+1} = \infty$$
$$d_0 = 0$$
$$\lambda_0 = 0$$

The Kaplan-Meier estimate $\hat{S}(t)$ for the survival function is computed as

$$\hat{S}(t) = \prod_{t_i < t} \left(1 - \frac{d_i}{n_i}\right)$$

Note that

$$\hat{S}(t_l^+) = \prod_{i=1}^{l} \left(1 - \frac{d_i}{n_i}\right), \quad l = 1, 2, \ldots, k.$$

$$\hat{S}(t_0^+) = 1$$

$$\hat{S}(t_{l+1}^+) = \hat{S}(t_l^+)\left(1 - \frac{d_{l+1}}{n_{l+1}}\right)$$

$\hat{S}(t_k^+) = 0$ if $n_k = d_k$ $(T_l = t_k$ and $\lambda_k = 0)$, otherwise

$$\hat{S}(t_k^+) = \prod_{l=1}^{k} \left(1 - \frac{d_l}{n_l}\right), \quad T_L \geq t \geq t_k$$

$\hat{S}(t_1^+), \ldots, \hat{S}(t_k^+)$ are the survival functions shown in the table.

The asymptotic standard error for $\hat{S}\left(t_l^+\right)$ is computed as the square root of

$$\operatorname{var}\left(\hat{S}\left(t_l^+\right)\right) = \left[\hat{S}\left(t_l^+\right)\right]^2 \sum_{i=1}^{l} \frac{d_i}{n_i\left(n_i - d_i\right)}, \qquad l = 1, \ldots, k.$$

Note: When $n_k = d_k$ $\left(T_L = t_k \text{ and } \lambda_k = 0\right)$, $\hat{S}\left(t_k^+\right) = 0$ and $\operatorname{var}\left(\hat{S}\left(t_k^+\right)\right) = 0$.

Estimation of Mean Survival Time and Standard Error

$$\hat{\mu} = \begin{cases} \sum_{i=0}^{k-1} \hat{S}\left(t_i^+\right)\left(t_{i+1} - t_i\right) & \text{if } T_L = t_k \\ \sum_{i=0}^{k-1} \hat{S}\left(t_i^+\right)\left(t_{i+1} - t_i\right) + \hat{S}\left(t_k^+\right)\left(T_L - t_k\right) & \text{otherwise} \end{cases}$$

The variance of the mean survival time is

$$\operatorname{var}\left(\hat{\mu}\right) = \sum_{i=1}^{k} \frac{a_i^2 d_i}{n_i\left(n_i - d_i\right)}$$

$$a_i = \sum_{l=i}^{k-1} \hat{S}\left(t_l^+\right)\left(t_{l+1} - t_l\right) + \hat{S}\left(t_k^+\right)\left(T_L - t_k\right)$$

$$d = \sum_{i=1}^{k} d_i$$

unless there are both censored and uncensored occurrences of the largest survival time. In that case,

$$\mathrm{var}\left(\hat{\mu}\right) = \frac{d}{d-1} \sum_{i=1}^{k-1} \frac{a_i^2 d_i}{n_i \left(n_i - d_i\right)}$$

$$a_i = \sum_{l=i}^{k-1} \hat{S}\left(t_l^+\right)\left(t_{l+1} - t_l\right)$$

The standard error is the square root of the variance.

Plots

Survival Functions versus Time

The survival function $\hat{S}(t)$ is plotted against *t*.

Log Survival Functions versus Time

$\ln\left(\hat{S}(t)\right)$ is plotted against *t*.

Cumulative Hazard Functions versus Time

$-\ln\left(\hat{S}(t)\right)$ is plotted against *t*.

Estimation of Percentiles and Standard Error

100*p* percentile of the survival time, where *p* is between 0 and 1, is computed as

$$t_p = \inf\left\{t_i \,|\left(\hat{S}(t_i) \le p\right)\right\}$$

The asymptotic variance of t_p is estimated by

$$\mathrm{var}\left(t_p\right) = \frac{\mathrm{var}\left(\hat{S}\left(t_p\right)\right)}{\left(\hat{f}\left(t_p\right)\right)^2}$$

where $\hat{f}\left(t_p\right)$ is computed as

$$\hat{f}\left(t_p\right) = \frac{\hat{S}\left(u_{p+0.05}\right) - \hat{S}\left(t_{p-0.05}\right)}{t_{p-0.05} - u_{p+0.05}}$$

where $u_q = \sup\left\{t_i \,|\left(\hat{S}(t_i) \geq q\right)\right\}$.

Testing the Equality of the Survival Functions

Three statistics are computed to test the equality of survival distributions in the presence of arbitrary right censorship. These statistics are the logrank (Mantel-Cox), the modified Wilcoxon test statistic (Breslow), and an alternative test statistic proposed by Tarone and Ware (1977). Using the regression model proposed by Cox (1972), all three test statistics have been modified for testing monotonic trend in hazard functions.

Test Statistics

Let $n^{(s)}$ be the number of subjects in stratum *s*. Let

$$t_1^{(s)} < \ldots < t_{m_s}^{(s)}$$

be the observed failure times (responses) and

$n_{li}^{(s)}$ = in stratum *s* the number of individuals in group *l* at risk just prior to $t_i^{(s)}$

$d_{li}^{(s)}$ = number of deaths at $t_i^{(s)}$ in group *l* and

$$d_i^{(s)} = \sum_{l=1}^{g} d_{li}^{(s)}$$

$$n_i^{(s)} = \sum_{l=1}^{g} n_{li}^{(s)}$$

Hence, the expected number of events in group l at time $t_i^{(s)}$ is given by

$$E_{li}^{(s)} = \frac{d_i^{(s)} n_{li}^{(s)}}{n_i^{(s)}}$$

Define

$$U_s = \left(U_1^{(s)}, \ldots, U_{g-1}^{(s)}\right)'$$

with

$$U_l^{(s)} = \sum_{i=1}^{m_s} w_i^{(s)} \left(d_{li}^{(s)} - E_{li}^{(s)}\right) \quad \text{for } l = 1, \ldots, g-1.$$

Also, let V_s be a $(g-1)\times(g-1)$ covariance matrix with

$$V_{jl}^{(s)} = \sum_{i=1}^{m_s} \left(w_i^{(s)}\right)^2 \frac{d_i^{(s)}\left(n_i^{(s)} - d_i^{(s)}\right)}{n_i^{(s)} - 1} \frac{n_{ji}^{(s)}}{n_i^{(s)}} \left(\delta_{jl} - \frac{n_{li}^{(s)}}{n_i^{(s)}}\right) \quad \text{for } j, l = 1, \ldots, g-1$$

where

$$w_i^{(s)} = 1 \text{ for log - rank test}$$

$$w_i^{(s)} = n_i^{(s)} \text{ for Breslow test}$$

$$w_i^{(s)} = \sqrt{n_i^{(s)}} \text{ for Tarone Ware test}$$

and

$$\delta_{jl} = \begin{cases} 1 & \text{if } j = l \\ 0 & \text{otherwise} \end{cases}$$

Define

$$U = \sum_{s=1}^{p} U_s$$

and

$$V = \sum_{s=1}^{p} V_s$$

The test statistic for the equality of the g survival functions is defined by

$$\chi^2 = U'V^{-1}U$$

χ^2 has an asymptotic chi-square distribution with $(g-1)$ degrees of freedom.

Test Statistic for Trend

Let

$$t = \left(t_1, \ldots, t_g\right)'$$

be a vector with $t_j =$ trend weighting coefficient for group j . Form the vector

$$U_{(s)} = \left(U_1^{(s)}, \ldots, U_g^{(s)}\right)'$$

$U_{(s)}$ differs from U_s only in the last component.

Let $V^{(s)}$ be a $g \times g$ matrix with element $V_{lj}^{(s)}$ for $1 \le l, j \le g$. The test statistic is defined by

$$\chi_t^2 = \frac{\left(t'U\right)^2}{t'Vt}$$

where

$$U = \sum_{s=1}^{p} U_{(s)}$$

$$V = \sum_{s=1}^{p} V_{(s)}$$

The logrank, Breslow, and Tarone Ware tests may involve trend. Each of the test statistics has a chi-square distribution with one degree of freedom.

The default trend is defined as follows:

$$t = \begin{cases} \left(-(g-1), \ldots, -3, -1, 1, 3, \ldots, (g-1)\right) & \text{if } g \text{ is even} \\ \left(-\dfrac{(g-1)}{2}, \ldots, -1, 0, 1, \ldots, \dfrac{(g-1)}{2}\right) & \text{otherwise} \end{cases}$$

References

Cox, D. R. 1972. Regression models and life tables (with discussion). *Journal of the Royal Statistical Society*, *Series B*, 34: 187–220.

Tarone, R. 1975. Tests for trend in life table analysis. *Biometrika*, 62: 679–682.

Tarone, R., and Ware, J. 1977. On distribution free tests for equality of survival distributions. *Biometrika*, **64**(1): 156–160.