

Non-inferiority Global Rank Test

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Purpose

Determining $E(U)$ and $var(U)$ according to the formula from Matsouaka and Betensky

Notation - General

Symbol	Description
$i = 0, 1$	denotes group, $i = 0$ denotes reference group, $i = 1$ denotes treatment group
n_i	sample size group in i
$n = n_0 + n_1$	total sample size
τ	time at which quantitative endpoint is determined

Assuming exponential distributions for times to event and normal distributions with common variance for quantitative endpoint.

Notation - Survival endpoint

Symbol	Description
t_{0k}	time to event for k-th individual in reference group
t_{1l}	time to event for l-th individual in treatment group
$f_i(t)$	probability density function of time to event random variable in group i
$F_i(t)$	distribution function of time to event random variable in group i
$S_i(t)$	survivor function of time to event random variable in group i
p_i	mortality in group i at time τ
$q_i = 1 - p_i$	survival probability in group i at time τ
d_{0k}	event indicator for k-th individual in reference group, i.e. $d_{0k} = 1$ if $t_{0k} < \tau$, 0 otherwise
d_{1l}	event indicator for l-th individual in treatment group, i.e. $d_{1l} = 1$ if $t_{1l} < \tau$, 0 otherwise
$\lambda_i = \frac{-\log(q_i)}{\tau}$	hazard in group i
$HR = \frac{\lambda_1}{\lambda_0}$	hazard ratio

Notation - Quantitative endpoint

Symbol	Description
x_{0k}	value of quantitative endpoint for k-th individual in reference group
x_{1l}	value of quantitative endpoint for l-th individual in treatment group
$g_i(x)$	probability density function of quantitative endpoint in group i
$G_i(x)$	distribution function of quantitative endpoint in group i
$\varphi(x)$	probability density function of the standard normal distribution
$\Phi(x)$	distribution function of the standard normal distribution
μ_i	mean in group i
σ	common standard deviation
$\delta = \mu_1 - \mu_0$	difference between group means
$\frac{\mu_1 - \mu_0}{\sigma}$	effect size

Formula by Matsouaka and Betensky

Matsouaka and Betensky derive a formula for mean and variance for the global rank test statistic U with the definitions for \tilde{X}_{0k} and \tilde{X}_{1l} from the paper.

$$U = \frac{1}{n_0 n_1} \sum_{k=1}^{n_0} \sum_{l=1}^{n_1} I(\tilde{X}_{0k} < \tilde{X}_{1l})$$

Then expectation and variance are (not just for the case of identical distributions in both groups) given by:

$$\mu_U = E(U) = p_0 p_1 \pi_{t1} + p_0 q_1 + q_0 q_1 \pi_{x1} = \pi_{U1}$$

$$\sigma_U^2 = \text{var}(U) =$$

$$(n_0 n_1)^{-1} (\pi_{U1} (1 - \pi_{U1}) + (n_0 - 1) (\pi_{U2} - \pi_{U1}^2) + (n_1 - 1) (\pi_{U3} - \pi_{U1}^2))$$

where

$$\pi_{U1} = p_0 p_1 \pi_{t1} + p_0 q_1 + q_0 q_1 \pi_{x1}$$

$$\pi_{U2} = p_0^2 q_1 + p_0^2 p_1 \pi_{t2} + 2 p_0 q_0 q_1 \pi_{x1} + q_0^2 q_1 \pi_{x2}$$

$$\pi_{U3} = p_0 q_1^2 + p_0 p_1^2 \pi_{t3} + 2 p_0 p_1 q_1 \pi_{t1} + q_0 q_1^2 \pi_{x3}$$

Formula by Matsouaka and Betensky continued

and

$$\pi_{t1} = P(t_{0k} < t_{1l} | d_{0k} = d_{1l} = 1)$$

$$\pi_{t2} = P(t_{0k} < t_{1l}, t_{0k'} < t_{1l'} | d_{0k} = d_{0k'} = d_{1l} = 1)$$

$$\pi_{t3} = P(t_{0k} < t_{1l}, t_{0k} < t_{1l'} | d_{0k} = d_{1l} = d_{1l'} = 1)$$

$$\pi_{x1} = P(x_{0k} < x_{1l})$$

$$\pi_{x2} = P(x_{0k} < x_{1l}, x_{0k'} < x_{1l'})$$

$$\pi_{x3} = P(x_{0k} < x_{1l}, x_{0k} < x_{1l'})$$

Terms in detail - π_{t1}

$$\begin{aligned}\pi_{t1} &= \frac{P(t_{0k} < t_{1l} < \tau)}{P(t_{0k} < \tau)P(t_{1l} < \tau)} = \frac{1}{p_0 p_1} \int_0^\tau f_0(u) \int_u^\tau f_1(v) dv du \\ &= \frac{1}{p_0 p_1} \int_0^\tau f_0(u) (F_1(\tau) - F_1(u)) du \\ &= \frac{1}{p_0 p_1} \left(p_0 p_1 - \int_0^\tau f_0(u) F_1(u) du \right)\end{aligned}$$

Terms in detail - π_{t2}

$$\begin{aligned}\pi_{t2} &= \frac{P(\max(t_{0k}, t_{0k'}) < t_{1l} < \tau)}{P(t_{0k} < \tau)P(t_{0k'} < \tau)P(t_{1l} < \tau)} \\&= \frac{1}{p_0^2 p_1} \int_0^\tau 2f_0(u)F_0(u) \int_u^\tau f_1(v)dvdu \\&= \frac{1}{p_0^2 p_1} \int_0^\tau 2f_0(u)F_0(u)(F_1(\tau) - F_1(u))du \\&= \frac{1}{p_0^2 p_1} \left(p_1 \int_0^\tau 2f_0(u)F_0(u)du - \int_0^\tau 2f_0(u)F_0(u)F_1(u)du \right) \\&= \frac{1}{p_0^2 p_1} \left(p_1 F_0^2(u)|_0^\tau - F_0^2(u)F_1(u)|_0^\tau + \int_0^\tau F_0^2(u)f_1(u)du \right) \\&= \frac{1}{p_0^2 p_1} \int_0^\tau F_0^2(u)f_1(u)du\end{aligned}$$

Terms in detail - π_{t3}

$$\begin{aligned}\pi_{t3} &= \frac{P(t_{0k} < t_{1l} < t_{1l'} < \tau) + P(t_{0k} < t_{1l'} < t_{1l} < \tau)}{P(t_{0k} < \tau)P(t_{1l} < \tau)P(t_{1l'} < \tau)} \\&= \frac{2P(t_{0k} < t_{1l} < t_{1l'} < \tau)}{P(t_{0k} < \tau)P(t_{1l} < \tau)P(t_{1l'} < \tau)} \\&= \frac{2}{p_0 p_1^2} \int_0^\tau f_0(u) \int_u^\tau f_1(v) \int_v^\tau f_1(w) dw dv du \\&= \frac{2}{p_0 p_1^2} \int_0^\tau f_0(u) \int_u^\tau f_1(v) (F_1(\tau) - F_1(v)) dv du \\&= \frac{2}{p_0 p_1^2} \int_0^\tau f_0(u) \left(p_1 (F_1(\tau) - F_1(u)) - \frac{1}{2} (F_1^2(\tau) - F_1^2(u)) \right) du \\&= \frac{1}{p_0 p_1^2} \left(p_0 p_1^2 - 2p_1 \int_0^\tau f_0(u) F_1(u) du + \int_0^\tau f_0(u) F_1^2(u) du \right)\end{aligned}$$

Distribution assumptions about $\pi_{t1}, \pi_{t2}, \pi_{t3}$

Now make use of the fact that $t_{ik} \sim \exp(\lambda_i)$, i. e. $f_i(t) = \lambda_i e^{-\lambda_i t}$ and $F_i(t) = 1 - e^{-\lambda_i t}$.

π_{t1}

$$\begin{aligned}\pi_{t1} &= \frac{1}{p_0 p_1} \left(p_0 p_1 - \int_0^\tau \lambda_0 e^{-\lambda_0 u} (1 - e^{-\lambda_1 u}) du \right) \\&= \frac{1}{p_0 p_1} \left(p_0 p_1 - p_0 - \frac{\lambda_0}{\lambda_0 + \lambda_1} (e^{-(\lambda_0 + \lambda_1)\tau} - 1) \right) \\&= \frac{1}{p_0 p_1} \left(p_0 p_1 - p_0 - \frac{1}{1 + HR} (q_0 q_1 - 1) \right) \\&= \frac{1}{p_0 p_1} \left(p_0 p_1 - p_0 - \frac{1}{1 + HR} (p_0 p_1 - p_0 - p_1) \right) \\&= \frac{1}{p_0 p_1} \left(p_0 (p_1 - 1) \left(1 - \frac{1}{1 + HR} \right) + \frac{1}{1 + HR} p_1 \right) \\&= \frac{1}{p_0 p_1 (1 + HR)} (p_0 (p_1 - 1) HR + p_1)\end{aligned}$$

π_{t2}

$$\begin{aligned}\pi_{t2} &= \frac{1}{p_0^2 p_1} \int_0^\tau (1 - e^{-\lambda_0 u})^2 \lambda_1 e^{-\lambda_1 u} du \\&= \frac{1}{p_0^2 p_1} \left(\int_0^\tau \lambda_1 e^{-\lambda_0 u} du - 2 \int_0^\tau \lambda_1 e^{-(\lambda_0 + \lambda_1)u} du \right. \\&\quad \left. + \int_0^\tau \lambda_1 e^{-(2\lambda_0 + \lambda_1)u} du \right) \\&= \frac{1}{p_0^2 p_1} \left(p_1 + \frac{2\lambda_1}{\lambda_0 + \lambda_1} (e^{-(\lambda_0 + \lambda_1)\tau} - 1) \right. \\&\quad \left. - \frac{\lambda_1}{2\lambda_0 + \lambda_1} (e^{-(2\lambda_0 + \lambda_1)\tau} - 1) \right) \\&= \frac{1}{p_0^2 p_1} \left(p_1 - \frac{2\lambda_1}{\lambda_0 + \lambda_1} (1 - q_0 q_1) + \frac{\lambda_1}{2\lambda_0 + \lambda_1} (1 - q_0^2 q_1) \right) \\&= \frac{1}{p_0^2 p_1} \left(p_1 - \frac{2HR}{1 + HR} (1 - q_0 q_1) + \frac{HR}{2 + HR} (1 - q_0^2 q_1) \right)\end{aligned}$$

π_{t3}

$$\begin{aligned}\pi_{t3} &= \frac{1}{p_0 p_1^2} \left(p_0 p_1^2 - 2p_1 \int_0^\tau \lambda_0 e^{-\lambda_0 u} (1 - e^{-\lambda_1 u}) du \right. \\ &\quad \left. + \int_0^\tau \lambda_0 e^{-\lambda_0 u} (1 - e^{-\lambda_1 u})^2 du \right) \\ &= \frac{1}{p_0 p_1^2} \left(p_0 p_1^2 - 2p_1 \left(p_0 + \frac{\lambda_0}{\lambda_0 + \lambda_1} (e^{-(\lambda_0 + \lambda_1)\tau} - 1) \right) \right. \\ &\quad \left. + p_0 + \frac{2\lambda_0}{\lambda_0 + \lambda_1} (e^{-(\lambda_0 + \lambda_1)\tau} - 1) \right. \\ &\quad \left. - \frac{\lambda_0}{\lambda_0 + 2\lambda_1} (e^{-(\lambda_0 + 2\lambda_1)\tau} - 1) \right) \\ &= \frac{1}{p_0 p_1^2} \left(p_0 p_1^2 - 2p_0 p_1 + p_0 + \frac{2}{1 + HR} (1 - p_1) (q_0 q_1 - 1) \right. \\ &\quad \left. - \frac{1}{2 + HR} (q_0 q_1^2 - 1) \right) \\ &= \frac{1}{p_0 p_1^2} \left(p_0 q_1^2 + \frac{2}{1 + HR} q_1 (q_0 q_1 - 1) - \frac{1}{2 + HR} (q_0 q_1^2 - 1) \right)\end{aligned}$$