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.

Notatation - 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 end-point 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:
$\mu_U = E(U) = p_0 p_1 \pi_{t1} + p_0 q_1 + q_0 q_1 \pi_{x1} = \pi_{U1}$
$\sigma_U^2 = var(U) =$
$(n_0 n_1)^{-1}(\pi_{U1}(1-\pi_{U1}) + (n_0-1)(\pi_{U2}-\pi_{U1}^2) + (n_1-1)(\pi_{U3}-\pi_{U1}^2))$
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}

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

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}

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

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}

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

π_{t2}

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

π_{t3}

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

π_{x1}, π_{x2} and π_{x3}

For π_{x1}, π_{x2} and π_{x3} note that $X_{0k} \sim \mathcal{N}(\mu_0, \sigma^2)$, $X_{1l} \sim \mathcal{N}(\mu_1, \sigma^2)$ and $\delta = \mu_1 - \mu_0$ and hence
$Y_{0k} := \frac{X_{0k}-\mu_0}{\sigma} \sim \mathcal{N}(0,1)$ and $Y_{1l} := \frac{X_{1l}-\mu_0}{\sigma} = \frac{X_{il}-\mu_1+\delta}{\sigma} \sim \mathcal{N}(\frac{\delta}{\sigma}, 1)$
Next step: Express π_{x1}, π_{x2} and π_{x3} in terms of the pdf, cdf of the standard normal distribution.

π_{x1}, π_{x2} and π_{x3}

$$
\begin{aligned}
\pi_{x1} &= P(X_{0k} < X_{1l}) = P(Y_{0k} < Y_{1l}) = \int_{-\infty}^{\infty} \varphi(x - \frac{\delta}{\sigma})\Phi(x)dx \\
\pi_{x2} &= P(\max(X_{0k}, X_{0k'}) < X_{1l}) = P(\max(Y_{0k}, Y_{0k'}) < Y_{1l}) \\
&= \int_{-\infty}^{\infty} \varphi(x - \frac{\delta}{\sigma})\Phi^2(x)dx \\
\pi_{x3} &= P(X_{0k} < \min(X_{1l}, X_{1l'})) = P(Y_{0k} < \min(Y_{1l}, Y_{1l'})) \\
&= \int_{-\infty}^{\infty} \Phi(x) \cdot 2\varphi(x - \frac{\delta}{\sigma})(1 - \Phi(\frac{\delta}{\sigma}))dx \\
&= \int_{-\infty}^{\infty} \varphi(x - \frac{\delta}{\sigma})\Phi(x)dx - \Big(\Phi^2(x - \frac{\delta}{\sigma})\Phi(x)|_{-\infty}^{\infty} \\
&\quad - \int_{-\infty}^{\infty} \Phi^2(x - \frac{\delta}{\sigma})\varphi(x)dx\Big) \\
&= 2\pi_{x1} - 1 + \int_{-\infty}^{\infty} \Phi^2(x - \frac{\delta}{\sigma})\varphi(x)dx
\end{aligned}
$$