Statistical Procedures for the Equivalence of Two Survival Rates Based on the Censored Data

Dongsheng Tu
NCIC Clinical Trials Group, Queen's University
82-84 Barrie Street
Kingston, Ontario, Canada
dtu@ctg.quuensu.ca

Yanyu Liu
Department of Mathematics and Statistics, Queen's University
Kingston, Ontario, Canada

In recent years, many medical studies were conducted with the main objective to demonstrate that two treatments or therapies are equivalent. A new treatment may still be considered useful if it is as effective as standard treatments but has fewer side effects, lower cost, greater convenience, or better quality of life. Conventional statistical procedures, which are based on the testing of null hypothesis that there is no difference between two treatments, are difficult to be applied in the design and analysis of these studies. When the outcome of a medical study is binary, Tu (1997a and b, 1998) proposed and evaluated some statistical procedures for the equivalence of two cure rates. The objective of this paper is to extend these procedures to the situation where the outcome of the study is a survival rate and the data may be censored.

For a given time M, let $S_N(M)$ and $S_S(M)$ be respectively the survival rate of a subject treated by a new (N) and standard (S) treatments. The equivalence of these two survival rates can be demonstrated by testing the following hypotheses:

$$H_0: S_S(M)-S_N(M) \le \theta_L \text{ or } S_S(M)-S_N(M) \ge \theta_U \qquad \textbf{vs.} \qquad H_1: \theta_L < S_S(M)-S_N(M) < \theta_U,$$

where $\theta_L<0$ and $\theta_U>0$ are the pre-specified lower and upper equivalence limits respectively, which are assumed constants. To test the above hypotheses, assume that that we have two independent samples, $\{T_i: i=1, \ldots, n_S\}$ and $\{T_i: i=n_S+1, \ldots, n_S+n_N\}$ of possibly right-censored survival times from subjects treated by standard and new treatments respectively, where n_S is the total number of patients in standard treatment group, and n_N is the total number of patients in new treatment group. Let $\hat{S}_S(t)$ and $\hat{S}_N(t)$ be the Kaplan-Meier estimates of $S_S(t)$ and $S_N(t)$ respectively, based on these data, and $\hat{V}[\hat{S}_S(t)]$ and $\hat{V}[\hat{S}_N(t)]$ the variance estimates of $\hat{S}_S(t)$ and $\hat{S}_N(t)$ respectively, based on Greenwood's

formula. Define the Hauck-Anderson corrected two-sided test statistics as: $Z_{LL} = \frac{\hat{S}_S(M) - \hat{S}_N(M) - \theta_L - C_0}{\sqrt{\hat{V}[\hat{S}_S(M)] + \hat{V}[\hat{S}_N(M)]}}$ and $Z_{UL} = \frac{\hat{S}_S(M) - \hat{S}_N(M) - \theta_U + C_0}{\sqrt{\hat{V}[\hat{S}_S(M)] + \hat{V}[\hat{S}_N(M)]}}$, where $C_0 = \frac{1}{2\min(n_N, n_S)}$. We can reject H_0 at level α and conclude that these two treatments are equivalent if $Z_{LL} > z_{1-\alpha}$ and $Z_{UL} < -z_{1-\alpha}$.

If the ratio is used as a measure for the relative effectiveness of two treatments, the equivalence of these two survival rates can also be demonstrated by testing the following hypotheses:

$$H_0: S_S(M)/S_N(M) \le \rho_L \text{ or } S_S(M)/S_N(M) \ge \rho_U \quad \textbf{vs.} \quad H_1: \rho_L < S_S(M)/S_N(M) < \rho_U,$$

where $\rho_L < 1$ and $\rho_U > 1$ are pre-specified lower and upper clinical limits, which are assumed to be constants. Define $Z_{LL} = \frac{[\hat{S}_S(M)/\hat{S}_N(M)] - \rho_L}{\hat{\sigma}_0}$ and $Z_{UL} = \frac{[\hat{S}_S(M)/\hat{S}_N(M)] - \rho_U}{\hat{\sigma}_0}$, where $\hat{\sigma}_0 = \frac{\hat{S}_S(M)}{\hat{S}_N(M)} \sqrt{\frac{\hat{V}[\hat{S}_S(M)]}{\hat{S}_S^2(M)} + \frac{\hat{V}[\hat{S}_N(M)]}{\hat{S}_N^2(M)}}$. We can reject H_0 at level α and conclude that both treatments are equivalent if $Z_{LL} > z_{1-\alpha}$ and $Z_{UL} < -z_{1-\alpha}$.

Other related statistical procedures are also defined. Details of these procedures and results of Monte-Carlo simulations to compare these procedures can be obtained from the first author.

REFERENCES

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RESUME

Dans cet article, nous basant sur deux différents groupes recensés, certaines procédures statistiques ont été proposées pour démontrer l'égalité entre les deux taux de survie des patients traités par les deux méthodes de traitement.