Group Project 1

Huanyu Chen, Shaolei Ma, Ruiqi Xue

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Abstract

This study compares the performance of three hypothesis tests for time-to-event data: the conventional log-rank test and two variants of the weighted log-rank test. We assess their effectiveness under scenarios involving both proportional and non-proportional hazard functions, using Monte Carlo simulation techniques to evaluate power across a range of coefficient values. Our analysis highlights nuanced differences in their ability to detect treatment effects, providing insights into selecting appropriate statistical methodologies for analyzing time-to-event data in clinical trials.

1 Introduction

In clinical trials, treatment efficacy is typically evaluated using time-to-event outcomes and the hazard ratio under the proportional hazards assumption. The log-rank test is used to compare observed and expected event counts. However, in real-world scenarios, the proportional hazards assumption may not always hold, requiring statistical adjustments. To address this issue, researchers have proposed weighted log-rank tests that incorporate parameters for different emphases on early or late events. To test the performance of various log-rank tests, we focus on both proportional hazards and non-proportional hazards based on exponential and Weibull distribution assumptions, and then evaluate the power of different parameters.

2 Methods

2.1 Proportional-Hazard Assumption

Under proportional-hazards assumption, the hazard function (Cox model) can be written as:

$$h(t|x) = h_0(t)exp(\beta' x)$$

where t is the time, x the vector of covariates, β the vector of regression coefficients, $h_0(t)$ is the baseline hazard function. Then, the survival function is

$$S(t|x) = exp[-H_0(t)exp(\beta' x)]$$

where

$$H_0(t) = \int_0^t h_0(u)du$$

Thus, the distribution function is

$$F(t|x) = 1 - exp[-H_0(t)exp(\beta' x)]$$

Let Y be a random variable with distribution function F, then $U = F(Y) \sim U(0,1)$, $(1-U) \sim U(0,1)$, i.e.

$$U = exp[-H_0(t)exp(\beta' x)] \sim U(0,1)$$

if $h_0(t) > 0$ for all t, then H_0 can be inverted and the survival time T of the model can be written as

$$T = H_0^{-1}[-log(U)exp(-\beta' x)]$$

where $U \sim U(0, 1)$.

To simply the problem, here we only consider one covariate x, which indicates whether the sample belongs to the control arm ($x = 0$) or the treatment arm ($x = 1$), and set a negative β under the assumption that the treatment has a consistent positive effect.

Now, we only need to know H_0^{-1} to simulate the survival time. To do so, we consider two commonly used survival time distributions: **Exponential distribution** and **Weibull distribution**.

2.1.1 Exponential Distribution

For exponential distribution with scale parameter $\lambda > 0$, the possibility density function is $f_0 = \lambda exp(-\lambda t)$. Thus, $T = -\lambda^{-1} log(U)exp(-\beta' x)$ where $U \sim U(0, 1)$.

2.1.2 Weibull Distribution

For Weibull distribution with the scale parameter λ, and is the shape parameter γ, the possibility density function is $f_0 = \lambda\gamma t^{\gamma-1} exp(-\lambda t^{\gamma})$. Thus, $T = \left(-\lambda^{-1} log(U)exp(-\beta' x)\right)^{1/\gamma}$ where $U \sim U(0, 1)$.

2.2 Non-Proportional-Hazard Assumption

Under Non-Proportional-Hazard Assumption, we still consider the exponential model and Weibull model.

2.2.1 Piecewise Exponential Model

To simplify the problem, we set the baseline hazard function to be a constant $\lambda_0 = 0.5$, which indicates that the survival time for the control arm follows exponential distribution.

Late Effect: We suppose the hazard function for the treatment arm is: $h(t|x = 1) = \begin{cases} \lambda_0 & t < 1 \\ \lambda_1 & t \geq 1 \end{cases}$

Thus, $T = \begin{cases} -\lambda_0^{-1} log(U) & U > exp(-\lambda_0) \\ \dfrac{\lambda_1 - log(U)}{\lambda_0 + \lambda_1} & U \leq exp(-\lambda_0) \end{cases}$

Early Effect: We can use the similar simulation method to generate piecewise exponential models in which the treatment arm shows early effect. The hazard function becomes: $h(t|x = 1) = \begin{cases} \lambda_0 & t \geq 1 \\ \lambda_1 & t < 1 \end{cases}$

Thus, $T = \begin{cases} -\lambda_0^{-1} log(U) & U \leq exp(-\lambda_0) \\ \dfrac{\lambda_1 - log(U)}{\lambda_0 + \lambda_1} & U > exp(-\lambda_0) \end{cases}$ where $U \sim U(0, 1)$.

2.2.2 Weibull Model

To simplify the problem, we assume the control and treatment arm share the same scale parameter λ. For the control arm, suppose the hazard function is: $h(t|x = 0) = \lambda\gamma_0 t^{(\gamma_0 - 1)}$. Thus, $T = \left(-\lambda^{-1} log(U)\right)^{1/\gamma_0}$.

Similarly, we can write the hazard function for the treatment arm as: $h(t|x = 1) = \lambda\gamma_1 t^{(\gamma_1 - 1)}$. We can derive that $T = \left(-\lambda^{-1} log(U)\right)^{1/\gamma_1}$.

3 Simulation Results

4 Conclusion

5 Referrence

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